

March 22, 2021

ATTORNEY GENERAL RAOUL TAKES ACTION TO CORRECT "FATALLY-FLAWED" TOXIC CHEMICAL RISK EVALUATION

Chicago — Attorney General Kwame Raoul, as part of a multistate coalition, today submitted a [petition for review](#) to remedy numerous deficiencies in the risk evaluation for the widely-prevalent, highly-toxic chemical 1,4-dioxane. The risk evaluation – released in the waning days of the previous presidential administration – minimizes or dismisses 1,4-dioxane’s dangers to workers, residents of low-income communities, communities of color and the general public, and attempts to restrict the U.S. Environmental Protection Agency (EPA) from implementing regulatory measures to eliminate the substantial health risks it poses.

“Exposure to 1,4-dioxane can cause many serious health issues, and its release can contaminate the air, water and soil in places where it is used. The federal government’s previous evaluation of the chemical failed to take into account the dangers it poses to workers and residents of communities of color and vulnerable communities,” Raoul said. “The federal government should reassess its use to ensure that the risk evaluation of 1,4-dioxane comprehensively covers the methods that people are exposed to this chemical.”

Raoul and the coalition seek to support the Biden administration’s anticipated efforts to correct the deficiencies in the 1,4-dioxane risk evaluation. Exposure to 1,4-dioxane poses serious harm to human health, including negative nervous system effects; liver, kidney and lung degeneration; and death. The EPA classifies 1,4-dioxane as “likely to be carcinogenic to humans.” 1,4-dioxane is widely used, among other things, in a variety of commercial and industrial applications. The chemical is also a byproduct of the breakdown of other chemicals in a variety of consumer products, including detergents, household cleaners and personal care products. 1,4-dioxane can be released into the air, water and soil at places where it is produced or used.

Because of its potential for substantial harm to public health and the environment, the EPA selected 1,4-dioxane as one of the initial 10 chemical substances subject to its initial risk evaluations required under the Toxic Substances Control Act (TSCA) amendments of 2016. That law requires the EPA to perform comprehensive evaluations of the risks associated with the “full range of exposures” people have to the chemical. Raoul and the coalition argue that the EPA’s 1,4-dioxane risk evaluation excludes many significant exposure pathways through which people are exposed to the chemical – such as contaminated drinking water, air, or soil. The EPA’s risk evaluation under the former administration found no “unreasonable risk” to the general public from 1,4-dioxane’s uses, but the exposure examined by the agency was limited to recreational swimming and did not include all the other, more important, ways – including drinking contaminated water – that 1,4-dioxane may harm people’s health.

Raoul and the coalition also argue that in violating the TSCA and EPA regulations, the EPA’s final risk evaluation failed to assess 1,4-dioxane’s exposure risks to infants, children, pregnant women, workers, the elderly and other “potentially exposed or susceptible subpopulations” who may be at greater risk than the general public. Further, the EPA’s evaluation underestimated 1,4-dioxane’s risk to workers in commercial and industrial settings based on the unfounded assumption that workers will use personal protective equipment, and that this equipment will protect against 1,4-dioxane exposure. Raoul and the coalition contend that the EPA understated the chemical’s risks to workers through these unsupported assumptions.

Before finalizing the 1,4-dioxane risk evaluation, the EPA expanded the scope to cover several additional consumer uses, including surface cleaners and laundry/dishwashing detergents. Raoul and the coalition note that the EPA expanded this scope in line with the urgings of industry trade groups which seek to block

related state-level policies. The EPA's subsequent final risk evaluation for 1,4-dioxane found no unreasonable risk to consumers from the chemical in these products.

Joining Raoul in filing the petition are the attorneys general of the District of Columbia, Hawaii, Maine, Maryland, Massachusetts, Minnesota, New Jersey, Oregon, Pennsylvania, Rhode Island, Vermont, Virginia and Washington, as well as the city of New York.

**IN THE UNITED STATES COURT OF APPEALS
FOR THE NINTH CIRCUIT**

State of New York, State of Hawai‘i, State of Illinois, Commonwealth of Massachusetts, State of Maine, State of Maryland, State of Minnesota, State of New Jersey, State of Oregon, Commonwealth of Pennsylvania, State of Rhode Island, State of Vermont, Commonwealth of Virginia, State of Washington, District of Columbia, and City of New York,

Petitioners,

v.

U.S. Environmental Protection Agency, and Michael S. Regan, as Administrator of the U.S. Environmental Protection Agency,

Respondents.

Case No. 21-_____

PETITION FOR REVIEW

Pursuant to Federal Rule of Appellate Procedure 15, sections 6(i)(1) and 19(a) of the Toxic Substances Control Act, 15 U.S.C. §§ 2605(i)(1), 2618(a), and section 10 of the Administrative Procedure Act, 5 U.S.C. §§ 701-706, the State of New York, State of Hawai‘i, State of Illinois, State of Maryland, Commonwealth of Massachusetts, State of Maine, State of Minnesota, State of New Jersey, State of Oregon, Commonwealth of Pennsylvania, State of Rhode Island, State of Vermont, Commonwealth of Virginia, State of Washington, District of Columbia, and City

of New York (collectively, the “State and Municipal Petitioners”), petition this Court to review the U.S. Environmental Protection Agency’s (“EPA”) final agency action whereby EPA issued a January 22, 2021 order determining that 1,4-dioxane “does not present an unreasonable risk of injury to health or the environment,” *see Final Risk Evaluation for 1,4-Dioxane*, Subsection 5.4.1; *1,4-Dioxane; Final Toxic Substances Control Act (TSCA) Risk Evaluation; Notice of Availability*, 86 Fed. Reg. 1,495 (Jan. 8, 2021).

A copy of the *Final Risk Evaluation for 1,4-Dioxane* is attached hereto as Attachment A.¹ A copy of the *1,4-Dioxane; Final Toxic Substances Control Act (TSCA) Risk Evaluation; Notice of Availability* is attached hereto as Attachment B.²

State and Municipal Petitioners seek a determination by this Court pursuant to section 19(c) of the Toxic Substances Control Act, 15 U.S.C. § 2618(c), that the order is unlawful and therefore must be vacated.

¹ See also <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0238-0092>.

² See also <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0238-0091>.

March 22, 2021

Respectfully Submitted,

FOR THE STATE OF NEW YORK

LETITIA JAMES
ATTORNEY GENERAL

/s/ Sarah K. Kam

Andrew G. Frank
Sarah K. Kam
Gavin G. McCabe
Assistant Attorneys General
Environmental Protection Bureau
28 Liberty Street
New York, NY 10005
(212) 416-8446
Andrew.Frank@ag.ny.gov
Sarah.Kam@ag.ny.gov
Gavin.McCabe@ag.ny.gov
Attorneys for Petitioner State of New York

FOR THE STATE OF HAWAI'I

CLARE E. CONNORS
ATTORNEY GENERAL

/s/ Wade H. Hargrove III

Wade H. Hargrove iii
Deputy Attorney General
Health Division
State of Hawaii Department of the
Attorney General
465 South King Street, Room 200
Honolulu, Hawaii 96813
(808) 587-3050
wade.h.hargrove@hawaii.gov
Attorneys for Petitioner State of Hawaii'i

FOR THE STATE OF ILLINOIS

KWAME RAOUL
ATTORNEY GENERAL

/s/ Daniel Rottenberg

Matthew J. Dunn
Chief, Environmental Enforcement/
Asbestos Litigation Division
Daniel I. Rottenberg
Assistant Attorney General
69 W. Washington St. Floor 18
Chicago, IL 60602
(312) 814-3816
drottenberg@atg.state.il.us
Attorneys for Petitioner State of Illinois

FOR THE STATE OF MAINE

AARON M. FREY
ATTORNEY GENERAL

/s/ Katherine Tierney

Katherine Tierney
Assistant Attorney General
6 State House Station
Augusta, Maine 04333
(207) 626-8897
katherine.tierney@maine.gov
*Attorneys for Petitioner State of
Maine*

FOR THE COMMONWEALTH OF
MASSACHUSETTS

MAURA HEALEY
ATTORNEY GENERAL

/s/ I. Andrew Goldberg

I. Andrew Goldberg
Assistant Attorney General
Environmental Protection Division
Massachusetts Attorney General's
Office
One Ashburton Place, 18th Flr.
Boston, MA 02108
(617) 963-2429
andy.goldberg@mass.gov
*Attorneys for Petitioner
Commonwealth of Massachusetts*

FOR THE STATE OF MARYLAND

BRIAN E. FROSH
ATTORNEY GENERAL

/s/ Joshua M. Segal

Joshua M. Segal
Special Assistant Attorney General
Office of the Attorney General
200 St. Paul Place
Baltimore, MD 21202
(410) 576-6446
jsegal@oag.state.md.us
*Attorneys for Petitioner State of
Maryland*

FOR THE STATE OF
MINNESOTA

KEITH ELLISON
ATTORNEY GENERAL

/s/ Peter N. Surdo

Peter N. Surdo
Special Assistant Attorney General
445 Minnesota Street, Suite 1400
Saint Paul, Minnesota 55101
(651) 757-1061
peter.surdo@ag.state.mn.us
*Attorneys for Petitioner State of
Minnesota*

FOR THE STATE OF NEW JERSEY

GURBIR S. GREWAL
ATTORNEY GENERAL

/s/ Willis Doerr

Willis Doerr
Deputy Attorney General
R.J. Hughes Justice Complex
25 Market Street
Trenton, NJ 08625-0093
(609) 376-2745
willis.doerr@law.njoag.gov
*Attorneys for Petitioner State of New
Jersey*

FOR THE STATE OF OREGON

ELLEN F. ROSENBLUM
ATTORNEY GENERAL

/s/ Paul Garrahan

Paul Garrahan
Attorney-in-Charge
Steve Novick
Special Assistant Attorney General
Natural Resources Section
Oregon Department of Justice
1162 Court St. NE
Salem, OR 97301-4096
(503) 947-4593
paul.garrahan@doj.state.or.us
steve.novick@doj.state.or.us
*Attorneys for Petitioner State of
Oregon*

FOR THE COMMONWEALTH OF
PENNSYLVANIA

JOSH SHAPIRO
ATTORNEY GENERAL

/s/ Aimee D. Thomson

Aimee D. Thomson
Deputy Attorney General
Ann Johnston
Senior Deputy Attorney General
Impact Litigation Section
Pennsylvania Office of Attorney
General
1600 Arch St., Suite 300
Philadelphia, PA 19103
(267) 374-2787
athomson@attorneygeneral.gov
ajohnston@attorneygeneral.gov
Attorneys for Petitioner
Commonwealth of Pennsylvania

FOR THE STATE OF RHODE
ISLAND

PETER F. NERONHA
ATTORNEY GENERAL

/s/ Alison B. Hoffman

Alison B. Hoffman
Special Assistant Attorney General
Rhode Island Office of the Attorney
General
150 South Main Street
Providence, RI 02903
(401) 274-4400 ext 2116
ahoffman@riag.ri.gov
Attorneys for Petitioner State of
Rhode Island

FOR THE STATE OF VERMONT

THOMAS J. DONOVAN, JR.
ATTORNEY GENERAL

/s/ Justin Kolber

Justin Kolber
Assistant Attorney General
Vermont Attorney General's Office
109 State Street
Montpelier VT 05609
(802) 828-3171
justin.kolber@vermont.gov
*Attorneys for Petitioner State of
Vermont*

FOR THE COMMONWEALTH OF
VIRGINIA

MARK R. HERRING
ATTORNEY GENERAL

DONALD D. ANDERSON
DEPUTY ATTORNEY GENERAL

/s/ Paul Kugelman, Jr.

Paul Kugelman, Jr.
Senior Assistant Attorney General
Chief, Environmental Section
Virginia Office of the Attorney
General
202 North 9th Street
Richmond, VA 23219
(804) 786-8480
PKugelman@oag.state.va.us
*Attorneys for Petitioner
Commonwealth of Virginia*

FOR THE STATE OF
WASHINGTON

ROBERT W. FERGUSON
ATTORNEY GENERAL

*/s/ Jonathan C. Thompson**

Jonathan C. Thompson
Assistant Attorney General
Office of the Attorney General
P.O. Box 40117
Olympia, WA 98504
(360) 586-6740
jonathan.thompson@atg.wa.gov
*Attorneys for Petitioner State of
Washington*
**Applying for Admission to Ninth
Circuit Bar*

FOR THE CITY OF NEW YORK

JAMES E. JOHNSON
CORPORATION COUNSEL

/s/ Shiva Prakash

Shiva Prakash
Assistant Corporation Counsel
100 Church Street
New York, NY 10007
(347) 738-1587
shprakas@law.nyc.gov
*Attorneys for Petitioner City of New
York*

FOR THE DISTRICT OF
COLUMBIA

KARL A. RACINE
ATTORNEY GENERAL

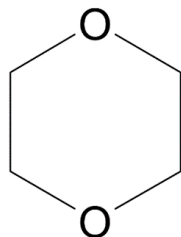
/s/ Loren AliKhan

Loren L. AliKhan
Solicitor General
Office of the Attorney General for
the District of Columbia
400 6th Street, NW, Suite 8100
Washington, D.C. 20001
(202) 727-6287
Loren.AliKhan@dc.gov
*Attorneys for Petitioner District of
Columbia*

ATTACHMENT A

Final Risk Evaluation for 1,4-Dioxane

CASRN: 123-91-1



December 2020

TABLE OF CONTENTS

TABLE OF CONTENTS	2
LIST OF TABLES	10
LIST OF FIGURES	13
LIST OF APPENDIX TABLES	13
LIST OF APPENDIX FIGURES	16
ACKNOWLEDGEMENTS	19
ABBREVIATIONS	20
EXECUTIVE SUMMARY	26
1 INTRODUCTION	36
1.1 Physical and Chemical Properties	38
1.2 Uses and Production Volume	39
1.3 Regulatory and Assessment History	40
1.4 Scope of the Evaluation	41
1.4.1 Conditions of Use Included in the Risk Evaluation	41
1.4.2 Exposure Pathways and Risks Addressed by Other EPA-Administered Statutes	47
1.4.3 Conceptual Models	56
1.5 Systematic Review	61
1.5.1 Data and Information Collection	61
1.5.2 Data Evaluation	69
1.5.3 Data Integration	70
2 EXPOSURES	72
2.1 Fate and Transport	72
2.2 Environmental Releases	74
2.2.1 Environmental Releases to Water	75
2.2.1.1 Results for Daily Release Estimate	75
2.2.1.2 Approach and Methodology	77
2.2.1.2.1 Water Release Estimates	77
2.2.1.2.2 Estimates of Number of Facilities	78
2.2.1.2.3 Estimates of Release Days	79
2.2.1.3 Assumptions and Key Sources of Uncertainty for Environmental Releases	81
2.2.1.3.1 Summary of Overall Confidence in Release Estimates	82
2.3 Environmental Exposures	88
2.3.1 Environmental Exposures – Aquatic Pathway	88
2.4 Human Exposures	89
2.4.1 Occupational Exposures	89
2.4.1.1 Occupational Exposures Approach and Methodology	91
2.4.1.1.1 Manufacturing	97
2.4.1.1.2 Import and Repackaging	98

2.4.1.1.3	Recycling.....	100
2.4.1.1.4	Industrial Uses.....	101
2.4.1.1.5	Functional Fluids (Open System).....	103
2.4.1.1.6	Functional Fluids (Closed System).....	106
2.4.1.1.7	Laboratory Chemicals.....	106
2.4.1.1.8	Film Cement.....	108
2.4.1.1.9	Spray Foam Application.....	110
2.4.1.1.10	Printing Inks (3D).....	113
2.4.1.1.11	Dry Film Lubricant.....	115
2.4.1.1.12	Disposal.....	116
2.4.1.1.13	Dermal Exposure Assessment.....	117
2.4.2	General Population Exposure.....	126
2.4.2.1	General Population Exposure Approach.....	127
2.4.2.1.1	Modeling Surface Water Concentrations.....	127
2.4.2.1.2	Measured Surface Water Concentrations.....	129
2.4.2.1.3	Estimating Incidental Oral Exposures from Swimming.....	129
2.4.2.1.4	Estimating Dermal Exposures from Swimming.....	130
2.4.2.2	General Population Exposure Results.....	131
2.4.3	Consumer Exposures.....	131
2.4.3.1	Consumer Conditions of Use and Routes of Exposure Evaluated.....	131
2.4.3.2	Consumer Exposure Modeling Approach.....	132
2.4.3.2.1	Modeling Air Concentrations and Inhalation Exposure.....	133
2.4.3.2.2	Modeling Dermal Exposure.....	134
2.4.3.3	Consumer Exposure Scenarios and Modeling Inputs.....	135
2.4.3.4	Consumer Exposure Results.....	139
2.4.3.4.1	Surface Cleaner.....	139
2.4.3.4.2	Antifreeze.....	140
2.4.3.4.3	Dish Soap.....	141
2.4.3.4.4	Dishwashing Detergent.....	142
2.4.3.4.5	Laundry Detergent.....	144
2.4.3.4.6	Paints and Floor Lacquer.....	145
2.4.3.4.7	Textile Dye.....	146
2.4.3.4.8	Spray Polyurethane Foam.....	147
3	HAZARDS (EFFECTS).....	149
3.1	Environmental Hazards.....	149
3.1.1	Approach and Methodology.....	149
3.1.2	Weight of Scientific Evidence.....	151
3.2	Human Health Hazards.....	153

3.2.1	Approach and Methodology	153
3.2.2	Toxicokinetics.....	155
3.2.3	Hazard Identification	159
3.2.3.1	Non-Cancer Hazards	160
3.2.3.2	Genetic Toxicity and Cancer Hazards	167
3.2.4	Potential Modes of Action for 1,4-Dioxane Toxicity	172
3.2.5	Weight of Scientific Evidence	174
3.2.6	Dose-Response Assessment.....	178
3.2.6.1	Potentially Susceptible Subpopulations	178
3.2.6.2	Points of Departure for Human Health Hazard Endpoints	178
3.2.6.2.1	Acute/Short-term POD for Inhalation Exposures	178
3.2.6.2.2	Acute/Short-term POD for Dermal Exposures Extrapolated from Inhalation Studies 180	
3.2.6.2.3	Acute/Short-term POD for Oral Exposures Extrapolated from Inhalation Studies 181	
3.2.6.2.4	Chronic Non-Cancer POD for Inhalation Exposures.....	182
3.2.6.2.5	Chronic Cancer Unit Risk for Inhalation Exposures <i>i.e.</i> , Inhalation Unit Risk (IUR) 186	
3.2.6.2.6	Chronic Non-Cancer POD for Dermal Exposures Extrapolated from Chronic Inhalation Studies.....	188
3.2.6.2.7	Chronic Non-Cancer POD for Dermal Exposures Extrapolated from Chronic Oral Studies 189	
3.2.6.2.8	Chronic Cancer Unit Risk for Dermal Exposures <i>i.e.</i> , Cancer Slope Factor (CSF) extrapolated from Chronic Inhalation Studies	192
3.2.6.2.9	Chronic Cancer Unit Risk for Dermal Exposures <i>i.e.</i> , Cancer Slope Factor (CSF) extrapolated from Chronic Oral Studies	193
3.2.7	Summary of Human Health Hazards.....	198
4	RISK CHARACTERIZATION	203
4.1	Environmental Risk.....	203
4.1.1	Risk Estimation Approach of 1,4-Dioxane.....	204
4.1.2	Risk Estimation for the Aquatic Environment.....	204
4.1.3	Risk Estimation for the Sediment Environment	209
4.1.4	Risk Estimation for the Terrestrial Environment.....	210
4.2	Human Health Risk	210
4.2.1	Human Health Risk Estimation Approach	210
4.2.2	Risk Estimate for Exposures for Occupational Use of 1,4-Dioxane	214
4.2.2.1	Occupational Risk Estimation for Effects of Acute/Short-term Inhalation Exposures	214
4.2.2.2	Occupational Risk Estimation for Non-Cancer Effects Following Chronic Inhalation Exposures.....	216
4.2.2.3	Occupational Risk Estimation for Cancer Effects Following Chronic Inhalation Exposures.....	218
4.2.2.4	Occupational Risk Estimation for Non-Cancer Effects Following Acute/Short-term Dermal Exposures.....	221

4.2.2.5	Occupational Risk Estimation for Non-Cancer Effects Following Chronic Dermal Exposures.....	222
4.2.2.6	Occupational Risk Estimation for Cancer Effects Following Dermal Exposures.....	223
4.2.3	Risk Estimates for Exposures from Consumer Use of 1,4-Dioxane	224
4.2.3.1	Risk Estimation for Inhalation Exposures to 1,4-Dioxane in Consumer Products	224
4.2.3.2	Risk Estimation for Dermal Exposure to 1,4-Dioxane in Consumer Products	226
4.2.4	Risk Estimates for Exposures from Incidental Exposure to 1,4-Dioxane in Surface Water.....	227
4.3	Assumptions and Key Sources of Uncertainty.....	231
4.3.1	Key Assumptions and Uncertainties in the Occupational Exposure Assessment	231
4.3.2	Key Assumptions and Uncertainties in the Consumer Exposure Estimation.....	236
4.3.2.1	Confidence in Consumer Exposure Estimates	239
4.3.3	Key Assumptions and Uncertainties in the General Population Exposure.....	244
4.3.3.1	Confidence in General Population Exposure Estimates.....	245
4.3.4	Key Assumptions and Uncertainties in Environmental Risk	246
4.3.5	Key Assumptions and Uncertainties in Human Health Hazards	247
4.3.6	Key Assumptions and Uncertainties in the Human Health Risk Characterization	248
4.4	Potentially Exposed or Susceptible Subpopulations (PESS)	249
4.5	Aggregate and Sentinel Exposures.....	251
4.6	Risk Conclusions.....	251
4.6.1	Summary of Environmental Risk	251
4.6.2	Summary of Human Health Risk.....	254
4.6.2.1	Summary of Risk for Workers and ONUs	254
4.6.2.2	Summary of Risk for Consumer Users and Bystanders	265
4.6.2.3	Summary of Risk for the General Population	270
5	RISK DETERMINATION	271
5.1	Overview	271
5.1.1	Human Health.....	272
5.1.1.1	Non-Cancer Risk Estimates.....	272
5.1.1.2	Cancer Risk Estimates	273
5.1.1.3	Determining Unreasonable Risk of Injury to Health.....	273
5.1.2	Environment	275
5.1.2.1	Determining Unreasonable Risk to Injury to the Environment.....	275
5.2	Detailed Unreasonable Risk Determinations by Condition of Use.....	275
5.2.1	Human Health.....	278
5.2.1.1	Manufacture – Domestic Manufacture – Domestic Manufacture	278
5.2.1.2	Manufacture – Import – Import/Repackaging (Bottle and Drum)	279
5.2.1.3	Processing – Repackaging – Repackaging (Bottle and Drum)	280
5.2.1.4	Processing – Recycling.....	281
5.2.1.5	Processing – Non-incorporative – Basic organic chemical manufacturing (process solvent)	282
5.2.1.6	Processing – Processing as a reactant – Polymerization catalyst.....	283
5.2.1.7	Distribution in Commerce	284
5.2.1.8	Industrial Use – Intermediate Use – Agricultural chemical intermediate; Plasticizer intermediate; Catalysts and reagents for anhydrous acid reactions, brominations and sulfonations	285

5.2.1.9	Industrial use – Processing aids, not otherwise listed – Wood pulping; Extraction of animal and vegetable oils; Wetting and dispersing agent in textile processing; Purification of process intermediates; Etching of fluoropolymers	286
5.2.1.10	Industrial use – Functional fluids, open system – Metalworking fluid; Cutting and tapping fluid; Polyalkylene glycol fluid	287
5.2.1.11	Industrial/commercial use – Laboratory chemicals – Chemical reagent, reference material; Spectroscopic and photometric measurement, liquid scintillation counting medium; Stable reaction medium, cryoscopic solvent for molecular mass determinations; Preparation of histological sections for microscopic examination	288
5.2.1.12	Industrial/commercial use – Adhesives and sealants – Film cement	289
5.2.1.13	Industrial/commercial use – Other uses – Spray polyurethane foam	290
5.2.1.14	Industrial/commercial use – Other uses – Printing and printing compositions	290
5.2.1.15	Industrial/commercial use – Other uses – Dry film lubricant	291
5.2.1.16	Consumer use – Arts, crafts and hobby materials – Textile dye	292
5.2.1.17	Consumer use – Automotive care products – Antifreeze	293
5.2.1.18	Consumer use – Cleaning and furniture care products – Surface cleaner	294
5.2.1.19	Consumer use – Laundry and dishwashing products – Dish soap	295
5.2.1.20	Consumer use – Laundry and dishwashing products – Dishwasher detergent	295
5.2.1.21	Consumer use – Laundry and dishwashing products – Laundry detergent	296
5.2.1.22	Consumer use – Paints and coatings – Paint and floor lacquer	297
5.2.1.23	Consumer use – Other uses – Spray Polyurethane Foam	298
5.2.1.24	Disposal – Disposal – Wastewater; Underground injection; Landfill; Incineration	298
5.2.2	Environment	299
5.3	Changes to the Unreasonable Risk Determination from Draft Risk Evaluation to Final Risk Evaluation.....	300
5.4	Unreasonable Risk Determination Conclusion	301
5.4.1	No Unreasonable Risk Determinations	301
5.4.2	Unreasonable Risk Determinations	302
6	REFERENCES	303
	APPENDICES.....	339
	Appendix A REGULATORY HISTORY	339
A.1	Federal Laws and Regulations	339
A.2	State Laws and Regulations	344
A.3	International Laws and Regulations	344
	Appendix B EXPOSURE SCENARIO MAPPING TO COU.....	347
	Appendix C LIST OF SUPPLEMENTAL DOCUMENTS.....	358
	Appendix D FATE AND TRANSPORT	359
	Appendix E ENVIRONMENTAL EXPOSURES	361
	Appendix F ENVIRONMENTAL RISK.....	371
F.1	Environmental Risk Tables	371
	Appendix G OCCUPATIONAL EXPOSURES	377
G.1	Systematic Review Summary Tables	377

G.1.1	Evaluation of Inhalation Data Sources Specific to 1,4-Dioxane	377
G.1.2	Evaluation of Cross-Cutting Data Sources	382
G.2	Equations for Calculating Acute and Chronic Inhalation Exposures.....	384
G.3	Sample Calculations for Calculating Acute and Chronic Inhalation Exposures.....	389
G.3.1	Example High-End ADC and LADC	389
G.3.2	Example Central Tendency ADC and LADC	390
G.4	Modeling Approach and Parameters for High-End and Central Tendency Inhalation Exposure Estimates for Import and Repackaging, Functional Fluids (Open System), Spray Foam Application, and Disposal	391
G.4.1	Model Design Equations.....	391
G.4.2	Model Parameters	393
G.4.3	Sample Monte Carlo Simulation Result	396
G.5	Approach for Estimating the Number of Workers	396
G.6	Occupational Exposure Scenario Grouping	402
G.6.1	Manufacturing.....	404
G.6.2	Import and Repackaging.....	408
G.6.3	Industrial Uses	411
G.6.4	Functional Fluids (Open System)	415
G.6.5	Laboratory Chemical Use	419
G.6.6	Film Cement	421
G.6.7	Spray Foam Application	423
G.6.8	Printing Inks (3D).....	427
G.6.9	Dry Film Lubricant	428
G.6.10	Disposal	431
G.7	Dermal Exposure Assessment Method	439
G.7.1	Incorporating the Effects of Evaporation	439
G.7.2	Calculation of f_{abs}	440
G.7.3	Potential for Occlusion	443
G.7.4	Incorporating Glove Protection	444
G.7.5	Proposed Dermal Dose Equation.....	445
G.7.6	Equations for Calculating Acute and Chronic (Non-Cancer and Cancer) Dermal Doses	446
Appendix H	CONSUMER EXPOSURES.....	452
H.1	Consumer Inhalation Exposure	452
H.1.1	CEM 2.1 and CEM	452
H.1.2	MCCEM	453
H.1.2.1	MCCEM Inputs for SPF Scenario.....	455
H.2	Consumer Dermal Exposure	456
H.3	Measured Emission Data.....	459
H.4	CEM Model Sensitivity Analysis Summary	461
H.4.1	Continuous Variables.....	461
H.4.2	Categorical Variables.....	464
Appendix I	HUMAN HEALTH HAZARDS	465
I.1	Hazard and Data Quality Summary Tables by study duration/endpoint.....	465
I.1.1	Hazard and Data Evaluation Summary for Human Studies	465
I.1.2	Hazard and Data Quality Evaluation Summary for Acute and Short-Term Studies	465
I.1.3	Hazard and Data Evaluation Summary for the Developmental Toxicity Study.....	467

I.1.4	Hazard and Data Evaluation Summary for Subchronic and Chronic Non-Cancer Studies..	467
I.1.5	Hazard and Data Evaluation Summary for Genotoxicity Studies	472
I.1.6	Data Evaluation Summary for Chronic Cancer Studies	478
I.1.7	Data Evaluation Summary for Mechanistic Studies	485
I.1.8	Hazard Data Tables.....	493

Appendix J MODE OF ACTION ANALYSIS..... 499

J.1	Introduction	499
J.2	Potential MOAs of 1,4-Dioxane Liver Carcinogenicity	499
J.3	MOA analysis for metabolic saturation, cytotoxicity and proliferative regeneration (MOA1) as the basis for 1,4-dioxane-induced liver carcinogenicity	500
J.3.1	Description of the hypothesized MOA	500
J.3.2	Description of experimental support for the hypothesized MOA	506
J.3.3	Strength, consistency, and specificity of association.....	506
J.3.4	Dose-response concordance between observed tumors and events in the proposed MOA..	508
J.3.5	Temporal relationship.....	510
J.3.6	Biological plausibility and coherence.....	511
J.3.7	Consideration of the Possibility of Other MOAs	511
J.3.8	Conclusions About the Hypothesized MOA	511

Appendix K BENCHMARK DOSE ANALYSIS..... 527

K.1	BMDS Summary of Centrilobular necrosis of the liver in male F344/DuCrj rats Kasai et al. (2009)	531
K.2	BMDS Summary of Squamous cell metaplasia of respiratory epithelium in male F433/DuCrj rats Kasai et al. (2009).....	534
K.3	BMDS Summary of Squamous cell hyperplasia of respiratory epithelium in male F433/DuCrj rats Kasai et al. (2009).....	536
K.4	Benchmark dose analysis of respiratory metaplasia of the olfactory epithelium in the nasal cavity of male F344/DuCrj rats Kasai et al. (2009)	539
K.5	BMDS Summary of Hydropic change (lamina propria) Kasai et al. (2009).....	547
K.6	BMDS Summary of Nasal cavity squamous cell carcinoma (male F344/DuCrj rats) Kasai et al. (2009)	550
K.7	BMDS Summary of Zymbal gland adenoma (male F344/DuCrj rats) Kasai et al. (2009).....	552
K.8	MS-Combo portal of entry tumors Kasai et al. (2009)	554
K.9	BMDS Summary of Hepatocellular adenoma or carcinoma (male F344/DuCrj rats) Kasai et al. (2009)	554
K.10	BMDS Summary of Renal cell carcinoma (male F344/DuCrj rats) Kasai et al. (2009).....	556
K.11	BMDS Summary of Peritoneal mesothelioma (male F344/DuCrj rats) Kasai et al. (2009).....	558
K.12	BMDS Summary of Mammary gland fibroadenoma (male F344/DuCrj rats) Kasai et al. (2009)	560
K.13	BMDS Summary of Subcutis fibroma (male F344/DuCrj rats, high dose dropped) Kasai et al. (2009)	563
K.14	MS-Combo Systemic (including liver) Kasai et al. (2009).....	564
K.15	MS-Combo Systemic (omitting liver) Kasai et al. (2009)	565
K.16	MS-Combo portal of entry + systemic (including liver) Kasai et al. (2009)	566
K.17	MS-Combo portal of entry + systemic (omitting liver) Kasai et al. (2009).....	567
K.18	BMDS Summary of Hepatocellular mixed foci in male F344/DuCrj rats Kano et al. (2009)..	567
K.19	BMDS Summary of Cortical tubule degeneration in female OM rats NCI (1978)	570

K.20	BMDS Summary of Nasal squamous cell carcinoma in Male F344/DuCrj rats Kano et al. (2009)	572
K.21	BMDS Summary of Peritoneum mesothelioma in Male F344/DuCrj rats Kano et al. (2009)	.574
K.22	BMDS Summary of Hepatocellular adenoma or carcinoma in Male F344/DuCrj rats Kano et al. (2009)	576
K.23	BMDS Summary of Subcutis fibroma in Male F344/DuCrj rats Kano et al. (2009)578
K.24	BMDS Summary of Nasal squamous cell carcinoma in female F344/DuCrj rats Kano et al. (2009)	579
K.25	BMDS Summary of Mammary adenoma in female F344/DuCrj rats Kano et al. (2009)582
K.26	BMDS Summary of Hepatocellular adenomas or carcinomas female F344/DuCrj rats Kano et al. (2009)583
K.27	BMDS Summary of Hepatocellular adenomas or carcinomas in male CrjBDF1 mice Kano et al. (2009)	585
K.28	BMDS Summary of Hepatocellular adenomas or carcinomas in female CrjBDF1 mice Kano et al. (2009)588
	K.28.1 Time-to-Tumor Modeling with Multistage Weibull Model589
	K.28.2 BMDS Modeling with Poly3 Adjusted Data596
K.29	BMDS Summary of Nasal cavity tumors in Sherman rats Kociba et al. (1974)601
K.30	BMDS Summary of Liver tumors in Sherman rats (male and female combined) Kociba et al. (1974)	602
K.31	BMDS Summary of Nasal squamous cell carcinomas in female OM rats (MS models) NCI (1978)	604
K.32	BMDS Summary of Hepatocellular adenoma in female OM rats NCI (1978)607
K.33	BMDS Summary of Hepatocellular adenomas or carcinomas in male B6C3F1 mice NCI (1978)	609
K.34	BMDS Summary of Hepatocellular adenomas or carcinomas in female B6C3F1 mice NCI (1978)	611
K.35	MS-Combo Result Kano et al. (2009), Male F344/ DuCrj rats, excluding liver613
K.36	MS-Combo Result Kano et al. (2009), Male F344/ DuCrj rats, including liver613
K.37	MS-Combo Result Kano et al. (2009), Female F344/ DuCrj rats, excluding liver614
K.38	MS-Combo Result Kano et al. (2009), Female F344/ DuCrj rats, including liver615

LIST OF TABLES

Table 1-1. Physical and Chemical Properties of 1,4-Dioxane	38
Table 1-2. Production Volume of 1,4-Dioxane in Chemical Data Reporting (CDR) Reporting Period (2012 to 2015) ^a	39
Table 1-3. Assessment History of 1,4-Dioxane	40
Table 1-4. Categories and Subcategories of Conditions of Use Included in the Scope of the Risk Evaluation	44
Table 1-5. Categorical Term Sets used in SQL Querying for 1,4-Dioxane consumer assessment	66
Table 1-6. PECO Statement 1,4-Dioxane Consumer Exposure Assessment (September 2020).....	68
Table 2-1. Environmental Fate Characteristics of 1,4-Dioxane	72
Table 2-2. Summary of EPA’s Daily Water Release Estimates for Each OES and EPA’s Overall Confidence in these Estimates	76
Table 2-3. Summary of EPA’s Estimates for the Number of Facilities for Each OES	79
Table 2-4. Summary of EPA’s Estimates for Release Days Expected for Each OES.....	79
Table 2-5. 1,4-Dioxane releases in TRI and DMR (2018)	80
Table 2-6. Summary of Overall Confidence in Release Estimates by OES	82
Table 2-7. Assigned Protection Factors for Respirators in OSHA Standard 29 CFR § 1910.134	95
Table 2-8. Manufacturing Worker Exposure Data Evaluation	97
Table 2-9. Acute and Chronic Inhalation Exposures of Worker for Manufacturing Based on Monitoring Data	98
Table 2-10. Import and Repackaging Data Source Evaluation.....	99
Table 2-11. Acute and Chronic Inhalation Exposures of Workers for Import and Repackaging Based on Modeling	100
Table 2-12. Industrial Uses Data Source Evaluation	102
Table 2-13. Acute and Chronic Inhalation Exposures of Worker for Industrial Uses Based on Monitoring Data	103
Table 2-14. Functional Fluids (Open System) Data Evaluation	104
Table 2-15. Acute and Chronic Inhalation Exposures of Worker for Open System Functional Fluids Based on Modeling	104
Table 2-16. Acute and Chronic ONU Inhalation Exposures for Open System Functional Fluids Based on Monitoring Data.....	105
Table 2-17. Laboratory Chemicals Data Evaluation.....	107
Table 2-18. Acute and Chronic Inhalation Exposures of Worker for Laboratory Chemicals Based on Monitoring Data.....	108
Table 2-19. Film Cement Data Evaluation	109
Table 2-20. Acute and Chronic Inhalation Exposures of Worker for the Use of Film Cement Based on Monitoring Data.....	109
Table 2-21. Acute and Chronic ONU Inhalation Exposures for the Use of Film Cement Based on Monitoring Data.....	110
Table 2-22. Spray Foam Application Data Source Evaluation.....	111
Table 2-23. Acute and Chronic Inhalation Exposures of Worker for Spray Application Based on Modeling	112
Table 2-24. Acute and Chronic Non-Sprayer Workers Inhalation Exposures for Spray Applications Based on Modeling	113
Table 2-25. Use of Printing Inks Data Evaluation	114
Table 2-26. Acute and Chronic Inhalation Exposures of Worker for Use of Printing Inks Based on Monitoring Data.....	114

Table 2-27. Dry Film Lubricant Data Source Evaluation.....	115
Table 2-28. Acute and Chronic Inhalation Exposures of Workers for the Use of Dry Film Lubricant Based on Exposure Data	116
Table 2-29. Disposal Data Source Evaluation	116
Table 2-30. Acute and Chronic Inhalation Exposures of Worker for Disposal Based on Modeling	117
Table 2-31. IHSkinPerm© Output Data for Various Dermal Exposure Scenarios of 1,4-Dioxane	120
Table 2-32. Exposure Control Efficiencies and Protection Factors for Different Dermal Protection Strategies.....	123
Table 2-33. Estimated Dermal Absorbed Dose ¹ (mg/day) for Workers in Various Conditions of Use.	126
Table 2-34 Modeled Surface Water Concentrations.....	128
Table 2-35 Incidental Oral Exposure Factors	130
Table 2-36 Dermal Exposure Factors	131
Table 2-37 Models Used Across Consumer Conditions of Use and Routes of Exposure	132
Table 2-38 Default Modeling Input Parameters	136
Table 2-39 Key Product-Specific Inputs for Inhalation Modeling.....	137
Table 2-40 Key Product-Specific Inputs for Dermal Modeling	138
Table 2-41 Estimated Inhalation Exposure: Surface Cleaner	139
Table 2-42 Estimated Dermal Exposure: Surface Cleaner	140
Table 2-43 Estimated Inhalation Exposure: Antifreeze.....	141
Table 2-44 Estimated Dermal Exposure: Antifreeze	141
Table 2-45 Estimated Inhalation Exposure: Dish Soap	141
Table 2-46 Estimated Dermal Exposure: Dish Soap	142
Table 2-47 Estimated Inhalation Exposure: Dishwasher Detergent	143
Table 2-48 Estimated Dermal Exposure: Dishwasher Detergent	143
Table 2-49 Estimated Inhalation Exposure: Laundry Detergent	144
Table 2-50 Estimated Dermal Exposure: Laundry Detergent.....	145
Table 2-51 Estimated Inhalation Exposure: Paints and Floor Lacquer	145
Table 2-52 Estimated Dermal Exposure: Paints and Floor Lacquer.....	146
Table 2-53 Estimated Inhalation Exposure: Textile Dye.....	146
Table 2-54 Estimated Dermal Exposure: Textile Dye.....	147
Table 2-55 Estimated Inhalation Exposure: SPF	147
Table 2-56 Estimated Dermal Exposure: SPF	148
Table 3-1. Acceptable acute aquatic toxicity studies that were evaluated for of 1,4-Dioxane.....	150
Table 3-2. Concentrations of Concern (COCs) for Aquatic Toxicity.....	153
Table 3-3. Acceptable Studies Evaluated for Toxicity of 1,4-Dioxane Following Acute or Short-term Exposure ^a	162
Table 3-4. Acceptable Studies Evaluated for Non-Cancer Subchronic or Chronic Toxicity of 1,4- Dioxane Following Inhalation Exposure	163
Table 3-5. Acceptable Subchronic and Chronic Studies Evaluated for Non-Cancer Toxicity of 1,4- Dioxane Following Oral Exposure	165
Table 3-6. Acceptable New Studies Evaluated for Genetic Toxicity of 1,4-Dioxane.....	168
Table 3-7. Studies Evaluated for Cancer Following Inhalation Exposure to 1,4-Dioxane.....	171
Table 3-8. Studies Evaluated for Cancer Following Oral Exposure to 1,4-Dioxane.....	172
Table 3-9. Model selection and duration-adjusted HEC estimates for BMCLs (from best fitting BMDS models) or NOAECs/LOAECs from the 2-year inhalation study by Kasai et al. 2009) in Male F344/DuCrj rats ^a	185

Table 3-10. Dose-response modeling summary results for male rat tumors associated with inhalation exposure to 1,4-dioxane for two years	187
Table 3-11. Dose-response modeling summary results for oral non-cancer liver, kidney, and nasal effects and route-to-route extrapolated applied dermal HEDs	191
Table 3-12. Cancer slope factor for dermal exposures extrapolated from studies for male rat tumors associated with inhalation exposure to 1,4-dioxane for two years	193
Table 3-13. Dose-response modeling summary results for oral CSFs and route-to-route extrapolated dermal CSFs.....	196
Table 3-14. Summary of Hazard Identification and Dose-Response Values	198
Table 4-1. Environmental Risk Estimation of 1,4-Dioxane from Industrial Releases into Surface Water from DMR Facilities in Year 2015 and 2016	207
Table 4-2. Environmental Risk Estimation of 1,4-Dioxane from Direct Industrial Releases into Surface Water from TRI Facilities in Year 2014 and 2015	208
Table 4-3. Environmental Risk Estimation of 1,4-Dioxane from Indirect Industrial Releases into Surface Water from TRI Facilities in Year 2014 and 2015	209
Table 4-4. Summary of Parameters for Risk Characterization	210
Table 4-5. Acute/Short-term Inhalation Exposure Risk to Workers; Benchmark MOE = 300	215
Table 4-6. Acute/Short-term Inhalation Exposure Risk to Occupational Non-Users: Non-Cancer; Benchmark MOE = 300	216
Table 4-7. Chronic Inhalation Exposure Risk to Workers: Non-Cancer; benchmark MOE=30	217
Table 4-8. Chronic Inhalation Exposure Risk to Occupational Non-Users: Non-Cancer; Benchmark MOE = 30	218
Table 4-9. Inhalation Exposure Risk Estimates to Workers: Cancer; Benchmark Risk = 1×10^{-4}	219
Table 4-10. Inhalation Exposures to Occupational Non-Users: Cancer; Benchmark Risk = 1×10^{-4}	220
Table 4-11. Dermal Exposure Risk Estimates to Workers for Acute/Short-term Exposures Non-Cancer; Liver Toxicity; Benchmark MOE = 300.....	221
Table 4-12. Dermal Exposure Risk Estimates to Workers: Non-Cancer; Liver Toxicity Benchmark MOE = 30	222
Table 4-13. Dermal Exposure Risk Estimates to Workers: Cancer; Benchmark Cancer Risk = 1×10^{-4}	223
Table 4-14. Risks from Acute Inhalation Exposure to 1,4-Dioxane in Consumer Products; Benchmark MOE= 300	224
Table 4-15. Risks from Chronic Inhalation Exposure to 1,4-Dioxane in Consumer Products. Benchmark Cancer Risk = 1×10^{-6}	225
Table 4-16. Risks from Acute Dermal Exposure to 1,4-Dioxane in Consumer Products; Benchmark MOE=300	226
Table 4-17. Risks from Chronic Dermal Exposure to 1,4-Dioxane in Consumer Products. Benchmark Cancer Risk = 1×10^{-6}	227
Table 4-18. Risk from Acute Oral Exposure Through Incidental Ingestion of Water; Benchmark MOE = 300.....	227
Table 4-19. Risk from Acute Dermal Exposure from Swimming; Benchmark MOE = 300	229
Table 4-20. Summary and Uncertainty Rating of Occupational Exposure of 1,4-dioxane for Various Conditions of Use	234
Table 4-21 Overall Confidence Ratings for Consumer Inhalation Exposure Estimates	240
Table 4-22 Overall Confidence Ratings for Consumer Dermal Exposure Estimates	242
Table 4-23. Summary of Human Health Risk From Occupational Exposures.....	256
Table 4-24. Summary of Human Health Risks from Consumer Exposures	266

Table 4-25. Summary of Human Health Risks from Incidental Exposure to 1,4-Dioxane in Surface Waters	270
---	-----

LIST OF FIGURES

Figure 1-1. 1,4-Dioxane Life Cycle Diagram.....	43
Figure 1-2. 1,4-Dioxane Conceptual Model for Industrial and Commercial Activities and Uses: Potential Exposures and Hazards	58
Figure 1-3. 1,4-Dioxane Conceptual Model for Consumer Activities and Uses: Consumer Exposures and Hazards	59
Figure 1-4. 1,4-Dioxane Conceptual Model for Environmental Releases and Wastes: Potential Exposures and Hazards	60
Figure 1-5. Literature Flow Diagram for Environmental Fate and Transport Data Sources	63
Figure 1-6. 1,4-Dioxane Literature Flow Diagram for Engineering Releases and Occupational Exposures	64
Figure 1-7. Literature Flow Diagram for Environmental Hazard Data Sources.....	65
Figure 1-8. Literature Flow Diagram for Human Health Hazard Data Sources	66
Figure 1-9. Literature Flow Diagram for General Population, Consumer and Environmental Exposure Data Sources	69
Figure 2-1 Environmental transport, partitioning, and degradation processes for 1,4-dioxane.	74
Figure 2-2. An Overview of How EPA Estimated Daily Water Releases for Each OES.....	75
Figure 2-3 Conceptual diagram showing various key factors that influence dermal exposures in the event of 1,4-dioxane releases (modified after Chattopadhyay and Taft, 2018).	119
Figure 2-4 Flux of 1,4-dioxane across human skin at various exposure conditions.....	122
Figure 3-1. EPA Approach to Human Health Hazard Identification and Dose-Response for 1,4-Dioxane	154
Figure 3-2. 1,4-Dioxane Metabolism Pathways	159
Figure 6-1. Hypothesized Liver Tumor MOA1 for 1,4-dioxane	502
Figure 6-2. Comparison of dose levels associated with increased incidence of liver tumor and various liver toxicity responses in 2-year and 13-week drinking water studies in female mice .	510

LIST OF APPENDIX TABLES

Table A-1. Federal Laws and Regulations.....	339
Table A-2. State Laws and Regulations.....	344
Table A-3. Regulatory Actions by other Governments and Tribes	344
Table B-1. Industrial and Commercial Occupational Exposure Scenarios for 1,4-Dioxane	347
Table B-2. Environmental Releases and Wastes Exposure Scenarios for 1,4-Dioxane	356
Table E-1. Summary of 1,4-Dioxane TRI Releases to the Environment in 2015 (lbs)	361
Table E-2. Facility Selection Characterization	363
Table E-3. Summary of Modeled Surface Water Concentrations for DMR Facilities.....	365
Table E-4. Summary of Modeled Surface Water Concentrations for TRI Facilities – Direct.....	367
Table G-1. Summary of Inhalation Monitoring Data Sources Specific to 1,4-Dioxane.....	378
Table G-2. Summary of Cross-Cutting Data Sources.....	382
Table G-3. Representative Worker Exposure Durations Considered for Risk Assessments.....	386

Table G-4. Overview of Average Worker Tenure from U.S. Census SIPP (Age Group 50+).....	388
Table G-5. Median Years of Tenure with Current Employer by Age Group.....	389
Table G-6. Summary of Parameter Values and Distributions Used in the Inhalation Exposure Model	394
Table G-7. SOCs with Worker and ONU Designations for All Conditions of Use Except Dry Cleaning	397
Table G-8. SOCs with Worker and ONU Designations for Dry Cleaning Facilities.....	398
Table G-9. Estimated Number of Potentially Exposed Workers and ONUs under NAICS 812320.....	399
Table G-10. Occupational Exposure Scenario Groupings.....	402
Table G-11 2017 1,4-Dioxane Production Monitoring Data BASF (2017).....	406
Table G-12. 2007-2011 1,4-Dioxane Production Monitoring Data BASF (2016).....	406
Table G-13. 2016 CDR Data and Assumed Container Types for Repackaging.....	410
Table G-14. Number of Totes and Containers per Site.....	410
Table G-15. Industrial Use NAICS Codes.....	413
Table G-16. DoD and 2002 EU Risk Assessment Industrial Use Inhalation Exposure Data.....	414
Table G-17. 1997 NIOSH HHE PBZ and Area Sampling Data for Metalworking Fluids.....	417
Table G-18. 2011 ESD on Metalworking Fluids Inhalation Exposure Estimates.....	419
Table G-19. Monitoring Data for Laboratory Chemicals.....	421
Table G-20. NIOSH HHE PBZ and Area Samples for Film Cement Use.....	423
Table G-21. Values Used for Daily Site Use Rate for SPF Application.....	425
Table G-22. Estimated Activity Exposure Durations.....	426
Table G-23. PBZ Task and TWA Monitoring Data for Dry Film Lubricant Manufacture and Spray Application at KCNSC.....	430
Table G-24. NAICS Codes with Workers and ONUs for Disposal.....	436
Table G-25. 2018 TRI Off-Site Transfers for 1,4-Dioxane.....	438
Table G-26. Estimated Fraction Evaporated and Absorbed (fabs) using Equation G-20.....	443
Table G-27. Exposure Control Efficiencies and Protection Factors for Different Dermal Protection Strategies from ECETOC TRA v3.....	445
Table I-1. Summary of Mechanistic Data for 1,4-Dioxane.....	485
Table I-2. Cancer Incidence for 1,4-Dioxane Studies with Acceptable Data Quality Ratings ¹	490
Table I-3. Incidences of non-neoplastic lesions in male F344 rats exposed to 1,4-dioxane via inhalation for 2 years (6 hours/day, 5 days/week) Kasai et al. (2009).....	494
Table I-4. Altered hepatocellular foci data in F344/DuCrj rats exposed to 1,4-dioxane via drinking water for 2 years (ad libitum) Kano et al. (2009).....	494
Table I-5. Incidence of cortical tubule degeneration in female Osborne-Mendel rats exposed to 1,4- dioxane via drinking water for 2 years (ad libitum) NCI (1978).....	494
Table I-6. Tumor incidence data in male F344 rats exposed to 1,4-dioxane via inhalation for 2 years (6 hours/day, 5 days/week) Kasai et al. (2009).....	495
Table I-7. Tumor Incidence data in male and female F344/DuCrj rats and Crj:BDF1 mice exposed to 1,4-dioxane via drinking water for 2 years (ad libitum) Kano et al. (2009).....	496
Table I-8. Tumor Incidence data in in male and female Sherman rats (combined) exposed to 1,4-dioxane via drinking water for 2 years (ad libitum) Kociba et al. (1974).....	497
Table I-9. Tumor Incidence data in male and female B6C3F1 mice, and female Osborne-Mendel rats exposed to 1,4-dioxane via drinking water for 2 years (ad libitum) NCI (1978).....	497
Table J-1. Supporting Evidence for Hypothesized Liver Tumor MOA1 for 1,4-dioxane.....	503
Table J-2. Liver histopathology and plasma enzymes in male F344/DuCrj rats exposed to 1,4-dioxane by inhalation for 13 weeks Kasai (2008).....	512

Table J-3. Liver histopathology and plasma enzymes in female F344/DuCrj rats exposed to 1,4-dioxane by inhalation for 13 weeks Kasai (2008)	513
Table J-4. Liver tumors, histopathology and plasma enzymes in male F344/DuCrj rats exposed to 1,4-dioxane by inhalation for 2 years Kasai et al. (2009)	514
Table J-5. Liver histopathology and plasma enzymes in male F344/DuCrj rats exposed to 1,4-dioxane in drinking water for 13 weeks Kano et al. (2008)	515
Table J-6. Liver tumors and histopathology in male F344/DuCrj rats exposed to 1,4-dioxane in drinking water for 2 years Kano et al. (2009; JBRC (1998)	516
Table J-7. Liver weights, histopathology and plasma enzymes in female F344/DuCrj rats exposed to 1,4-dioxane in drinking water for 13 weeks Kano et al. (2008).....	517
Table J-8. Liver tumors, histopathology, and plasma enzymes in female F344/DuCrj rats exposed to 1,4-dioxane in drinking water for 2 years Kano et al. (2009; JBRC (1998).....	518
Table J-9. Liver histopathology and plasma enzymes in male Crj:BDF1 mice exposed to 1,4-dioxane in drinking water for 13 weeks Kano et al. (2008)	519
Table J-10. Liver tumors, histopathology and plasma enzymes in male Crj:BDF1 mice exposed to 1,4-dioxane in drinking water for 2 years Kano et al. (2009; JBRC (1998).....	520
Table J-11. Liver weights, histopathology and plasma enzymes in female Crj:BDF1 mice exposed to 1,4-dioxane in drinking water for 13 weeks Kano et al. (2008)	521
Table J-12. Liver tumors, weights, histopathology and plasma enzymes in female Crj:BDF1 mice exposed to 1,4-dioxane in drinking water for 2 years Kano et al. (2009; JBRC (1998). 522	
Table J-13. Tumor and histopathology incidence in male Sherman rats exposed to 1,4-dioxane in drinking water for 2 years Kociba et al. (1974).....	523
Table J-14. Tumor and histopathology incidence in female Sherman rats exposed to 1,4-dioxane in drinking water for 2 years Kociba et al. (1974).....	524
Table J-15. Tumor and histopathology incidence in male B6C3F1 mice exposed to 1,4-dioxane in drinking water 90 weeks McConnell (2013) reexamination of slides from NCI 1978). 525	
Table J-16. Tumor and histopathology incidence in female B6C3F1 mice exposed to 1,4-dioxane in drinking water 90 weeks McConnell (2013) reexamination of slides from NCI 1978). 526	
Table K-1. Summary of BMD Modeling Results for Centrilobular necrosis of the liver in male F344/DuCrj rats Kasai et al. (2009).....	531
Table K-2. Summary of BMD Modeling Results for Squamous cell metaplasia of respiratory epithelium in male F433/DuCrj rats Kasai et al. (2009).....	534
Table K-3. Summary of BMD Modeling Results for Squamous cell hyperplasia of respiratory epithelium in male F433/DuCrj rats Kasai et al. (2009).....	536
Table K-4. Summary of BMD Modeling Results for Hydropic change (lamina propria) Kasai et al. (2009).....	547
Table K-5. Summary of BMD Modeling Results for Nasal cavity squamous cell carcinoma (male F344/DuCrj rats) Kasai et al. (2009).....	550
Table K-6. Summary of BMD Modeling Results for Zymbal gland adenoma (male F344/DuCrj rats) Kasai et al. (2009).....	552
Table K-7. Summary of BMD Modeling Results for Hepatocellular adenoma or carcinoma (male F344/DuCrj rats) Kasai et al. (2009).....	554
Table K-8. Summary of BMD Modeling Results for Renal cell carcinoma (male F344/DuCrj rats) Kasai et al. (2009)	557
Table K-9. Summary of BMD Modeling Results for Peritoneal mesothelioma (male F344/DuCrj rats) Kasai et al. (2009).....	559

Table K-10. Summary of BMD Modeling Results for Mammary gland fibroadenoma (male F344/DuCrj rats) Kasai et al. (2009).....	561
Table K-11. Summary of BMD Modeling Results for Subcutis fibroma (male F344/DuCrj rats, high dose dropped) Kasai et al. (2009)	563
Table K-12. Summary of BMD Modeling Results for Hepatocellular mixed foci in male F344/DuCrj rats Kano et al. (2009).....	567
Table K-13. Summary of BMD Modeling Results for Cortical tubule degeneration in female OM rats NCI (1978)	570
Table K-14. Summary of BMD Modeling Results for Nasal squamous cell carcinoma in Male F344/DuCrj rats Kano et al. (2009)	572
Table K-15. Summary of BMD Modeling Results for Peritoneum mesothelioma in Male F344/DuCrj rats Kano et al. (2009).....	574
Table K-16. Summary of BMD Modeling Results for Hepatocellular adenoma or carcinoma in Male F344/DuCrj rats Kano et al. (2009)	576
Table K-17. Summary of BMD Modeling Results for Subcutis fibroma in Male F344/DuCrj rats Kano et al. (2009).....	578
Table K-18. Summary of BMD Modeling Results for Nasal squamous cell carcinoma in female F344/DuCrj rats Kano et al. (2009)	580
Table K-19. Summary of BMD Modeling Results for Mammary adenoma in female F344/DuCrj rats Kano et al. (2009)	582
Table K-20. Summary of BMD Modeling Results for Hepatocellular adenomas or carcinomas female F344/DuCrj rats Kano et al. (2009)	584
Table K-21. Summary of BMD Modeling Results for Hepatocellular adenomas or carcinomas in male CrjBDF1 mice Kano et al. (2009).....	586
Table K-22. Summary of BMD Modeling Results for Nasal cavity tumors in Sherman rats Kociba et al. (1974).....	601
Table K-23. Summary of BMD Modeling Results for Liver tumors in Sherman rats (male and female combined) Kociba et al. (1974)	603
Table K-24. Summary of BMD Modeling Results for Nasal squamous cell carcinomas in female OM rats (MS models) NCI (1978)	605
Table K-25. Summary of BMD Modeling Results for Hepatocellular adenoma in female OM rats NCI (1978).....	607
Table K-26. Summary of BMD Modeling Results for Hepatocellular adenomas or carcinomas in male B6C3F1 mice NCI (1978).....	609
Table K-27. Summary of BMD Modeling Results for Hepatocellular adenomas or carcinomas in female B6C3F1 mice NCI (1978).....	611

LIST OF APPENDIX FIGURES

Figure D-1. EPI Suite™ welcome screen set up for 1,4-dioxane model run.....	359
Figure G-1. Example of Monte Carlo Simulation results for the Disposal Scenario	396
Figure G-2. Generic Manufacturing Process Flow Diagram	404
Figure G-3. General Process Flow Diagram for Import and Repackaging.....	408
Figure G-4. Generic Industrial Use Process Flow Diagram	411
Figure G-5. Process Flow Diagram for Open System Functional Fluids	416
Figure G-6. General Laboratory Use Process Flow Diagram.....	420

Figure G-7. Process Flow Diagram for Film Cement Application.....	422
Figure G-8. Process Flow Diagram for Spray Application.....	424
Figure G-9. Process Flow Diagram for Printing Inks (3D)	427
Figure G-10. Process Flow Diagram for Dry Film Lubricant in Nuclear Weapon Applications.....	429
Figure G-11. Typical Waste Disposal Process	433
Figure G-12. Typical Industrial Incineration Process.....	434
Figure G-13. General Process Flow Diagram for Solvent Recovery Processes	436
Figure H-1. Elasticities (≥ 0.05) for Parameters Applied in E1.....	462
Figure H-2. Elasticities (≥ 0.05) for Parameters Applied in E4.....	463
Figure H-3. Elasticities (≥ 0.05) for Parameters Applied in P_DER2b.....	464
Figure K-1. Plot of incidence rate by dose with fitted curve for the unrestricted LogProbit (left) and restricted LogLogistic (right) models for Centrilobular necrosis of the liver in male F344/DuCrj rats Kasai et al. (2009); dose shown in ppm. Restricted LogLogistic has the lowest AIC but exhibits higher residuals for all dose groups.	532
Figure K-2. Plot of incidence rate by dose with fitted curve for LogProbit model for Squamous cell metaplasia of respiratory epithelium in male F433/DuCrj rats Kasai et al. (2009); dose shown in ppm.....	534
Figure K-3. Plot of incidence rate by dose with fitted curve for Quantal-Linear model for Squamous cell hyperplasia of respiratory epithelium in male F433/DuCrj rats; dose shown in ppm. ...	537
Figure K-4. Plot of incidence rate by dose with fitted curve for LogLogistic model for Hydropic change (lamina propria) Kasai et al. (2009); dose shown in ppm.....	548
Figure K-5. Plot of incidence rate by dose with fitted curve for Multistage-Cancer 1° model for Nasal cavity squamous cell carcinoma (male F344/DuCrj rats) Kasai et al. (2009); dose shown in ppm.	550
Figure K-6. Plot of incidence rate by dose with fitted curve for Multistage-Cancer 1° model for Zymbal gland adenoma (male F344/DuCrj rats) Kasai et al. (2009); dose shown in ppm.	552
Figure K-7. Plot of incidence rate by dose with fitted curve for Multistage-Cancer 1° model for Hepatocellular adenoma or carcinoma (male F344/DuCrj rats) Kasai et al. (2009); dose shown in ppm.....	555
Figure K-8. Plot of incidence rate by dose with fitted curve for Multistage-Cancer 1° model for Renal cell carcinoma (male F344/DuCrj rats) Kasai et al. (2009); dose shown in ppm.....	557
Figure K-9. Plot of incidence rate by dose with fitted curve for Multistage-Cancer 1° model for Peritoneal mesothelioma (male F344/DuCrj rats) Kasai et al. (2009); dose shown in ppm.	559
Figure K-10. Plot of incidence rate by dose with fitted curve for Multistage-Cancer 1° model for Mammary gland fibroadenoma (male F344/DuCrj rats) Kasai et al. (2009); dose shown in ppm.	561
Figure K-11. Plot of incidence rate by dose with fitted curve for Multistage-Cancer 1° model for Subcutis fibroma (male F344/DuCrj rats, high dose dropped) Kasai et al. (2009); dose shown in ppm.....	563
Figure K-12. Plot of incidence rate by dose with fitted curve for LogLogistic model for Hepatocellular mixed foci in male F344/DuCrj rats Kano et al. (2009); dose shown in mg/kg-d.....	568
Figure K-13. Plot of incidence rate by dose with fitted curve for Weibull model for Cortical tubule degeneration in female OM rats NCI (1978); dose shown in mg/kg-d.....	570
Figure K-14. Plot of incidence rate by dose with fitted curve for Multistage-Cancer 2° model for Nasal squamous cell carcinoma in Male F344/DuCrj rats Kano et al. (2009); dose shown in mg/kg-d.....	572

Figure K-15. Plot of incidence rate by dose with fitted curve for Multistage-Cancer 2° model for Peritoneum mesothelioma in Male F344/DuCrj rats Kano et al. (2009); dose shown in mg/kg-d. 574

Figure K-16. Plot of incidence rate by dose with fitted curve for Multistage-Cancer 2° model for Hepatocellular adenoma or carcinoma in Male F344/DuCrj rats Kano et al. (2009); dose shown in mg/kg-d. 576

Figure K-17. Plot of incidence rate by dose with fitted curve for Multistage-Cancer 1° model for Subcutis fibroma in Male F344/DuCrj rats Kano et al. (2009); dose shown in mg/kg-d. 578

Figure K-18. Plot of incidence rate by dose with fitted curve for Multistage-Cancer 1° model for Nasal squamous cell carcinoma in female F344/DuCrj rats Kano et al. (2009); dose shown in mg/kg-d. 580

Figure K-19. Plot of incidence rate by dose with fitted curve for Multistage-Cancer 1° model for Mammary adenoma in female F344/DuCrj rats Kano et al. (2009); dose shown in mg/kg-d. 582

Figure K-20. Plot of incidence rate by dose with fitted curve for Multistage-Cancer 2° model for Hepatocellular adenomas or carcinomas female F344/DuCrj rats Kano et al. (2009); dose shown in mg/kg-d. 584

Figure K-21. Plot of incidence rate by dose with fitted curve for Multistage-Cancer 1° model for Hepatocellular adenomas or carcinomas in male CrjBDF1 mice Kano et al. (2009); dose shown in mg/kg-d. 586

Figure K-22. Plot of incidence rate by dose with fitted curve for Multistage-Cancer 2° model for Nasal cavity tumors in Sherman rats Kociba et al. (1974); dose shown in mg/kg-d. 601

Figure K-23. Plot of incidence rate by dose with fitted curve for Multistage-Cancer 1° model for Liver tumors in Sherman rats (male and female combined) Kociba et al. (1974); dose shown in mg/kg-d. 603

Figure K-24. Plot of incidence rate by dose with fitted curve for Multistage-Cancer 1° model for Nasal squamous cell carcinomas in female OM rats (MS models) NCI (1978); dose shown in mg/kg-d. 605

Figure K-25. Plot of incidence rate by dose with fitted curve for Multistage-Cancer 1° model for Hepatocellular adenoma in female OM rats NCI (1978); dose shown in mg/kg-d. 607

Figure K-26. Plot of incidence rate by dose with fitted curve for Multistage-Cancer 1° model for Hepatocellular adenomas or carcinomas in male B6C3F1 mice NCI (1978); dose shown in mg/kg-d. 609

Figure K-27. Plot of incidence rate by dose with fitted curve for Multistage-Cancer 1° model for Hepatocellular adenomas or carcinomas in female B6C3F1 mice NCI (1978); dose shown in mg/kg-d. 611

ACKNOWLEDGEMENTS

This report was developed by the United States Environmental Protection Agency (U.S. EPA), Office of Chemical Safety and Pollution Prevention (OCSPP), Office of Pollution Prevention and Toxics (OPPT) with support from the Office of Research and Development (ORD).

Acknowledgements

The OPPT Assessment Team gratefully acknowledges participation and/or input from Intra-agency reviewers that included multiple offices within EPA, Inter-agency reviewers that included multiple Federal agencies, and assistance from EPA contractors GDIT (Contract No. CIO-SP3, HHSN316201200013W), ERG (Contract No. EP-W-12-006), Versar (Contract No. EP-W-17-006), ICF (Contract No. EPC14001), Abt (Contract No. EP-W-16-009), and SRC (Contract No. EP-W-12-003).

Docket

Supporting information can be found in public docket: [EPA-HQ-OPPT-2016-0723](https://www.epa.gov/docket/epa-hq-oppt-2016-0723).

Disclaimer

Reference herein to any specific commercial products, process or service by trade name, trademark, manufacturer or otherwise does not constitute or imply its endorsement, recommendation or favoring by the United States Government.

Authors

Stan Barone (Deputy Division Director), Yvette Selby-Mohamadu (Management Lead), Nikki Bass (Staff Lead), Yousuf Ahmad, Michelle Angrish, Joseph Avcin, Marcy Card, Sandip Chattopadhyay, Allen Davis, Jeff Dean, Ingrid Druwe, Jeff Gift, Belinda Hawkins, Brandon Huston, Amuel Kennedy, Nagalakshmi Keshava, Niva Kramek, Albert Monroe, Aaron Murray, Shannon Rebersak, James Sanders, Stephanie Sarraino, Alan Sasso, John Stanek, Lily Wang, Susanna Wegner, Cindy Wheeler, Paul White, Jay Zhao.

ABBREVIATIONS

°C	Degrees Celsius
AAL	Allowable Ambient Levels
ACC	American Chemistry Council
ACGIH	American Conference of Governmental Industrial Hygienists
ADC	Average Daily Concentration
ADME	Absorption, Distribution, Metabolism, and Elimination
AEC	Acute Exposure Concentration
AEGL	Acute Exposure Guideline Level
AES	Alkyl Ethoxysulphates
AF	Assessment Factor
AIC	Akaike Information Criterion
APF	Assigned Protection Factor
AQS	Air Quality System
ARD	Acute Retained Doses
AT _{acute}	Acute Averaging Time
atm	atmosphere(s)
ATSDR	Agency for Toxic Substances and Disease Registry
AWD	Annual Working Days
BCF	Bioconcentration Factor
BLS	Bureau of Labor Statistics
BMC	Benchmark Concentration
BMCL	Benchmark Concentration Limit
BMD	Benchmark Dose
BMDL	Benchmark Dose Level
BMDS	Benchmark Dose Modeling Software
BMDU	Benchmark Dose Upper bound
BMR	Benchmark Response
BSER	Best System of Emission Reduction
BW	Body Weight
CAA	Clean Air Act
CASRN	Chemical Abstract Service Registry Number
CBI	Confidential Business Information
CCL	Candidate Contaminant List
CCP	Commercial Chemical Product
CDC	Centers for Disease Control and Prevention
CDR	Chemical Data Reporting
CERCLA	Comprehensive Environmental Response, Compensation and Liability Act
CFR	Code of Federal Regulations
CHIRP	Chemical Risk Information Platform
CNS	Central Nervous System
COC	Concentrations of Concern
COU	Condition of Use
CPS	Current Population Survey
CPSC	Consumer Product Safety Commission
CRD	Chronic Retained Doses
CSCL	Chemical Substances Control Law

CSF	Cancer Slope Factor
CT	Central Tendency
CWA	Clean Water Act
DAF	Dosimetric Adjustment Factor
DHHS	Department of Health and Human Services
DIY	Do It Yourself
DMBA	Dimethylbenz[a]anthracene
DMR	Discharge Munitions Report
DoD	Department of Defense
DOE	Department of Energy
DOEHRS-IH	Defense Occupational and Environmental Health Readiness System – Industrial Hygiene
DOT	Department of Transportation
EASE	Estimation and Assessment of Substance Exposure
EC ₅₀	Effective Median Concentration
EC	European Commission
ECETOC TRA	European Centre for Ecotoxicology and Toxicology of Chemicals Targeted Risk Assessment
ECHA	European Chemicals Agency
ECHO	Enforcement and Compliance History Online
ECJRC	European Commission Joint Research Centre
ED	Exposure Duration
EF	Exposure Frequency
E-FAST	Exposure and Fate Assessment Screening Tool
ELCR	Excess Lifetime Cancer Risk
EPA	Environmental Protection Agency
EPCRA	Emergency Planning and Community Right-to-Know Act
ERG	Eastern Research Group
ESD	Emission Scenario Document
EU	European Union
EUSES	European Union System for the Evaluation of Substances
f _{abs}	Fraction Absorbed
FDA	Food and Drug Administration
FEI	Finnish Environmental Institute
FFDCA	Federal Food, Drug, and Cosmetic Act
FRS	Facility Registry Service
GACT	Generally Available Control Technology
GC-FID	Gas Chromatography with Flame-Ionization Detection
GDIT	General Dynamics Information Technology
GESTIS	Substance Database; contains information for the safe handling of hazardous substances and other chemical substances at work
GNIS	Geographic Names Information System
GS	Generic Scenarios
HAP	Hazardous Air Pollutant
HE	High End
HEAA	β-Hydroxyethoxy Acetic Acid
HEC	Human Equivalent Factor
HED	Human Equivalent Dose

HEEG	Human Exposure Expert Group
Hg	Mercury
HHE	Health Hazard Evaluation
HPLC	High Performance Liquid Chromatography
HPV	High Production Volume
IARC	International Agency for Research on Cancer
IBC	Intermediate Bulk Container
ICMM	International Council on Mining and Metal
ICRP	International Commission on Radiological Protection
ICSC	International Chemical Safety Cards
IE	Immature Erythrocytes
IFA	Institut für Arbeitsschutz der
IGHRC	Interdepartmental Group on the Health Risks of Chemicals
IH	Industrial Hygiene
IHA	Industrial Hygiene Analyses
ILO	International Labor Organization
IRIS	Integrated Risk Information System
IS	Industry Sector
ISHA	Industrial Safety and Health Act
IUR	Inventory Update Reporting Rule; or Inhalation Unit Risk
JR	Juvenile Rat
KCNSC	Kansas City National Security Campus
kg	Kilogram(s)
K _{oc}	Organic Carbon: Water Partition Coefficient
K _{ow}	Octanol:Water Partition Coefficient
LADC	Lifetime Average Daily Concentration
lb	Pound
LC ₅₀	50% Lethal Concentration
LEV	Local Exhaust Ventilation
LOAEC	Lowest Observed Adverse Effect Concentration
LOAEL	Lowest Observed Adverse Effect Level
LOD	Limit of Detection
LOEC	Lowest Observed Effect Concentration
Log K _{ow}	Logarithmic Octanol:Water Partition Coefficient
LT	Lifetime Years
MACT	Maximum Achievable Control Technology
MATC	Maximum Acceptable Toxicant Concentration
mg	Milligram(s)
MGD	Million Gallons Per Day
µg	Microgram(s)
MIR	Maximum Individual Risk
MNH	Micronucleated Hepatocytes
MNIE	Micronucleated Immature Erythrocytes
MOA	Mode of Action
MOE	Margin of Exposure
MP&M	Metal Products and Machinery
MRL	Minimal Risk Level

MW	Molecular Weight
MWC	Municipal Waste Combustor
MWF	Metalworking Fluids
NAC	National Advisory Committee
NAICS	North American industrial Classification System
NAS	National Academies of Science
NATA	National Air-Toxics Assessment
NCEA	National Center for Environmental Assessment
ND	Non-detect
NEI	National Emissions Inventory
NESHAP	National Emission Standards for Hazardous Air Pollutants
NHD	National Hydrography Dataset
NICNAS	National Industrial Chemicals Notification and Assessment Scheme
NIOSH	National Institute for Occupational Safety and Health
NIST	National Institute of Standards and Technology
NITE	National Institute of Technology and Evaluation
NNSA	National Nuclear Security Administration
NOEC	No Observed Effect Concentration
NOAEL	No Observed Adverse Effect Level
NP	Not Provided
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NPRI	Canada's National Pollutant Release Inventory
NRC	National Research Council
NSPS	New Source Performance Standards
NTP	National Toxicology Program
NWIS	National Water Information System
OAR	Office of Air and Radiation
OARS	Occupational Alliance for Risk Science
OCF	One Component Foam
OCSP	Office of Chemical Safety and Pollution Prevention
OD _{site}	Operating Days per Site
OECD	Organisation for Economic Co-operation and Development
OEHHA	Office of Environmental Health Hazard Assessment (California)
OEL	Occupational Exposure Limit
OES	Occupational Exposure Scenario
OLEM	Office of Land and Emergency Management
ONU	Occupational non-user
OPP	Office of Pesticides Program
OPPT	Office of Pollution Prevention and Toxics
ORD	Office of Research and Development
OSHA	Occupational Safety and Health Administration
OSWER	Office of Solid Waste and Emergency Response
OW	Office of Water
PAPR	Power Air-Purifying Respirator
PBPK	Physiologically Based Pharmacokinetic
PBT	Persistent Bioaccumulative Toxic

PBZ	Personal Breathing Zone
PDE	Permitted Daily Exposure
PDM	Probabilistic Dilution Model
PEC	Predicted Environmental Concentration
PECO	Populations, Exposures, Comparators, and Outcomes
PEL	Permissible Exposure Limit
PESO	Pathways and Processes, Exposure, Setting or Scenario, and Outcomes
PESS	Potentially Exposed or Susceptible Subpopulations
PF	Protection Factor
PFIA	Problem Formulation and Initial Assessment
PH	Partial Hepatectomy
PNOR	Particulates, Not Otherwise Regulated
POD	Point of Departure
POTW	Publicly Owned Treatment Works
ppb	Parts per Billion
PPE	Personal Protective Equipment
ppm	Parts per Million
PV	Production Volume
PWS	Public Water System
QAPP	Quality Assurance Project Plan
QSAR	Quantitative Structure Activity Relationship
RA	Risk Assessment
RAR	Risk Assessment Report
RCRA	Resource Conservation and Recovery Act
RDF	Refuse-Derived Fuel
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
REL	Recommended Exposure Level
RESO	Receptors, Exposure, Setting or Scenario, and Outcomes
RfC	Reference Concentration
RfD	Reference Dose
RGDR	Regional Gas Dose Ratio
RQ	Risk Quotient
SAR	Supplied-Air Respirator
SCBA	Self-Contained Breathing Apparatus
SDS	Safety Data Sheet
SDWA	Safe Drinking Water Act
SIC	Standard Industrial Classification
SIDS	Screening Information Data Set
SIFT-MS	Selected Ion Flow Tube-Mass Spectrometry
SIPP	Survey of Income and Program Participation
SOC	Standard Occupational Classification
SOP	Standard Operation Procedure
SPFs	Spray Polyurethane Foams
SRC	SRC Inc., formerly Syracuse Research Corporation
STEL	Short-term Exposure Limit
STORET	Storage and Retrieval
STP	Sewage Treatment Plants

SUSB	Statistics of US Businesses
TCA	1,1,1-Trichloroethane
TIAC	Time Integrated Air Concentration
TLC	Thin-layer Chromatography
TLV	Threshold Limit Value
TO	Toxic Organic
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TSDF	Treatment, Storage and Disposal Facility
TWA	Time Weighted Average
UCMR	Unregulated Contaminant Monitoring Rule
UF	Uncertainty Factor
US	United States
VCCEP	Voluntary Children's Chemical Evaluation Program
V_c	Container Volume
V_m	Molar Volume
VOC	Volatile Organic Carbon
VP	Vapor Pressure
WEEL	Workplace Environmental Exposure Level
WHO	World Health Organization
WWTP	Wastewater Treatment Plant
WY	Working Year
Y_{derm}	weight fraction of the chemical of interest in the liquid
Yr	Year

EXECUTIVE SUMMARY

This final risk evaluation for 1,4-dioxane was performed in accordance with the Frank R. Lautenberg Chemical Safety for the 21st Century Act and is being issued following public comment and peer review. The Frank R. Lautenberg Chemical Safety for the 21st Century Act amended the Toxic Substances Control Act (TSCA), the Nation's primary chemicals management law, in June 2016. Under the amended statute, EPA is required, under TSCA § 6(b), to conduct risk evaluations to determine whether a chemical substance presents unreasonable risk of injury to health or the environment, under the conditions of use, without consideration of costs or other non-risk factors, including an unreasonable risk to potentially exposed or susceptible subpopulations (PESS), identified as relevant to the risk evaluation. Also, as required by TSCA § (6)(b), EPA established, by rule, a process to conduct these risk evaluations. [*Procedures for Chemical Risk Evaluation Under the Amended Toxic Substances Control Act* \(82 FR 33726\)](#) (Risk Evaluation Rule). This risk evaluation is in conformance with TSCA § 6(b), and the Risk Evaluation Rule, and is to be used to inform risk management decisions. In accordance with TSCA Section 6(b), if EPA finds unreasonable risk from a chemical substance under its conditions of use in any final risk evaluation, the Agency will propose actions to address those risks within the timeframe required by TSCA. However, any proposed or final determination that a chemical substance presents unreasonable risk under TSCA Section 6(b) is not the same as a finding that a chemical substance is "imminently hazardous" under TSCA Section 7. The conclusions, findings, and determinations in this final risk evaluation are for the purpose of identifying whether the chemical substance presents unreasonable risk or no unreasonable risk under the conditions of use, in accordance with TSCA Section 6, and are not intended to represent any findings under TSCA Section 7.

TSCA § 26(h) and (i) require EPA, when conducting risk evaluations, to use scientific information, technical procedures, measures, methods, protocols, methodologies and models consistent with the best available science and to base its decisions on the weight of the scientific evidence.¹ To meet these TSCA § 26 science standards, EPA used the TSCA systematic review process described in the Application of Systematic Review in TSCA Risk Evaluations document ([U.S. EPA, 2018b](#)). The data collection, data evaluation and data integration stages of the systematic review process are used to develop the exposure, fate and hazard assessments for risk evaluations.

1,4-Dioxane is a clear volatile liquid used primarily as a solvent and is subject to federal and state regulations and reporting requirements. 1,4-Dioxane has been reportable as a Toxics Release Inventory (TRI) chemical under Section 313 of the Emergency Planning and Community Right-to-Know Act (EPCRA) since 1987. It is designated a Hazardous Air Pollutant (HAP) under the Clean Air Act (CAA), and is a hazardous substance under the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). It was listed on the Safe Drinking Water (SDWA) Candidate Contaminant List (CCL) and identified in the third Unregulated Contaminant Monitoring Rule (UCMR3).

¹ Weight of the scientific evidence means a systematic review method, applied in a manner suited to the nature of the evidence or decision, that uses a pre-established protocol to comprehensively, objectively, transparently, and consistently identify and evaluate each stream of evidence, including strengths, limitations, and relevance of each study and to integrate evidence as necessary and appropriate based upon strengths, limitations, and relevance.

1,4-Dioxane is currently manufactured, processed, distributed, used in industrial and commercial processes, and disposed of.² Manufacturing sites produce 1,4-dioxane in liquid form at concentrations greater than or equal to 90% [EPA-HQ-OPPT-2016-0723-0012; [BASF \(2017\)](#)] and 1,4-dioxane is also imported. The total annual production volume is approximately 1 million pounds ([U.S. EPA, 2016c](#)). 1,4-Dioxane may also be found as a contaminant in consumer products. It is present as a result of byproduct formation during manufacture of ethoxylated chemicals that are subsequently formulated into products. EPA evaluated the following conditions of use: manufacturing; processing; industrial and commercial use in functional fluids in open and closed systems, laboratory chemicals, adhesives and sealants (professional film cement), spray polyurethane foam, printing and printing compositions, and dry film lubricant; consumer use in arts, crafts, and hobby materials (textile dye), automotive care products (antifreeze), cleaning and furniture care products (surface cleaner), laundry and dishwashing products (dish soap, dishwasher detergent, laundry detergent), paints and coatings (paint and floor lacquer), and other uses (spray polyurethane foam); and disposal of waste materials containing 1,4-dioxane. EPA has exercised its authority in TSCA Section 6(b)(4)(D) to exclude from the scope of this risk evaluation conditions of use associated with 1,4-dioxane generated as a byproduct in manufacturing, industrial and commercial uses. While use of 1,4-dioxane as a process solvent and as an intermediate in the manufacture of pharmaceuticals was included in the problem formulation and draft risk evaluation, upon further analysis of the details of these processes, EPA has determined that these uses fall outside TSCA's definition of "chemical substance." Under TSCA § 3(2)(B)(vi), the definition of "chemical substance" does not include any food, food additive, drug, cosmetic, or device (as such terms are defined in section 201 of the Federal Food, Drug, and Cosmetic Act) when manufactured, processed, or distributed in commerce for use as a food, food additive, drug, cosmetic, or device. EPA has concluded that 1,4-dioxane use as a process solvent and an intermediate during pharmaceutical manufacturing falls outside TSCA's definition of a chemical substance when used for these purposes. As a result, the use of 1,4-dioxane as a process solvent and an intermediate during pharmaceutical manufacturing are not included in the scope of this risk evaluation.

Approach

EPA used reasonably available information (defined in 40 CFR 702.33 in part as "*information that EPA possesses, or can reasonably obtain and synthesize for use in risk evaluations, considering the deadlines . . . for completing the evaluation . . .*"), in a fit-for-purpose approach, to develop a risk evaluation that relies on the best available science and is based on the weight of the scientific evidence. EPA used previous analyses as a starting point for identifying key and supporting studies to inform the exposure, fate and hazard assessments. EPA also evaluated other studies that were published since these reviews. EPA reviewed reasonably available information and evaluated the quality of the methods and reporting of results of the individual studies using the evaluation strategies described in *Application of Systematic Review in TSCA Risk Evaluations* ([U.S. EPA, 2018b](#)). To satisfy requirements in TSCA Section 26(j)(4) and 40 CFR 702.51(e), EPA has provided a list of studies considered in carrying out the risk evaluation and the results of those studies are included in the Systematic Review Data Quality Evaluation Documents (see Appendix C and related supplemental files).

In the problem formulation and draft risk evaluation, EPA identified the conditions of use and presented two conceptual models and an analysis plan. These have been updated in the final risk evaluation where EPA has quantitatively evaluated the risk to the environment and human health, using both monitoring

² Although EPA has identified both industrial and commercial uses here for purposes of distinguishing scenarios in this analysis, the Agency interprets the authority over "any manner or method of commercial use" under TSCA section 6(a)(5) to reach both.

data and modeling approaches, for the conditions of use identified in Section 1.4.1 of this risk evaluation.³

Exposure

EPA utilized environmental fate parameters, physical-chemical properties, and/or exposure modeling, to assess environmental exposures through surface water, sediment, and land-applied biosolids. EPA evaluated these pathways based on a qualitative assessment of the physical-chemical properties and fate of 1,4-dioxane in the environment for sediment and land-applied biosolids, and a quantitative exposure analysis for aquatic organisms. While 1,4-dioxane is present in various environmental media such as groundwater, surface water, and air, EPA determined during problem formulation that no further analysis beyond what was presented in the problem formulation document would be done for those environmental exposure pathways in this risk evaluation. However, risk determinations were not made as part of problem formulation; therefore, the results from these analyses are presented in this risk evaluation and are used to inform the risk determination section. Environmental exposure analyses and information are presented in Sections 2.1, 2.3, and Appendix E.

EPA evaluated acute and chronic inhalation exposures to workers and occupational non-users (ONUs), and acute and chronic dermal exposures to workers in association with 1,4-dioxane for the conditions of use identified. ONUs are workers at the facility who neither directly perform activities near the 1,4-dioxane source area nor regularly handle 1,4-dioxane. The job classifications for ONUs could be dependent on the conditions of use. EPA used inhalation monitoring data that was from literature sources where reasonably available and that met data evaluation criteria and modeling approaches to estimate potential inhalation exposures. EPA also estimated dermal doses for workers in these scenarios since dermal monitoring data were not reasonably available. These analyses are described in Section 2.4.1.

An evaluation of general population exposures via the ambient water pathway is included in Section 2.4.2. EPA evaluated acute, incidental oral and dermal exposures to the general population from recreational activities (i.e., swimming) in surface waters. EPA modeled releases associated with the industrial and commercial conditions of use, as well as surface water monitoring data submitted during the public comment period of the draft risk evaluation.

EPA evaluated acute and chronic inhalation and dermal exposures to consumers through the use of consumer products that contain 1,4-dioxane as a contaminant. EPA evaluated acute inhalation exposures to bystanders where such products may be used. These analyses are described in Section 2.4.3. EPA used reasonably available information obtained through systematic review to estimate dermal and inhalation exposure levels.

³ EPA did not identify any “legacy uses” (i.e., circumstances associated with activities that do not reflect ongoing or prospective manufacturing, processing, or distribution) or “associated disposal” (i.e., future disposal from legacy uses) of 1,4-dioxane, as those terms are described in EPA’s Risk Evaluation Rule, 82 FR 33726, 33729 (July 20, 2017). Therefore, no such uses or disposals were added to the scope of the risk evaluation for 1,4-dioxane following the issuance of the opinion in *Safer Chemicals, Healthy Families v. EPA*, 943 F.3d 397 (9th Cir. 2019). EPA did not evaluate “legacy disposal” (i.e., disposals that have already occurred) in the risk evaluation, because legacy disposal is not a “condition of use” under *Safer Chemicals*, 943 F.3d 397.

Hazard

In the environmental hazards section, EPA evaluated the reasonably available information and identified hazard endpoints for aquatic species, including the derivation of acute and chronic concentrations of concern (COCs) for aquatic species. The environmental hazard evaluation is presented in Section 3.1.

In the human health hazards section, EPA evaluated the reasonably available information and identified hazard endpoints including acute/chronic toxicity, non-cancer effects, and cancer for inhalation and dermal exposure for relevant chronic exposures. EPA used an approach based on the Framework for Human Health Risk Assessment to Inform Decision Making ([U.S. EPA, 2014d](#)) to evaluate, extract and integrate 1,4-dioxane's human health hazard and dose-response information. EPA reviewed key and supporting information from previous hazard assessments [EPA IRIS Assessments ([U.S. EPA, 2013d, 2010](#)), an ATSDR Toxicological Profile [ATSDR \(2012\)](#), a Canadian Screening Assessment ([Health Canada, 2010](#)), a European Union (EU) Risk Assessment Report ([ECJRC, 2002](#)), and an Interim AEGL ([U.S. EPA, 2005b](#))]. EPA also screened and evaluated new studies that were published since these reviews (*i.e.*, from 2013 – 2018).

EPA developed a hazard and dose-response analysis for inhalation and oral hazard endpoints identified based on the weight of the scientific evidence considering EPA, National Research Council (NRC), and European Chemicals Agency (ECHA) risk assessment guidance and selected the points of departure (POD) for acute/chronic, non-cancer endpoints, and inhalation unit risk and cancer slope factors for cancer risk estimates. Potential health effects of 1,4-dioxane exposure described in the literature include effects on the liver, kidneys, respiratory system, neurological endpoints, and cancer. EPA identified acute PODs for inhalation, dermal and oral exposures based on acute liver toxicity observed in rats ([Mattie et al., 2012](#)). The chronic POD for inhalation exposures are based on effects on the olfactory epithelium in rats ([Kasai et al., 2009](#)). EPA provided chronic PODs for dermal exposure that extrapolated from effects on the olfactory epithelium attributed to systemic delivery following exposure through inhalation ([Kasai et al., 2009](#); [Kociba et al., 1974](#)) and from liver toxicity following exposure through drinking water ([Kano et al., 2009](#); [NCI, 1978](#); [Kociba et al., 1974](#)). Derivation of PODs is described in Section 3.2.6. EPA also considered the reasonable available information for potential modes of action that would support either a threshold approach or a linear non-threshold approach for estimating cancer risk (Section 3.2.4 and Appendix J). The risk evaluation ultimately calculated cancer risk with a linear model using cancer slope factors based on evidence of increased risk of cancer in rats or mice exposed to 1,4-dioxane through air or drinking water ([Kano et al., 2009](#); [Kasai et al., 2009](#)).

Risk Characterization

For environmental risk, EPA estimated risks based on a qualitative assessment of the physical-chemical properties and fate of 1,4-dioxane in the environment for sediment and land-applied biosolids, and a quantitative comparison of hazards and exposures for aquatic organisms. EPA utilized a risk quotient (RQ) to compare the environmental concentration to the effect level to characterize the risk to aquatic organisms. Tables 5-2 in this risk evaluation summarizes the RQs for acute and chronic risks of 1,4-dioxane for aquatic organisms. EPA included a qualitative assessment describing 1,4-dioxane exposure in sediments and land-applied biosolids. 1,4-Dioxane is not expected to accumulate in sediments and is expected to be mobile in soil and to migrate to water or volatilize to air. The results of the risk characterization are in Section 4.1.

EPA evaluated cancer and non-cancer human health risks for occupational and consumer exposures as well as acute non-cancer health risks from general population exposures. EPA used a Margin of

Exposure (MOE) approach to identify potential non-cancer human health risks. This approach allows for a range of risk estimates. EPA estimated potential cancer risk from chronic exposures to 1,4-dioxane by multiplying inhalation unit risk or dermal cancer slope factors by the chronic exposure levels. Risk estimates for each COU were compared to benchmark MOEs or cancer risk benchmarks. EPA identified cancer and non-cancer risks relative to risk benchmarks for acute and chronic inhalation and dermal occupational exposures for several COUs. EPA did not identify risks relative to benchmarks for consumers, bystanders or the general population for any of the COUs evaluated. The results of these analyses are presented in Section 4.2. Unreasonable risk determinations based on these risk estimates are presented in Section 5.2.

Uncertainties: 1,4-Dioxane is a multi-site carcinogen and may have more than one MOA. There was a high degree of uncertainty in each of the MOA hypotheses considered in this evaluation (*e.g.*, mutagenic mode of action or threshold response to cytotoxicity and regenerative hyperplasia for liver tumors). Chronic non-cancer risk estimates from inhalation exposures were based on effects in the respiratory tract attributed to systemic delivery. These effects are relevant to inhalation exposures and are more sensitive than the other observed systemic effects.

Dermal extrapolation and dermal absorption were also sources of uncertainty in the dermal risk assessment for both dermal cancer and noncancer estimates of risk. Inhalation to dermal and oral to dermal route-to-route extrapolations were compared for relevance to dermal exposures.

EPA's assessments, risk estimations, and risk determinations account for uncertainties throughout the risk evaluation. EPA used reasonably available information, in a fit-for-purpose approach, to develop a risk evaluation that relies on the best available science and is based on the weight of the scientific evidence. For instance, systematic review was conducted to identify reasonably available information related to 1,4-dioxane hazards and exposures. If no applicable monitoring data were identified, exposure scenarios were assessed using a modeling approach that requires the input of various key process parameters related to 1,4-dioxane and exposure factors. When possible, default model input parameters were used based on 1,4-dioxane-specific inputs available in the literature. The consideration of uncertainties supports the Agency's risk determinations, each of which is supported by substantial evidence, as set forth in detail in later sections of this final risk evaluation. See Section 4.3 for a discussion of uncertainties.

Potentially Exposed or Susceptible Subpopulations: TSCA § 6(b)(4) requires that EPA conduct a risk evaluation to “*determine whether a chemical substance presents an unreasonable risk of injury to health or the environment, without consideration of cost or other non-risk factors, including an unreasonable risk to a potentially exposed or susceptible subpopulation identified as relevant to the risk evaluation by the Administrator, under the conditions of use.*” TSCA § 3(12) defines the term “potentially exposed or susceptible subpopulation” as “*a group of individuals within the general population identified by the Administrator who, due to either greater susceptibility or greater exposure, may be at greater risk than the general population of adverse health effects from exposure to a chemical substance or mixture, such as infants, children, pregnant women, workers, or the elderly.*”

In developing the risk evaluation, the EPA analyzed the reasonably available information to ascertain whether some human receptor groups may have greater exposure or greater susceptibility than the general population to the hazard posed by a chemical. Some subpopulations may be more biologically susceptible to the effects of 1,4-dioxane due to genetic variability, pre-existing health conditions, lifestage, or other factors that alter metabolism or increase target organ susceptibility. There is limited

data on reproductive and developmental toxicity and a lack of quantitative information on how genetics, pre-existing disease, or other factors may contribute to increased susceptibility. For consideration of the most highly exposed groups, EPA considered 1,4-dioxane exposures to potentially exposed or susceptible subpopulations of interest, including workers and ONUs, adult and child consumers and bystanders, and adults and children in the general population who recreate in surface waters receiving discharges of 1,4-dioxane. EPA's decision for unreasonable risk are based on high-end exposure estimates for workers and high intensity use scenarios for consumers and bystanders. because these exposure estimates represent the high-end of exposures expected for PESS. See additional discussions in Section 4.4.

Aggregate and Sentinel Exposures: Section 2605(b)(4)(F)(ii) of TSCA requires EPA, as a part of the Risk Evaluation, to describe whether aggregate or sentinel exposures under the conditions of use were considered and the basis for their consideration. EPA has defined aggregate exposure as “*the combined exposures to an individual from a single chemical substance across multiple routes and across multiple pathways (40 CFR Section 702.33).*” Exposures to 1,4-dioxane were evaluated by inhalation and dermal routes separately. Inhalation and dermal exposures are assumed to occur simultaneously for workers and consumers. Dermal and oral exposures are assumed to occur simultaneously for general population exposures through swimming. EPA chose not to employ simple additivity of exposure pathways within a condition of use because of the uncertainties present in the current exposure estimation procedures.

EPA defines sentinel exposure as “*the exposure to a single chemical substance that represents the plausible upper bound of exposure relative to all other exposures within a broad category of similar or related exposures (40 CFR Section 702.33).*” In this Risk Evaluation, EPA considered sentinel exposure the highest exposure given the details of the conditions of use and the potential exposure scenarios. Sentinel exposures for workers are the high-end scenarios with no assumption of PPE use within each OES. EPA considered sentinel exposures in this Risk Evaluation by considering risks to populations who may have upper bound (*e.g.*, high-end, high intensities of use) exposures. EPA's decision for unreasonable risk are based on high-end exposure estimates to capture individuals with sentinel exposure.

Additional details on how aggregate and sentinel exposures were considered in this Risk Evaluation are provided in Section 4.5.

Unreasonable Risk Determination

In each risk evaluation under TSCA Section 6(b), EPA determines whether a chemical substance presents an unreasonable risk of injury to health or the environment, under the conditions of use. The determination does not consider costs or other non-risk factors. In making this determination, EPA considers relevant risk-related factors, including, but not limited to: the effects of the chemical substance on health and human exposure to such substance under the conditions of use (including cancer and non-cancer risks); the effects of the chemical substance on the environment and environmental exposure under the conditions of use; the population exposed (including any potentially exposed or susceptible subpopulations, as determined by EPA); the severity of hazard (including the nature of the hazard, the irreversibility of the hazard); and uncertainties. EPA also takes into consideration the Agency's confidence in the data used in the risk estimate. This includes an evaluation of the strengths, limitations, and uncertainties associated with the information used to inform the risk estimate and the risk characterization. The rationale for the unreasonable risk determination is discussed in Section 5.2. The

Agency's risk determinations are supported by substantial evidence, as set forth in detail in later sections of this final risk evaluation.

Unreasonable Risk of Injury to the Environment: Based on its physical-chemical properties, 1,4-dioxane does not partition to or accumulate in sediments and land-applied biosolids. Therefore, EPA determined that there is no unreasonable risk to terrestrial organisms from all conditions of use. For all conditions of use, EPA did not identify any exceedances of benchmarks to aquatic organisms from exposures to 1,4-dioxane in surface waters. Because the concentrations of 1,4-dioxane in sediment pore water from environmental releases is assumed to be similar to the concentrations of the overlying water, EPA has determined that 1,4-dioxane does not present an unreasonable risk to aquatic organisms or sediment-dwelling organisms under the conditions of use. Based on the risk estimates, the environmental effects of 1,4-dioxane, the exposures, physical-chemical properties of 1,4-dioxane, and consideration of uncertainties, EPA determined that there is no unreasonable risk of injury to the environment from all conditions of use of 1,4-dioxane.

Unreasonable Risks of Injury to Health: EPA's determination of unreasonable risk for specific conditions of use of 1,4-dioxane listed below are based on health risks to workers, ONUs, consumers, bystanders, and the general population. For acute and chronic exposures to workers and ONUs, EPA evaluated unreasonable risks for adverse non-cancer effects based on liver toxicity and effects in the olfactory epithelium, as well as unreasonable risks of cancer from chronic exposures. For acute exposures to the general population, consumers, and bystanders, EPA evaluated unreasonable risks for adverse non-cancer effects based on liver toxicity. For chronic exposures to consumers, EPA evaluated unreasonable risks of cancer.

Unreasonable Risk of Injury to Health of Workers: EPA evaluated non-cancer effects from acute and chronic inhalation and dermal occupational exposures and cancer from chronic inhalation and dermal occupational exposures to determine if there was unreasonable risk of injury to workers' health. The drivers for EPA's determination of unreasonable risk of injury for workers are liver toxicity, olfactory epithelium effects, and cancer resulting from acute and chronic inhalation exposures and acute and chronic dermal exposures.

EPA generally assumes compliance with OSHA requirements for protection of workers, including the implementation of the hierarchy of controls. OSHA's PEL for 1,4-dioxane, established in 1971, is 100 ppm. OSHA has acknowledged that many of the PELs adopted shortly after enactment of the Occupational Safety and Health Act in 1970 are outdated and inadequate for ensuring protection of worker health. OSHA provides an annotated list of PELs on its website, including alternate exposure levels. For 1,4-dioxane, the alternates provided are the California OSHA PEL of 0.28 ppm and the [ACGIH TLV](#) of 20 ppm. EPA assumes some use of PPE due to these alternate exposure levels. In support of this assumption, EPA used reasonably available information indicating that some employers, particularly in the industrial setting, are providing appropriate engineering or administrative controls or PPE to their employees consistent with these alternate exposure levels. EPA does not have reasonably available information to either support or contradict this assumption for each condition of use; however, EPA does not believe that the Agency must presume, in the absence of such information, a lack of compliance with existing regulatory programs and practices. Rather, EPA assumes there is compliance with worker protection standards unless case-specific facts indicate otherwise, and therefore the alternate exposure levels will result in use of appropriate PPE in a manner that achieves the stated APF or PF. EPA's decisions for unreasonable risk to workers are based on high-end exposure estimates, in

order to account for the uncertainties related to whether or not workers are using PPE. EPA's approach for evaluating risk to workers and ONUs is to use the reasonably available information and professional judgement to construct exposure scenarios that reflect the workplace practices involved in the conditions of use of the chemicals and addresses uncertainties regarding availability and use of PPE.

For each condition of use of 1,4-dioxane with an identified risk for workers, EPA assumes, as a baseline, the use of a respirator with an APF of 10 or 50. Similarly, EPA assumes the use of gloves with PF of 10 in commercial settings and gloves with PF of 20 in industrial settings. However, EPA assumes that for some conditions of use, the use of appropriate respirators is not a standard industry practice, based on best professional judgement given the burden associated with the use of supplied-air respirators, including the expense of the equipment and the necessity of fit-testing and training for proper use.

The unreasonable risk determinations reflect the severity of the effects associated with the occupational exposures to 1,4-dioxane and incorporate consideration of the PPE that EPA assumes. A full description of EPA's unreasonable risk determination for each condition of use, including the PPE assumptions, is in Section 5.2.

Unreasonable Risk of Injury to Health of Occupational Non-Users (ONUs): ONUs are workers who do not directly handle 1,4-dioxane but perform work in an area where 1,4-dioxane is present. EPA evaluated non-cancer effects to ONUs from acute and chronic inhalation occupational exposures and cancer from chronic inhalation occupational exposures to determine if there was unreasonable risk of injury to ONUs' health. The unreasonable risk determinations reflect the severity of the effects associated with the occupational exposures to 1,4-dioxane and the assumed absence of PPE for ONUs, since ONUs do not directly handle the chemical and are instead doing other tasks in the vicinity of 1,4-dioxane use. Non-cancer effects and cancer from dermal occupational exposures to ONUs were not evaluated because ONUs are not dermally exposed to 1,4-dioxane. For inhalation exposures, EPA, where possible, estimated ONUs' exposures and described the risks separately from workers directly exposed. When the difference between ONUs' exposures and workers' exposures cannot be quantified, EPA assumed that ONU's inhalation exposures are lower than inhalation exposures for workers directly handling the chemical substance, and EPA considered the central tendency risk estimate when determining ONU risk. A full description of EPA's unreasonable risk determination for each condition of use is in Section 5.2.

Unreasonable Risk of Injury to Health of Consumers: 1,4-Dioxane may be found as a contaminant in consumer products. It is present as a result of byproduct formation during manufacture of ethoxylated chemicals that are subsequently formulated into products. In a supplemental analysis, EPA evaluated eight consumer uses of products that contain 1,4-dioxane as a contaminant to determine if there was unreasonable risk of injury to consumers' health. For each of the eight conditions of use, EPA evaluated non-cancer effects to consumers from acute inhalation and dermal exposures. For four of the conditions of use, based on the exposure assessment, EPA also evaluated cancer risks to consumers from chronic inhalation and dermal exposures. A full description of EPA's draft unreasonable risk determination for each condition of use is in Section 5.

Unreasonable Risk of Injury to Bystanders (from consumer uses): In a supplemental analysis, EPA evaluated hazards and exposures for bystanders from consumer uses of products that contain 1,4-dioxane as a contaminant. Bystanders include men, women, and children of all ages. Specifically, EPA evaluated non-cancer effects to bystanders from acute inhalation exposures from eight consumer uses of products that contain 1,4-dioxane as a contaminant to determine if there was unreasonable risk of injury

to bystanders' health. EPA did not estimate chronic inhalation exposures to bystanders because bystanders would be exposed to lower levels than the user based on the model bystander placement in the home during the product's use. EPA also did not evaluate non-cancer effects from dermal exposures to bystanders because bystanders are not dermally exposed to 1,4-dioxane. A full description of EPA's unreasonable risk determination for each condition of use is in Section 5.

Unreasonable Risk of Injury to Health of the General Population: As part of the Problem Formulation for 1,4-Dioxane ([U.S. EPA, 2018c](#)), EPA found that exposures to the general population may occur from the conditions of use due to releases to air, water or land. During the course of the risk evaluation process for 1,4-dioxane, OPPT worked closely with the offices within EPA that administer and implement regulatory programs under the Clean Air Act (CAA), the Safe Drinking Water Act (SDWA), the Clean Water Act (CWA), the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), and the Resource Conservation and Recovery Act (RCRA). Through this intra-agency coordinate, EPA determined that 1,4-dioxane exposures to the general population via drinking water, ambient air and sediment pathways fall under the jurisdiction of other environmental statutes administered by EPA, *i.e.*, CAA, SDWA, CERCLA, and RCRA. As explained in more detail in section 1.4.2, EPA believes it is both reasonable and prudent to tailor TSCA risk evaluations when other EPA offices have expertise and experience to address specific environmental media, rather than attempt to evaluate and regulate potential exposures and risks from those media under TSCA. EPA believes that coordinated action on exposure pathways and risks addressed by other EPA-administered statutes and regulatory programs is consistent with the statutory text and legislative history, particularly as they pertain to TSCA's function as a "gap-filling" statute, and also furthers EPA aims to efficiently use Agency resources, avoid duplicating efforts taken pursuant to other Agency programs, and meet the statutory deadlines for completing risk evaluations. EPA has therefore tailored the scope of the risk evaluations for 1,4-dioxane using authorities in TSCA Sections 6(b) and 9(b)(1). EPA did not evaluate hazards or exposures to the general population from ambient air, drinking water, and sediment pathways for any of the conditions of use in this risk evaluation, and as such the unreasonable risk determinations for relevant conditions of use do not account for exposures to the general population from ambient air, drinking water, and sediment pathways.

EPA evaluated acute incidental exposures via oral and dermal routes from recreational swimming in ambient water that receives discharges from the industrial and commercial conditions of use for 1,4-dioxane. EPA has determined that this activity presents no unreasonable risk to the general population. In addition, because 1,4-dioxane has low bioaccumulation potential, EPA has determined that fish consumption does not present an unreasonable risk to the general population.

Summary of Unreasonable Risk Determinations:

In conducting risk evaluations, "EPA will determine whether the chemical substance presents an unreasonable risk of injury to health or the environment under each condition of use within the scope of the risk evaluation..." 40 CFR 702.47. Pursuant to TSCA Section 6(i)(1), a determination of "no unreasonable risk" shall be issued by order and considered to be final agency action. Under EPA's implementing regulations, "[a] determination by EPA that the chemical substance, under one or more of the conditions of use within the scope of the risk evaluation, does not present an unreasonable risk of injury to health or the environment will be issued by order and considered to be a final Agency action, effective on the date of issuance of the order." 40 CFR 702.49(d).

EPA has determined that the following conditions of use of 1,4-dioxane do not present an unreasonable risk of injury to health or the environment. These determinations are considered final agency action and are being issued by order pursuant to TSCA Section 6(i)(1). The details of these determinations are in section 5.2, and the TSCA Section 6(i)(1) order is contained in Section 5.4.1 of this final risk evaluation.

Conditions of Use that Do Not Present an Unreasonable Risk

- Distribution in commerce
- Industrial/commercial use: Functional Fluids, open system
- Industrial/commercial use: Other uses – Spray polyurethane foam
- Consumer use: Arts, crafts, and hobby materials – Textile dye
- Consumer use: Automotive care products – Antifreeze
- Consumer use: Cleaning and furniture care products – Surface cleaner
- Consumer use: Laundry and dishwashing products – Dish soap
- Consumer use: Laundry and dishwashing products – Dishwasher detergent
- Consumer use: Laundry and dishwashing products – Laundry detergent
- Consumer use: Paints and coatings – Paint and floor lacquer
- Consumer use: Other uses – Spray polyurethane foam

EPA has determined that the following conditions of use of 1,4-dioxane present an unreasonable risk of injury. EPA will initiate TSCA Section 6(a) risk management actions on these conditions of use as required under TSCA Section 6(c)(1). Pursuant to TSCA Section 6(i)(2), the unreasonable risk determinations for these conditions of use are not considered final agency action. The details of these determinations are in Section 5.2.

Manufacturing that Presents an Unreasonable Risk

- Manufacture: Domestic manufacture
- Manufacture: Import/repackaging

Processing that Presents an Unreasonable Risk

- Processing: Repackaging
- Processing: Recycling
- Processing: Non-incorporative
- Processing: Processing as a reactant

Industrial and Commercial Uses that Present an Unreasonable Risk

- Industrial/commercial use: Intermediate
- Industrial/commercial use: Processing aid
- Industrial/commercial use: Laboratory chemicals
- Industrial/commercial use: Adhesives and sealants
- Industrial/commercial use: Printing and printing compositions
- Industrial/commercial use: Dry film lubricant

Disposal that Presents an Unreasonable Risk

- Disposal

1 INTRODUCTION

This document presents the final risk evaluation for 1,4-dioxane under the Frank R. Lautenberg Chemical Safety for the 21st Century Act. The Frank R. Lautenberg Chemical Safety for the 21st Century Act amended the Toxic Substances Control Act, the Nation’s primary chemicals management law, in June 2016.

The Agency published the Scope of the Risk Evaluation for 1,4-dioxane ([U.S. EPA, 2017e](#)) in June 2017, and the problem formulation in June, 2018 ([U.S. EPA, 2018c](#)), which represented the analytical phase of risk evaluation in which “*the purpose for the assessment is articulated, the problem is defined, and a plan for analyzing and characterizing risk is determined*” as described in Section 2.2 of the [Framework for Human Health Risk Assessment to Inform Decision Making](#). The EPA received comments on the published problem formulation and draft risk evaluation for 1,4-dioxane and has considered the comments specific to 1,4-dioxane, as well as more general comments regarding the EPA’s chemical risk evaluation approach for developing the risk evaluations for the first 10 chemicals the EPA is evaluating.

The problem formulation identified the conditions of use and presented two conceptual models and an analysis plan. In this risk evaluation, EPA evaluated the risk to workers from inhalation and dermal exposures by comparing the estimated occupational exposures to acute and chronic human health hazards. While 1,4-dioxane is present in various environmental media such as groundwater, surface water, and air, EPA determined during problem formulation that no further analysis of the environmental release pathways via ambient water or land-applied biosolids for aquatic, sediment-dwelling, and terrestrial organisms was needed based on a qualitative assessment of the physical-chemical properties and fate of 1,4-dioxane in the environment and a quantitative comparison of hazards and exposures for aquatic organisms. The result of these preliminary analyses indicated that risks were not identified for aquatic, sediment-dwelling, or terrestrial organisms. Screening-level analyses can be conducted with limited data based on high-end exposure assumptions and were used by EPA during problem formulation to identify which exposure pathways warrant more analysis. These approaches are being brought forward from the problem formulation to this document to make final risk determinations because the initial evaluation was sufficient to make these risk determinations.

EPA used reasonably available information consistent with best available science for physical and chemical properties, environmental fate properties, occupational exposure, environmental hazard, and human health hazard studies according to the systematic review process. For human exposure pathways, EPA evaluated inhalation exposures to vapors and mists for workers and occupational non-users and dermal exposures for skin contact with liquids for workers. For environmental release pathways, EPA characterized risks to ecological receptors from surface water, sediment, and land-applied biosolids in

the risk characterization section of this risk evaluation based on the analyses presented in the problem formulation.

The document is structured such that Introduction, Section 1, presents the basic physical-chemical properties of 1,4-dioxane, as well as a background on uses, regulatory history, conditions of use and conceptual models, with emphasis on any changes since the publication of the problem formulation. Section 1 also includes a discussion of the systematic review process utilized in this risk evaluation. Exposures, Section 2, provides a discussion and analysis of the exposures, both human and environmental, based on the conditions of use for 1,4-dioxane. Hazards, Section 2.4.2.1.4, discusses environmental and human health hazards of 1,4-dioxane. Risk characterization is in Section 4, which integrates and assesses reasonably available information on human health and environmental hazards and exposures, as required by TSCA (15 U.S.C 2605(b)(4)(F)). Section 4 also includes a discussion of any uncertainties and how they impact the risk evaluation. In Risk Determination, Section 5, the agency presents the determination of whether the chemical presents an unreasonable risk under the conditions of use, as required under TSCA (15 U.S.C. 2605(b)(4)).

As per EPA's final rule, [*Procedures for Chemical Risk Evaluation Under the Amended Toxic Substances Control Act*](#) (82 FR 33726), this risk evaluation was subject to both public comment and peer review, which are distinct but related processes. EPA provided 60 days for public comment on any and all aspects of this risk evaluation, including the submission of any additional information that might be relevant to the science underlying the risk evaluation and the outcome of the systematic review associated with 1,4-dioxane. This satisfied TSCA (15 U.S.C 2605(4)(H)), which requires the EPA to provide public notice and an opportunity for comment on a risk evaluation prior to publishing a final risk evaluation.

Peer review was conducted in accordance with EPA's regulatory procedures for chemical risk evaluations, including using the [*EPA Peer Review Handbook*](#) and other methods consistent with section 26 of TSCA (See 40 CFR § 702.45). As explained in the Risk Evaluation Rule, the purpose of peer review is for the independent review of the science underlying the risk assessment. Peer review addressed aspects of the underlying science as outlined in the charge to the peer review panel such as hazard assessment, assessment of dose-response, exposure assessment, and risk characterization. Peer-review supports scientific rigor and enhances transparency in the risk evaluation process.

As the EPA explained in the Risk Evaluation Rule, it is important for peer reviewers to consider how the underlying risk evaluation analyses fit together to produce an integrated risk characterization, which will form the basis of an unreasonable risk determination. The EPA believes peer reviewers will be most effective in this role if they receive the benefit of public comments on risk evaluations prior to peer review. For this reason, and consistent with standard Agency practice, EPA provided the opportunity for public comment before peer review on this risk evaluation. The final risk evaluation reflects changes in response to public comments received on the risk evaluation and/or in response to peer review, which itself may be informed by public comments. The EPA responded to public and peer review comments received on the risk evaluation in this final risk evaluation and the associated response to comments document.

In response to peer review and public comment on the draft risk evaluation, EPA added eight consumer conditions of use not included in the original draft risk evaluation, as well as general population exposures from recreational swimming in ambient water. EPA performed a supplemental analysis to the

draft risk evaluation of 1,4-dioxane to evaluate these additional uses and exposures and provided 20 days for public comment on this supplemental analysis. EPA has exercised its authority in TSCA Section 6(b)(4)(D) to exclude from the scope of this risk evaluation conditions of use associated with 1,4-dioxane generated as a byproduct in manufacturing, industrial and commercial uses.

EPA solicited input on the first 10 chemicals, including 1,4-dioxane, as it developed use dossiers, scope documents, and problem formulations. At each step, EPA received information and comments specific to individual chemicals and of a more general nature relating to various aspects of the risk evaluation process, technical issues, and the regulatory and statutory requirements. EPA has considered comments and information received at each step in the process and factored in the information and comments as the Agency deemed appropriate and relevant including comments on the published problem formulation of 1,4-dioxane.

1.1 Physical and Chemical Properties

1,4-Dioxane is a clear liquid at room temperature and has a cyclic structure with two oxygen molecules attached at the first and fourth bonds, each with free electrons ([U.S. EPA, 2006b](#)). 1,4-Dioxane typically volatilize based on its high vapor pressure (40 mm Hg at 25 °C) ([U.S. EPA, 2009](#)). 1,4-Dioxane has a Log K_{ow} value of -0.27, indicating that this chemical is hydrophilic and readily miscible in water ([U.S. EPA, 2009](#)). A summary of the physical and chemical properties of 1,4-dioxane are listed in Table 2-1.

Table 1-1. Physical and Chemical Properties of 1,4-Dioxane

Property	Value ^a	References	Data Quality Rating
Molecular formula	C ₄ H ₈ O ₂		
Molecular weight	88.1 g/mole	Haynes et al. (2014)	High
Physical form	Colorless liquid; ethereal	O'Neil et al. (2001)	High
Melting point	11.75°C	Haynes et al. (2014)	High
Boiling point	101.1°C	O'Neil et al. (2006)	High
Density	1.0329 g/cm ³ at 20°C	O'Neil et al. (2006)	High
Vapor pressure	40 mm Hg at 25°C	Lewis (2000)	High
Vapor density	3.02 (air=1)	Lewis (2012)	High
Water solubility	>8.00 × 10 ² g/L at 25°C	Yalkowsky et al. (2010)	High
Octanol:water partition coefficient (Log K _{ow})	-0.27	Hansch et al. (1995)	High
Henry's Law constant	4.8 × 10 ⁻⁶ atm-m ³ /mole at 25°C 4.93 × 10 ⁻⁴ atm-m ³ /mole at 40°C	Park et al. (1987) as cited in Sander (2017)	High

Flash point	18.3°C (open cup)	Larranaga Md (2016)	High
Autoflammability	180 °C at atmospheric pressure	USCG (1999)	High
Viscosity	0.0120 cP at 25°C	O'Neil (2013)	High
Refractive index	1.4224 at 20°C	Haynes et al. (2014)	High
Dielectric constant	2.209 Farad per meter	Bruno and PDN (2006)	High

^a Measured unless otherwise noted

1.2 Uses and Production Volume

The EPA's [Chemical Data Reporting](#) (CDR) database ([U.S. EPA, 2016c](#)) reported that there were two manufacturers producing or importing 1,059,980 pounds of 1,4-dioxane in the U.S. in 2015 (see Table 1-2.). The total volume (in lbs.) of 1,4-dioxane manufactured (including imports) in the U.S. from 2012 to 2015 indicates that production has varied over that time. Historically, 90% of 1,4-dioxane production was used as a stabilizer in chlorinated solvents such as 1,1,1-trichloroethane (TCA) ([ATSDR, 2012](#); however, use of 1,4-dioxane has decreased since TCA was phased out by the Montreal Protocol in 1995 [NTP, 2011](#); [ECJRC, 2002](#)). Based on the lack of information on reported uses ([Sapphire Group, 2007](#)), EPA concludes that many other industrial, commercial and consumer uses have also been discontinued.

Table 1-2. Production Volume of 1,4-Dioxane in Chemical Data Reporting (CDR) Reporting Period (2012 to 2015) ^a

Reporting Year	2012	2013	2014	2015
Total Aggregate Production Volume (lbs.)	894,505	1,043,627	474,331	1,059,980

^a The CDR data for the 2016 reporting period is available via ChemView (<https://java.epa.gov/chemview>) ([U.S. EPA, 2014a](#)). The CDR numbers in Chem View reflect the original submissions for the 2016 reporting period, including one for which the CBI claim was subsequently released. The CDR data displayed in Chem View are static data and not updated regularly.

1,4-Dioxane is currently manufactured, processed, distributed and used in industrial processes and for industrial and commercial uses. Manufacturing sites produce 1,4-dioxane in liquid form at concentrations greater or equal to 90% [EPA-HQ-OPPT-2016-0723-0012; [BASF \(2017\)](#)] and 1,4-dioxane is also imported. Industrial processing includes: 1) Processing as a reactant or intermediate, 2) Non-incorporative processing, 3) Repackaging, and 4) Recycling. Disposal of waste materials containing 1,4-dioxane is also a condition of use.

The major conditions of use identified for 1,4-dioxane are:

- Use in processing aids (not otherwise listed) (270,000 lbs.),
- Use in functional fluids in open and closed systems (<150,000 lbs.),
- Use in laboratory chemicals (<150,000 lbs.),
- Use in adhesives and sealants (professional film cement),
- Use in spray polyurethane foam,

- Use in printing and printing compositions,
- Disposal of waste materials containing 1,4-dioxane, and
- Use in dry film lubricant.

1.3 Regulatory and Assessment History

EPA conducted a search of existing domestic and international laws, regulations and assessments pertaining to 1,4-dioxane. EPA compiled this summary from data available from federal, state, international and other government sources, as cited in Appendix A.

Federal Laws and Regulations

1,4-Dioxane is subject to federal statutes or regulations, other than TSCA, that are implemented by other offices within EPA and/or other federal agencies/departments. A summary of federal laws, regulations and implementing authorities is provided in Appendix A.1.

State Laws and Regulations

1,4-Dioxane is subject to state statutes or regulations. A summary of state laws, regulations and implementing authorities is provided in Appendix A.2.

Laws and Regulations in Other Countries and International Treaties or Agreements

1,4-Dioxane is subject to statutes or regulations in countries other than the United States and/or international treaties and/or agreements. A summary of these laws, regulations, treaties and/or agreements is provided in Appendix A.3.

EPA identified numerous previous assessments conducted within EPA and by other organizations (see Table 1-3.). Depending on the source, these assessments may include information on conditions of use, hazards, exposures and potentially exposed or susceptible subpopulations.

Table 1-3. Assessment History of 1,4-Dioxane

Authoring Organization	Assessment
EPA assessments	
EPA, Office of Chemical Safety and Pollution Prevention (OCSPP), Office of Pollution Prevention and Toxics (OPPT)	TSCA Work Plan Chemical Problem Formulation and Initial Assessment: 1,4-Dioxane (CASRN 123-91-1) (2015)
EPA, National Center for Environmental Assessment (NCEA)	Toxicological Review of 1,4-Dioxane (With Inhalation Update) (CASRN 123-91-1) (2013d)
EPA, NCEA	Toxicological review of 1,4-Dioxane (CAS No. 123-91-1) (2010)
EPA, Office of Water (OW)	Drinking Water Health Advisory (2012a)
Other U.S.-based organizations	
National Toxicology Program (NTP)	Report on Carcinogens, Fourteenth Edition, 1,4-Dioxane (2016)

Authoring Organization	Assessment
Agency for Toxic Substances and Disease Registry (ATSDR)	Toxicological Profile for 1,4-Dioxane (2012)
National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL Committee)	Interim Acute Exposure Guideline Levels (AEGL) for 1,4-Dioxane (CAS Reg. No. 123-91-1) (2005b)
International	
International Cooperation on Cosmetics Regulation	Report of the ICCR Working Group: Considerations on Acceptable Trace Level of 1,4-Dioxane in Cosmetic Products (2017)
International Agency for Research on Cancer (IARC)	IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Volume 71 (1999)
Government of Canada, Environment Canada, Health Canada	Screening Assessment for the Challenge. 1,4-Dioxane. CASRN 123-91-1 (2010)
Research Center for Chemical Risk Management, National Institute of Advanced Industrial Science and Technology, Japan	Estimating Health Risk from Exposure to 1,4-Dioxane in Japan (2006)
World Health Organisation (WHO)	1,4-Dioxane in Drinking-water (2005)
Employment, Social Affairs, and Inclusion, European Commission (EC)	Recommendation from the Scientific Committee on Occupational Exposure Limits for 1,4-dioxane (2004)
European Chemicals Bureau, Institute for Health and Consumer Protection	European Union Risk Assessment Report. 1,4-dioxane. CASRN 123-91-1. EINECS No: 204-661-8. (2002)
National Industrial Chemicals Notification and Assessment Scheme (NICNAS), Australian Government	1,4-Dioxane. Priority Existing Chemical No. 7. Full Public Report (1998)
Organisation for Economic Co-operation and Development (OECD), Screening Information Data Set (SIDS)	1,4-Dioxane. SIDS initial assessment profile (1999)

1.4 Scope of the Evaluation

1.4.1 Conditions of Use Included in the Risk Evaluation

TSCA Section 3(4) defines the conditions of use as “the circumstances, as determined by the Administrator, under which a chemical substance is intended, known, or reasonably foreseen to be manufactured, processed, distributed in commerce, used, or disposed of.” The conditions of use are described below in Table 1-4..

Information on additional conditions of use was submitted to EPA during the public comment period for the problem formulation and noted in the draft risk evaluation. Specifically, EPA received information indicating that the Department of Energy's Kansas City National Security Campus uses 1,4-dioxane as a constituent of a dry film lubricant in the manufacture of components for weapons systems. Although not reflected in the scope or problem formulation, this condition of use is included in this final risk evaluation.

As explained in the scope document for 1,4-dioxane, EPA anticipates the production of 1,4-dioxane as a byproduct from ethoxylation of other chemicals and presence as a contaminant in industrial, commercial and consumer products. In particular, 1,4-dioxane may be produced as a reaction byproduct in chemicals produced through ethoxylation, including alkyl ether sulphates (AES, anionic surfactants) and other ethoxylated substances, such as alkyl, alkylphenol and fatty amine ethoxylates; polyethylene glycols and their esters; and sorbitan ester ethoxylates. 1,4-Dioxane may also be present at residual concentrations in commercial and consumer products that contain ethoxylated chemicals. Examples of products potentially containing 1,4-dioxane as a residual contaminant are paints, coatings, lacquers, ethylene glycol-based antifreeze coolants, spray polyurethane foam, household detergents, cosmetics/toiletries, textile dyes, foods, agricultural and veterinary products ([ATSDR, 2012](#); [Health Canada, 2010](#); [FDA, 2007](#); [ECJRC, 2002](#)).⁴ In the [Draft Risk Evaluation for 1,4-Dioxane](#), the manufacture of 1,4-dioxane as a byproduct from ethoxylation of other chemicals, use and disposal of 1,4-dioxane at residual concentrations in industrial, commercial and consumer products containing ethoxylated chemicals were excluded from the scope of the risk evaluation.

EPA received peer review and public comments regarding consumer use of materials containing 1,4-dioxane as byproducts, and in response made a policy decision to expand the scope of the risk evaluation to include consumer COUs. EPA added eight consumer conditions of use not included in the original draft risk evaluation, as well as general population exposures from recreational swimming in ambient water. EPA performed a supplemental analysis to the draft risk evaluation of 1,4-dioxane to evaluate these additional uses and exposures. For each of the eight uses, EPA evaluated non-cancer effects to consumers from acute inhalation and dermal exposures. For four of the products, based on the exposure assessment, EPA also evaluated cancer risks to consumers from chronic inhalation and dermal exposures. EPA will consider other conditions of use where 1,4-dioxane is a byproduct as part of the future risk evaluations for chemicals that produce it as byproduct.

⁴ However, under TSCA § 3(2)(B)(vi), the definition of "chemical substance" does not include any food, food additive, drug, cosmetic, or device (as such terms are defined in section 201 of the Federal Food, Drug, and Cosmetic Act) when manufactured, processed, or distributed in commerce for use as a food, food additive, drug, cosmetic, or device.

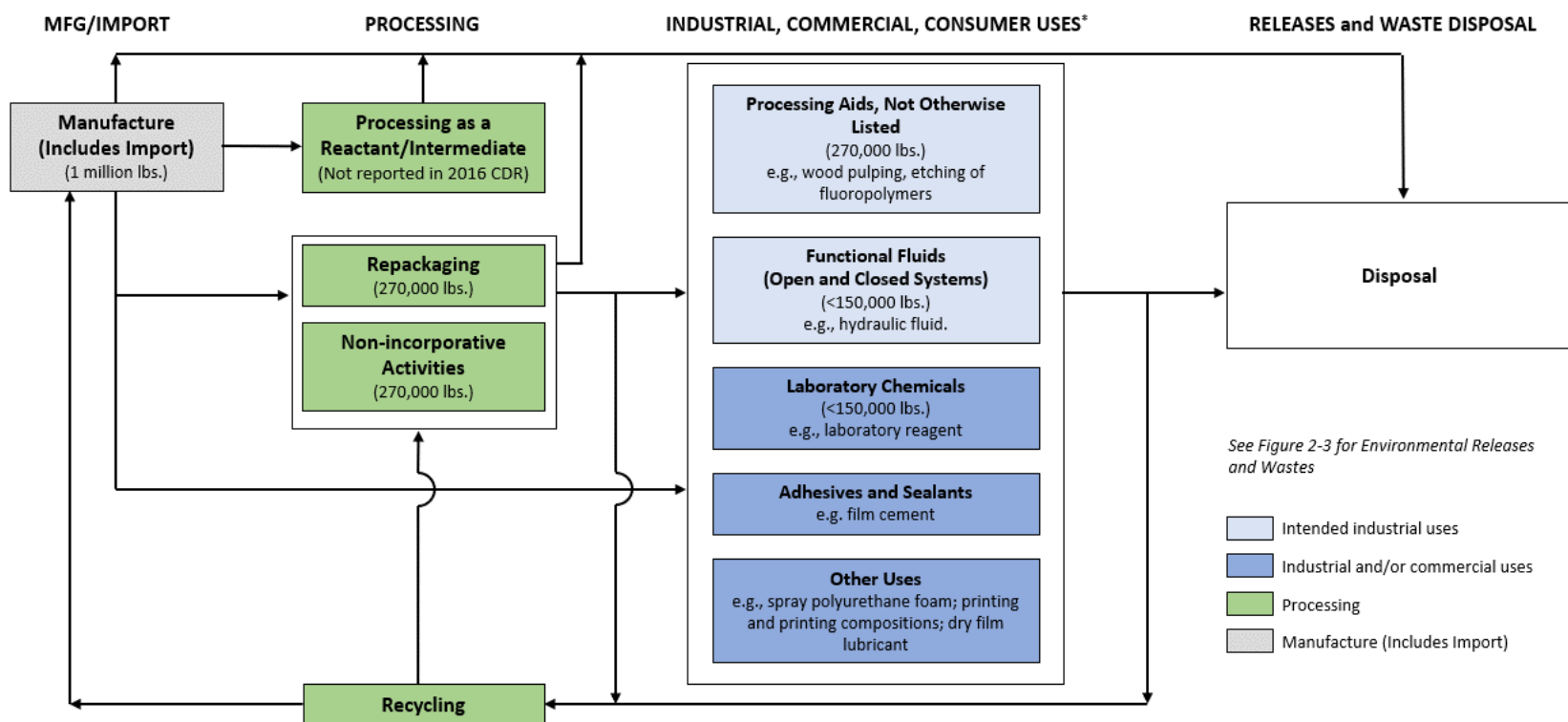


Figure 1-1. 1,4-Dioxane Life Cycle Diagram

The life cycle diagram depicts the conditions of use that are within the scope of the risk evaluation during various life cycle stages including manufacturing, processing, use (industrial or commercial) and disposal. The production volumes shown are for reporting year 2015 from the 2016 CDR reporting period ([U.S. EPA, 2016c](#)).

^a See Table 1-4. for additional uses that are not mentioned specifically in this diagram, including consumer conditions of use that were evaluated for 1,4-dioxane present as a byproduct.

Table 1-4. Categories and Subcategories of Conditions of Use Included in the Scope of the Risk Evaluation

Life Cycle Stage	Category ^a	Subcategory ^b	References
Manufacture	Domestic manufacture	Domestic manufacture	Use document, EPA-HQ-OPPT-2016-0723-0003 ; Public Comment, EPA-HQ-OPPT-2016-0723-0012
	Import	Import	Use document, EPA-HQ-OPPT-2016-0723-0003
		Repackaging	Public Comment, EPA-HQ-OPPT-2016-0723-0012
Processing	Processing as a reactant		
		Polymerization catalyst	Use document, EPA-HQ-OPPT-2016-0723-0003
	Non-incorporative	Basic organic chemical manufacturing (process solvent)	Public Comment, EPA-HQ-OPPT-2016-0723-0012
	Recycling	Recycling	U.S. EPA (2017g)
Distribution in commerce	Distribution	Distribution	Use document, EPA-HQ-OPPT-2016-0723-0003
Industrial use	Intermediate use	Plasticizer intermediate	Use document, EPA-HQ-OPPT-2016-0723-0003
		Catalysts and reagents for anhydrous acid reactions, brominations and sulfonations	Use document, EPA-HQ-OPPT-2016-0723-0003
	Processing aids, not otherwise listed	Wood pulping ^c	Use document, EPA-HQ-OPPT-2016-0723-0003
		Extraction of animal and vegetable oils ^c	Use document, EPA-HQ-OPPT-2016-0723-0003

Life Cycle Stage	Category ^a	Subcategory ^b	References
		Wetting and dispersing agent in textile processing ^c	Use document, EPA-HQ-OPPT-2016-0723-0003
		Polymerization catalyst	Use document, EPA-HQ-OPPT-2016-0723-0003
		Purification of process intermediates	Use document, EPA-HQ-OPPT-2016-0723-0003
		Etching of fluoropolymers	Public Comment, EPA-HQ-OPPT-2016-0723-0012
	Functional fluids (open and closed system)	Polyalkylene glycol lubricant	Use document, EPA-HQ-OPPT-2016-0723-0003
		Synthetic metalworking fluid	Use document, EPA-HQ-OPPT-2016-0723-0003
		Cutting and tapping fluid	Use document, EPA-HQ-OPPT-2016-0723-0003
		Hydraulic fluid	Use document, EPA-HQ-OPPT-2016-0723-0003
Industrial use, potential commercial use	Laboratory chemicals	Chemical reagent	Use document, EPA-HQ-OPPT-2016-0723-0003 ; Public Comment, EPA-HQ-OPPT-2016-0723-0009
		Reference material	Use document, EPA-HQ-OPPT-2016-0723-0003
		Spectroscopic and photometric measurement	Use document, EPA-HQ-OPPT-2016-0723-0003 ; Public Comment, EPA-HQ-OPPT-2016-0723-0009
		Liquid scintillation counting medium	Use document, EPA-HQ-OPPT-2016-0723-0003

Life Cycle Stage	Category ^a	Subcategory ^b	References
		Stable reaction medium	Use document, EPA-HQ-OPPT-2016-0723-0003
		Cryoscopic solvent for molecular mass determinations	Use document, EPA-HQ-OPPT-2016-0723-0003
		Preparation of histological sections for microscopic examination	Use document, EPA-HQ-OPPT-2016-0723-0003
	Adhesives and sealants	Film cement	Use document, EPA-HQ-OPPT-2016-0723-0003 ; Public Comment, EPA-HQ-OPPT-2016-0723-0021
	Other uses	Spray polyurethane foam Printing and printing compositions, including 3D printing Dry film lubricant	Use document, EPA-HQ-OPPT-2016-0723-0003 ; Public Comment, EPA-HQ-OPPT-2016-0723-0012
Consumer uses	Paints and Coatings	Latex Wall Paint or Floor Lacquer	TSCA Work Plan Chemical Problem Formulation and Initial Assessment: 1,4-Dioxane (CASRN 123-91-1) (2015)
	Cleaning and Furniture Care Products	Surface Cleaner	
	Laundry and Dishwashing Products	Dish Soap Dishwasher Detergent Laundry Detergent	
	Arts, Crafts and Hobby Materials	Textile Dye	
	Automotive Care Products	Antifreeze	
	Other Consumer Uses	Spray Polyurethane Foam	
Disposal	Disposal	Industrial pre-treatment	U.S. EPA (2017g)
		Industrial wastewater treatment	
		Publicly owned treatment works (POTW)	
		Underground injection	

Life Cycle Stage	Category ^a	Subcategory ^b	References
		Municipal landfill	
		Hazardous landfill	
		Other land disposal	
		Municipal waste incinerator	
		Hazardous waste incinerator	
		Off-site waste transfer	
<p>^a These categories of conditions of use appear in the initial life cycle diagram, reflect CDR codes and broadly represent conditions of use for 1,4-dioxane in industrial and/or commercial settings.</p> <p>^b These subcategories reflect more specific uses of 1,4-dioxane.</p> <p>^c These uses were evaluated but are no longer current uses of 1,4-dioxane.</p>			

1.4.2 Exposure Pathways and Risks Addressed by Other EPA-Administered Statutes

In its TSCA Section 6(b) risk evaluations, EPA is coordinating action on certain exposure pathways and risks falling under the jurisdiction of other EPA-administered statutes or regulatory programs. More specifically, EPA is exercising its TSCA authorities to tailor the scope of its risk evaluations, rather than focusing on environmental exposure pathways addressed under other EPA-administered statutes or regulatory programs or risks that could be eliminated or reduced to a sufficient extent by actions taken under other EPA-administered laws. EPA considers this approach to be a reasonable exercise of the Agency’s TSCA authorities, which include:

- TSCA Section 6(b)(4)(D): “The Administrator shall, not later than 6 months after the initiation of a risk evaluation, publish the scope of the risk evaluation to be conducted, including the hazards, exposures, conditions of use, and the potentially exposed or susceptible subpopulations the Administrator expects to consider...”
- TSCA Section 9(b)(1): “The Administrator shall coordinate actions taken under this chapter with actions taken under other Federal laws administered in whole or in part by the Administrator. If the Administrator determines that a risk to health or the environment associated with a chemical substance or mixture could be eliminated or reduced to a sufficient extent by actions taken under the authorities contained in such other Federal laws, the Administrator shall use such authorities to protect against such risk unless the Administrator determines, in the Administrator’s discretion, that it is in the public interest to protect against such risk by actions taken under this chapter.”
- TSCA Section 9(e): “[I]f the Administrator obtains information related to exposures or releases of a chemical substance or mixture that may be prevented or reduced under another Federal law, including a law not administered by the Administrator, the Administrator shall make such information available to the relevant Federal agency or office of the Environmental Protection Agency.”

- TSCA Section 2(c): “It is the intent of Congress that the Administrator shall carry out this chapter in a reasonable and prudent manner, and that the Administrator shall consider the environmental, economic, and social impact of any action the Administrator takes or proposes as provided under this chapter.”
- TSCA Section 18(d)(1): “Nothing in this chapter, nor any amendment made by the Frank R. Lautenberg Chemical Safety for the 21st Century Act, nor any rule, standard of performance, risk evaluation, or scientific assessment implemented pursuant to this chapter, shall affect the right of a State or a political subdivision of a State to adopt or enforce any rule, standard of performance, risk evaluation, scientific assessment, or any other protection for public health or the environment that— (i) is adopted or authorized under the authority of any other Federal law or adopted to satisfy or obtain authorization or approval under any other Federal law...”

TSCA authorities supporting tailored risk evaluations and intra-agency referrals

TSCA Section 6(b)(4)(D)

TSCA Section 6(b)(4)(D) requires EPA, in developing the scope of a risk evaluation, to identify the hazards, exposures, conditions of use, and potentially exposed or susceptible subpopulations the Agency “expects to consider” in a risk evaluation. This language suggests that EPA is not required to consider all conditions of use, hazards, or exposure pathways in risk evaluations.

In the problem formulation documents for many of the first 10 chemicals undergoing risk evaluation, EPA applied this authority and rationale to certain exposure pathways, explaining that “EPA is planning to exercise its discretion under TSCA 6(b)(4)(D) to focus its analytical efforts on exposures that could present the greatest concern and consequently merit a risk evaluation under TSCA, by excluding, on a case-by-case basis, certain exposure pathways that fall under the jurisdiction of other EPA-administered statutes.” This approach is informed by the legislative history of the amended TSCA, which supports the Agency’s exercise of discretion to focus the risk evaluation on areas that raise the greatest potential for risk. See June 7, 2016 Cong. Rec., S3519-S3520. Consistent with the approach articulated in the problem formulation documents, and as described in more detail below, EPA is exercising its authority under TSCA to tailor the scope of exposures evaluated in TSCA risk evaluations, rather than focusing on environmental exposure pathways addressed under other EPA-administered, media-specific statutes and regulatory programs.

TSCA Section 9(b)(1)

In addition to TSCA Section 6(b)(4)(D), the Agency also has discretionary authority under the first sentence of TSCA Section 9(b)(1) to “coordinate actions taken under [TSCA] with actions taken under other Federal laws administered in whole or in part by the Administrator.” This broad, freestanding authority provides for intra-agency coordination and cooperation on a range of “actions.” In EPA’s view, the phrase “actions taken under [TSCA]” in the first sentence of section 9(b)(1) is reasonably read to encompass more than just risk management actions, and to include actions taken during risk evaluation as well. More specifically, the authority to

coordinate intra-agency actions exists regardless of whether the Administrator has first made a definitive finding of risk, formally determined that such risk could be eliminated or reduced to a sufficient extent by actions taken under authorities in other EPA-administered Federal laws, and/or made any associated finding as to whether it is in the public interest to protect against such risk by actions taken under TSCA. TSCA Section 9(b)(1) therefore provides EPA authority to coordinate actions with other EPA offices without ever making a risk finding, or following an identification of risk. This includes coordination on tailoring the scope of TSCA risk evaluations to focus on areas of greatest concern rather than exposure pathways addressed by other EPA-administered statutes and regulatory programs, which does not involve a risk determination or public interest finding under TSCA Section 9(b)(2).

In a narrower application of the broad authority provided by the first sentence of TSCA Section 9(b)(1), the remaining provisions of section 9(b)(1) provide EPA authority to identify risks and refer certain of those risks for action by other EPA offices. Under the second sentence of section 9(b)(1), “[i]f the Administrator determines that a risk to health or the environment associated with a chemical substance or mixture could be eliminated or reduced to a sufficient extent by actions taken under the authorities contained in such other Federal laws, the Administrator shall use such authorities to protect against such risk unless the Administrator determines, in the Administrator’s discretion, that it is in the public interest to protect against such risk by actions taken under [TSCA].” Coordination of intra-agency action on risks under TSCA Section 9(b)(1) therefore entails both an identification of risk, and a referral of any risk that could be eliminated or reduced to a sufficient extent under other EPA-administered laws to the EPA office(s) responsible for implementing those laws (absent a finding that it is in the public interest to protect against the risk by actions taken under TSCA).

Risk may be identified by OPPT or another EPA office, and the form of the identification may vary. For instance, OPPT may find that one or more conditions of use for a chemical substance present(s) a risk to human or ecological receptors through specific exposure routes and/or pathways. This could involve a quantitative or qualitative assessment of risk based on reasonably available information (which might include, *e.g.*, findings or statements by other EPA offices or other federal agencies). Alternatively, risk could be identified by another EPA office. For example, another EPA office administering non-TSCA authorities may have sufficient monitoring or modeling data to indicate that a particular condition of use presents risk to certain human or ecological receptors, based on expected hazards and exposures. This risk finding could be informed by information made available to the relevant office under TSCA Section 9(e), which supports cooperative actions through coordinated information-sharing.

Following an identification of risk, EPA would determine if that risk could be eliminated or reduced to a sufficient extent by actions taken under authorities in other EPA-administered laws. If so, TSCA requires EPA to “use such authorities to protect against such risk,” unless EPA determines that it is in the public interest to protect against that risk by actions taken under TSCA. In some instances, EPA may find that a risk could be sufficiently reduced or eliminated by future action taken under non-TSCA authority. This might include, *e.g.*, action taken under the authority of the Safe Drinking Water Act to address risk to the general population from a chemical substance in drinking water, particularly if the Office of Water has taken preliminary steps such as listing the subject chemical substance on the Contaminant Candidate List. This sort

of risk finding and referral could occur during the risk evaluation process, thereby enabling EPA to use more a relevant and appropriate authority administered by another EPA office to protect against hazards or exposures to affected receptors.

Legislative history on TSCA Section 9(b)(1) supports both broad coordination on current intra-agency actions, and narrower coordination when risk is identified and referred to another EPA office for action. A Conference Report from the time of TSCA's passage explained that section 9 is intended "to assure that overlapping or duplicative regulation is avoided while attempting to provide for the greatest possible measure of protection to health and the environment." S. Rep. No. 94-1302 at 84. See also H. Rep. No. 114-176 at 28 (stating that the 2016 TSCA amendments "reinforce TSCA's original purpose of filling gaps in Federal law," and citing new language in section 9(b)(2) intended "to focus the Administrator's exercise of discretion regarding which statute to apply and to encourage decisions that avoid confusion, complication, and duplication"). Exercising TSCA Section 9(b)(1) authority to coordinate on tailoring TSCA risk evaluations is consistent with this expression of Congressional intent.

Legislative history also supports a reading of section 9(b)(1) under which EPA coordinates intra-agency action, including information-sharing under TSCA Section 9(e), and the appropriately-positioned EPA office is responsible for the identification of risk and actions to protect against such risks. See, e.g., Senate Report 114-67, 2016 Cong. Rec. S3522 (under TSCA Section 9, "if the Administrator finds that disposal of a chemical substance may pose risks that could be prevented or reduced under the Solid Waste Disposal Act, the Administrator should ensure that the relevant office of the EPA receives that information"); H. Rep. No. 114-176 at 28, 2016 Cong. Rec. S3522 (under section 9, "if the Administrator determines that a risk to health or the environment associated with disposal of a chemical substance could be eliminated or reduced to a sufficient extent under the Solid Waste Disposal Act, the Administrator should use those authorities to protect against the risk"). Legislative history on TSCA Section 9(b)(1) therefore supports coordination with and referral of action to other EPA offices, especially when statutes and associated regulatory programs administered by those offices could address exposure pathways or risks associated with conditions of use, hazards, and/or exposure pathways that may otherwise be within the scope of TSCA risk evaluations.

TSCA Sections 2(c) & 18(d)(1)

Finally, TSCA Sections 2(c) and 18(d) support coordinated action on exposure pathways and risks addressed by other EPA-administered statutes and regulatory programs. Section 2(c) directs EPA to carry out TSCA in a "reasonable and prudent manner" and to consider "the environmental, economic, and social impact" of its actions under TSCA. Legislative history from around the time of TSCA's passage indicates that Congress intended EPA to consider the context and take into account the impacts of each action under TSCA. S. Rep. No. 94-698 at 14 ("the intent of Congress as stated in this subsection should guide each action the Administrator takes under other sections of the bill").

Section 18(d)(1) specifies that state actions adopted or authorized under any Federal law are not preempted by an order of no unreasonable risk issued pursuant to TSCA Section 6(i)(1) or a rule to address unreasonable risk issued under TSCA Section 6(a). Thus, even if a risk evaluation

were to address exposures or risks that are otherwise addressed by other federal laws and, for example, implemented by states, the state laws implementing those federal requirements would not be preempted. In such a case, both the other federal and state laws, as well as any TSCA Section 6(i)(1) order or TSCA Section 6(a) rule, would apply to the same issue area. See also TSCA Section 18(d)(1)(A)(iii). In legislative history on amended TSCA pertaining to section 18(d), Congress opined that “[t]his approach is appropriate for the considerable body of law regulating chemical releases to the environment, such as air and water quality, where the states have traditionally had a significant regulatory role and often have a uniquely local concern.” Sen. Rep. 114-67 at 26.

EPA’s careful consideration of whether other EPA-administered authorities are available and more appropriate for addressing certain exposures and risks is consistent with Congress’s intent to maintain existing federal requirements and the state actions adopted to locally and more specifically implement those federal requirements, and to carry out TSCA in a reasonable and prudent manner. EPA believes it is both reasonable and prudent to tailor TSCA risk evaluations in a manner reflective of expertise and experience exercised by other EPA and State offices to address specific environmental media, rather than attempt to evaluate and regulate potential exposures and risks from those media under TSCA. This approach furthers Congressional direction and EPA aims to efficiently use Agency resources, avoid duplicating efforts taken pursuant to other Agency and State programs, and meet the statutory deadline for completing risk evaluations.

EPA-administered statutes and regulatory programs that address specific exposure pathways and/or risks

During the course of the risk evaluation process for 1,4-dioxane, OPPT worked closely with the offices within EPA that administer and implement regulatory programs under the Clean Air Act (CAA), the Safe Drinking Water Act (SDWA), the Clean Water Act (CWA), the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), and the Resource Conservation and Recovery Act (RCRA). Through intra-agency coordination, EPA determined that specific exposure pathways are well-regulated by the EPA statutes described in the following paragraphs.

Ambient Air Pathway

The CAA contains a list of hazardous air pollutants (HAP) and provides EPA with the authority to add to that list pollutants that present, or may present, a threat of adverse human health effects or adverse environmental effects. For stationary source categories emitting HAP, the CAA requires issuance of technology-based standards and, if necessary, additions or revisions to address developments in practices, processes, and control technologies, and to ensure the standards adequately protect public health and the environment. The CAA thereby provides EPA with comprehensive authority to regulate emissions to ambient air of any hazardous air pollutant.

1,4-Dioxane is a HAP. See 42 U.S.C. 7412. EPA has issued a number of technology-based standards for source categories that may emit 1,4-dioxane to ambient air and, as appropriate, has

reviewed, or will review remaining risks. See Appendix A of this risk evaluation; 42 U.S.C. 7412(f)(2). Because stationary source releases of 1,4-dioxane to ambient air are addressed under the CAA, EPA is not evaluating emissions to ambient air from commercial and industrial stationary sources or associated inhalation exposure of the general population or terrestrial species under any of the conditions of use in this TSCA risk evaluation, and as such the unreasonable risk determinations for relevant conditions of use do not account for ambient air exposures to the general population.

Drinking Water Pathway

The SDWA requires EPA to publish a Contaminant Candidate List (CCL) every 5 years. The CCL is a list of unregulated contaminants that are known or anticipated to occur in public water systems and that may require regulation. The SDWA specifies that the Agency place those contaminants on the list that present the greatest health concern. The SDWA also requires EPA to make Regulatory Determinations (RegDet) to regulate (or not) at least five CCL contaminants every 5 years. To regulate a contaminant, EPA must conclude in accordance with SDWA Section 1412(b)(1)(A) that the contaminant may have adverse health effects, occurs or is substantially likely to occur in public water systems at a level of concern, and that regulation, in the sole judgement of the Administrator, presents a meaningful opportunity for health risk reduction for persons served by public water systems. If after considering public comment on a preliminary determination, the Agency makes a determination to regulate a contaminant, the Agency initiates the process for issuing a drinking water regulation. When proposing and promulgating drinking water regulations, the Agency must conduct a number of analyses.

Currently, EPA is evaluating 1,4 Dioxane through the SDWA statutory processes for developing a National Primary Drinking Water regulation. 1,4-Dioxane is currently one of 109 contaminants listed on EPA's Fourth Contaminant Candidate List (CCL 4), see 81 FR 81099, and was subject to occurrence monitoring in public water systems under the third Unregulated Contaminant Monitoring Rule (UCMR 3), see 77 FR 26072. Under UCMR 3, water systems were monitored for 1,4-dioxane during 2013-2015. Of the 4,915 water systems monitored, 1,077 systems had detections of 1,4-dioxane in at least one sample.

In March 2020, EPA published Preliminary Regulatory Determinations for Contaminants on the Fourth Drinking Water Contaminant Candidate List pursuant to SDWA authority, see 85 FR 14098. The Agency did not make a preliminary determination under SDWA for 1,4-dioxane. EPA will continue to evaluate 1, 4-dioxane prior to making a regulatory determination. Among other things, the Agency intends to consider the findings in this risk evaluation, the Canadian guideline technical document and other relevant new science which may provide clarity as to whether 1,4-dioxane meets all the criteria to establish a NPDWR under SDWA 1412(b)(1)(A). The Regulatory Determination 4 Support Document (USEPA, 2019a) and the Occurrence Data from the Third Unregulated Contaminant Monitoring Rule (UCMR 3) (USEPA, 2019b) present additional information and analyses supporting the Agency's evaluation of 1,4-dioxane.

OCSPP has coordinated with the Office of Water regarding 1,4-dioxane contamination in drinking water. As noted above, in the Preliminary Regulatory Determinations for Contaminants on the Fourth Drinking Water Contaminant Candidate List (85 FR 14098 (Mar. 10, 2020)), EPA

found that 1,4-dioxane is occurring in finished drinking water above a health reference level and therefore, for purposes of TSCA section 9(b), EPA has found risk from 1,4-dioxane contamination at certain levels in drinking water that could be addressed under EPA's SDWA authorities.⁵ However, EPA has deferred a determination to regulate 1,4-dioxane under SDWA because SDWA section 1412(b)(1)(B)(ii) requires that EPA determine after opportunity for public comment that regulation of 1,4-dioxane meets all three criteria for regulation under SDWA section 1412(b)(1)(A), and EPA is awaiting new information that can inform the evaluation of these three criteria (i.e. adverse effect, level of public health concern and meaningful opportunity for health risk reduction). EPA will continue to evaluate 1,4-dioxane under SDWA authorities to determine whether or not to regulate 1,4-dioxane in drinking water, and the information produced in the risk evaluation process will be considered by the Office of Water as part of future SDWA actions.

As described above, EPA has regular analytical processes to identify and evaluate drinking water contaminants of potential regulatory concern for public water systems under SDWA. The Office of Water evaluates the regulatory determination criteria under SDWA Section 1412(b)(1)(A) to determine whether or not to initiate the development of a National Primary Drinking Water Regulation. EPA promulgates National Primary Drinking Water Regulations (NPDWRs) under SDWA when the Agency concludes a contaminant may have adverse health effects, occurs or is substantially likely to occur in public water systems at a level of concern and that regulation, in the sole judgement of the Administrator, presents a meaningful opportunity for health risk reduction. For each contaminant with NPDWRs, EPA sets an enforceable Maximum Contaminant Level (MCL) as close as feasible to a health based, non-enforceable Maximum Contaminant Level Goals (MCLG) or establishes a treatment technique. Feasibility refers to both the ability to treat water to meet the MCL and the ability to monitor water quality at the MCL, SDWA Section 1412(b)(4)(D). Public water systems are generally required to monitor for the regulated chemical based on a standardized monitoring schedule to ensure compliance with the maximum contaminant level (MCL). Under SDWA, EPA must also review existing drinking water regulations every 6 years, and if appropriate, revise them. SDWA, originally passed by Congress in 1974, thereby is the main federal statute to protect public health by regulating the

⁵ EPA does not find that the science standards of TSCA section 26(h) and (i) apply to this finding of risk, the Agency's determination that the risk could be eliminated or reduced to a sufficient extent by action under the SDWA, or the corresponding tailoring of this risk evaluation. TSCA sections 26(h) and (i) are triggered by EPA "decisions" made under TSCA sections 4, 5, and 6, and the risk finding and associated determination described herein are both made pursuant to TSCA section 9(b). Neither the finding of risk nor the subsequent determination implements TSCA section 6. Further, following an EPA determination that risk from drinking water from 1,4-dioxane contamination could be eliminated or reduced to a sufficient extent by action taken under SDWA, in accordance with TSCA section 9(b)(1), EPA will take appropriate action under SDWA in lieu of TSCA (absent a public interest finding described in TSCA section 9(b), which EPA did not make). Thus, TSCA itself compels EPA to narrow the scope of the risk evaluation following the Agency's section 9(b)(1) determination, and there is no separate EPA "decision" subject to TSCA sections 26(h) and (i).

nation's public drinking water supply and authorizing EPA to set national health-based standards and take other actions to protect against contaminants that may be found in drinking water.

Ambient Water Pathway

EPA develops recommended water quality criteria under section 304(a) of the CWA for pollutants in surface water that are protective of aquatic life or human health designated uses. A criterion is a hazard assessment only; *i.e.*, there is no exposure assessment or risk estimation. When states adopt criteria that EPA approves as part of a state's regulatory water quality standards, exposure is considered when state permit writers determine if permit limits are needed and at what level for a specific discharger of a pollutant to ensure protection of the designated uses of the receiving water. This is the process used under the CWA to address risk to human health and aquatic life from exposure to a pollutant in ambient waters.

Under Section 304(a) of the Clean Water Act, EPA develops, publishes, and from time to time revises criteria based on the latest scientific knowledge for surface waters to protect various designated uses, including those associated with aquatic life or human health. These criteria are not regulatory, they are recommendations only. States and tribal governments may adopt the EPA Clean Water Act Section 304(a) criteria guidance or may adopt their own criteria that differ from EPA's recommendations, subject to EPA's approval, using scientifically defensible methods. States implement EPA-approved criteria as part of their regulatory water quality standards, and exposure is considered by states in permits and listing decisions. EPA has not developed CWA section 304(a) recommended water quality criteria for the protection of aquatic life or human health for 1,4-dioxane. Human exposure to a receptor using the waters for recreation and exposures to aquatic life were evaluated in this risk evaluation under TSCA.

Onsite Releases to Land Pathway

The Comprehensive Environmental Response, Compensation, and Liability Act, otherwise known as CERCLA or Superfund, provides EPA with broad authority to address uncontrolled or abandoned hazardous-waste sites as well as accidents, spills, and other releases of hazardous substances, pollutants and contaminants into the environment. Through CERCLA, EPA is provided authority to conduct a response action and seek reimbursement of cleanup costs from potentially responsible parties, or in certain circumstances, order a potentially responsible party to conduct a cleanup.

CERCLA Section 101(14) defines "hazardous substance" by referencing other environmental statutes, including toxic pollutants listed under CWA Section 307(a); hazardous substances designated pursuant to CWA Section 311(b)(2)(A); hazardous air pollutants listed under CAA Section 112; TSCA Section 7; and hazardous wastes having characteristics identified under or listed pursuant to RCRA Section 3001. See 40 CFR 302.4. CERCLA Sections 102(a) and 103 of CERCLA also authorizes EPA to promulgate regulations designating as hazardous substances those substances which, when released into the environment, may present substantial danger to the public health or welfare or the environment. EPA must also promulgate regulations establishing the quantity of any hazardous substance the release of which must be reported under Section 103. Section 103 requires persons in charge of vessels or facilities to report to the

National Response Center if they have knowledge of a release of a hazardous substance above the reportable quantity threshold.

1,4-Dioxane is a hazardous substance under CERCLA. Releases of 1,4-dioxane in excess of 100 pounds within a 24-hour period must be reported (40 CFR 302.4, 302.6). The scope of this EPA TSCA risk evaluation does not include on-site releases to the environment of 1,4-dioxane at Superfund sites and subsequent exposure of the general population or non-human species. As such, EPA is not evaluating exposures to the general population or non-human species from this exposure pathway under any of the conditions of use in the risk evaluation under TSCA, and as such the unreasonable risk determinations for relevant conditions of use do not account for exposures to the general population or non-human species from on-site releases to land.

Disposal Pathway

1,4-Dioxane is included on the list of hazardous wastes pursuant to RCRA 3001 (40 CFR § 261.33) as a listed waste on the F and U lists. The general standard in RCRA section 3004(a) for the technical criteria that govern the management (treatment, storage, and disposal) of hazardous waste are those "necessary to protect human health and the environment," RCRA 3004(a). The regulatory criteria for identifying "characteristic" hazardous wastes and for "listing" a waste as hazardous also relate solely to the potential risks to human health or the environment. 40 C.F.R. §§ 261.11, 261.21-261.24. RCRA statutory criteria for identifying hazardous wastes require EPA to "tak[e] into account toxicity, persistence, and degradability in nature, potential for accumulation in tissue, and other related factors such as flammability, corrosiveness, and other hazardous characteristics." Subtitle C controls cover not only hazardous wastes that are landfilled, but also hazardous wastes that are incinerated (subject to joint control under RCRA Subtitle C and the CAA hazardous waste combustion MACT) or injected into UIC Class I hazardous waste wells (subject to joint control under Subtitle C and SDWA).

EPA is not evaluating emissions to ambient air from municipal and industrial waste incineration and energy recovery units or associated exposures to the general population or terrestrial species under any of the conditions of use in the risk evaluation under TSCA, as these emissions are regulated under section 129 of the Clean Air Act. CAA section 129 requires EPA to review and, if necessary, add provisions to ensure the standards adequately protect public health and the environment for 1,4-dioxane, and as such the unreasonable risk determinations for relevant conditions of use do not account for exposures to the general population or terrestrial species from industrial waste incineration and energy recovery units.

EPA is not evaluating on-site releases to land that go to underground injection or associated exposures to the general population or terrestrial species under any of the conditions of use in its risk evaluation under TSCA, and as such the unreasonable risk determinations for relevant conditions of use do not account for exposures to the general population or terrestrial species from underground injection. Environmental disposal of 1,4-dioxane injected into Class I hazardous well types are covered under the jurisdiction of RCRA and SDWA and disposal of 1,4-dioxane via underground injection is not likely to result in environmental and general population exposures. See 40 CFR parts 144, 146.

EPA is not evaluating on-site releases to land from RCRA Subtitle C hazardous waste landfills or exposures of the general population or terrestrial species from such releases under any of the

conditions of use in the TSCA evaluation, and as such the unreasonable risk determinations for relevant conditions of use do not account for exposures to the general population or terrestrial species from RCRA Subtitle C hazardous waste landfills. Design standards for Subtitle C landfills require double liner, double leachate collection and removal systems, leak detection system, run on, runoff, and wind dispersal controls, and a construction quality assurance program. They are also subject to closure and post-closure care requirements including installing and maintaining a final cover, continuing operation of the leachate collection and removal system until leachate is no longer detected, maintaining and monitoring the leak detection and groundwater monitoring system. Bulk liquids may not be disposed in Subtitle C landfills. Subtitle C landfill operators are required to implement an analysis and testing program to ensure adequate knowledge of waste being managed, and to train personnel on routine and emergency operations at the facility. Hazardous waste being disposed in Subtitle C landfills, including 1,4-dioxane (listed as a hazardous waste in 40 CFR 261.33), must also meet RCRA waste treatment standards before disposal. See 40 CFR part 264.

EPA is not evaluating on-site releases to land from RCRA Subtitle D municipal solid waste (MSW) landfills or exposures of the general population or terrestrial species from such releases under any of the conditions of use in the TSCA risk evaluation, and as such the unreasonable risk determinations for relevant conditions of use do not account for exposures to the general population or terrestrial species from RCRA Subtitle D MSW landfills. While permitted and managed by the individual states, municipal solid waste landfills are required by federal regulations to implement some of the same requirements as Subtitle C landfills. MSW landfills generally must have a liner system with leachate collection and conduct groundwater monitoring and corrective action when releases are detected. MSW landfills are also subject to closure and post-closure care requirements, and must have financial assurance for funding of any needed corrective actions. MSW landfills have also been designed to allow for the small amounts of hazardous waste generated by households and very small quantity waste generators (less than 220 lbs per month). Bulk liquids, such as free solvent, may not be disposed of at MSW landfills. See 40 CFR part 258.

EPA is not evaluating on-site releases to land from industrial non-hazardous waste and construction/demolition waste landfills or associated exposures to the general population or terrestrial species under any of the conditions of use in the 1,4-dioxane risk evaluation, and as such the unreasonable risk determinations for relevant conditions of use do not account for exposures to the general population or terrestrial species from industrial non-hazardous waste and construction/demolition waste landfills. Industrial non-hazardous and construction/demolition waste landfills are primarily regulated under authorized state regulatory programs. States must also implement limited federal regulatory requirements for siting, groundwater monitoring and corrective action and a prohibition on open dumping and disposal of bulk liquids. States may also establish additional requirements such as for liners, post-closure and financial assurance, but are not required to do so. See, *e.g.*, RCRA section 3004(c), 4007; 40 CFR part 257.

1.4.3 Conceptual Models

The conceptual models for this risk evaluation are shown in figures **Figure 1-2**, **Figure 1-3**, and **Figure 1-4**. EPA considered the potential for hazards to workers and occupational non-users (ONUs) from inhalation and dermal exposure and hazards to the environment resulting from

exposure to aquatic species as shown in the preliminary conceptual models and analysis plan of the 1,4-dioxane scope document ([U.S. EPA, 2017e](#)). EPA considered the potential for hazards to consumers from inhalation and dermal routes and to bystanders from the inhalation route via use of household products containing 1,4-dioxane as a byproduct and hazards from incidental exposure to the general population via releases to ambient water as shown in the conceptual models.

The conceptual models indicate the exposure pathways and exposure routes of 1,4-dioxane to workers and ONUs from industrial and commercial activities, consumers and bystanders from use of consumer products, and human and environmental receptors from environmental releases and wastes. The problem formulation and the draft supplemental analysis to the draft risk evaluation documents refined the initial conceptual models and analysis plans that were provided in the scope documents ([U.S. EPA, 2018c](#)). EPA has included the mapping tables that described all possible scenarios and whether they would be further evaluated. This was developed during problem formulation and is presented in Appendix B. The environmental characterization for the pathways included in the risk evaluation is described in Section 4.1.

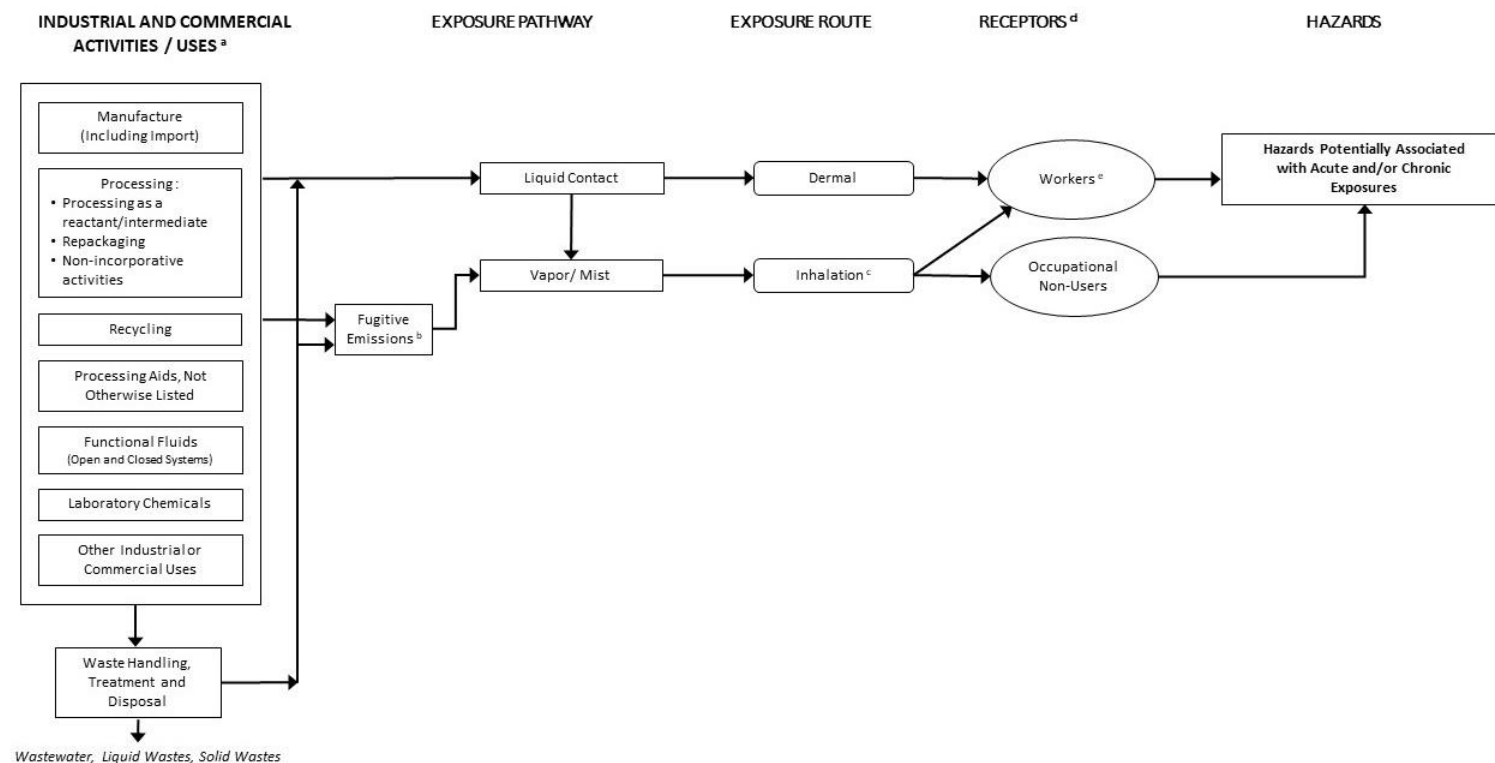


Figure 1-2. 1,4-Dioxane Conceptual Model for Industrial and Commercial Activities and Uses: Potential Exposures and Hazards

The conceptual model presents the exposure pathways, exposure routes and hazards to human receptors from industrial and commercial activities and uses of 1,4-dioxane that EPA analyzed in this risk evaluation.

^a Additional uses of 1,4-dioxane are included in Table 1-4..

^b Fugitive air emissions are those that are not stack emissions (emissions that occur through stacks, confined vents, ducts, pipes or other confined air streams), and include fugitive equipment leaks from valves, pump seals, flanges, compressors, sampling connections, open-ended lines; evaporative losses from surface impoundment and spills; and releases from building ventilation systems.

^c Based on physical chemical properties, 1,4-dioxane in mists that deposit in the upper respiratory tract will likely be rapidly absorbed in the respiratory tract or evaporate and were considered in the inhalation exposure assessment.

^d Receptors include potentially exposed or susceptible subpopulations.

^e EPA considered the effect that engineering/administrative controls and/or personal protective equipment (PPE) have on occupational exposure levels.

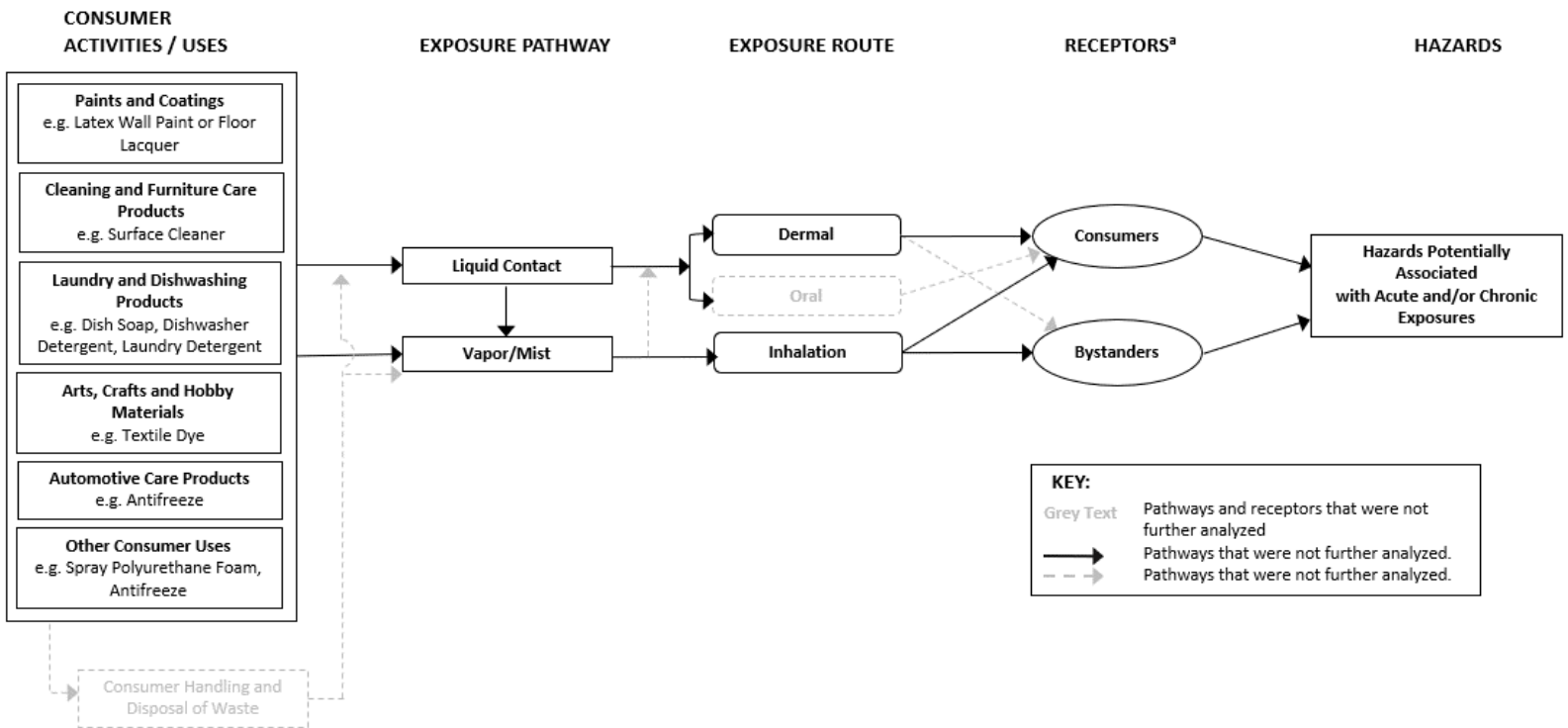


Figure 1-3. 1,4-Dioxane Conceptual Model for Consumer Activities and Uses: Consumer Exposures and Hazards

The conceptual model presents the exposure pathways, exposure routes and hazards to human receptors from consumer activities and uses of 1,4-dioxane that EPA analyzed in this risk evaluation.

^a Receptors include potentially exposed or susceptible subpopulations.

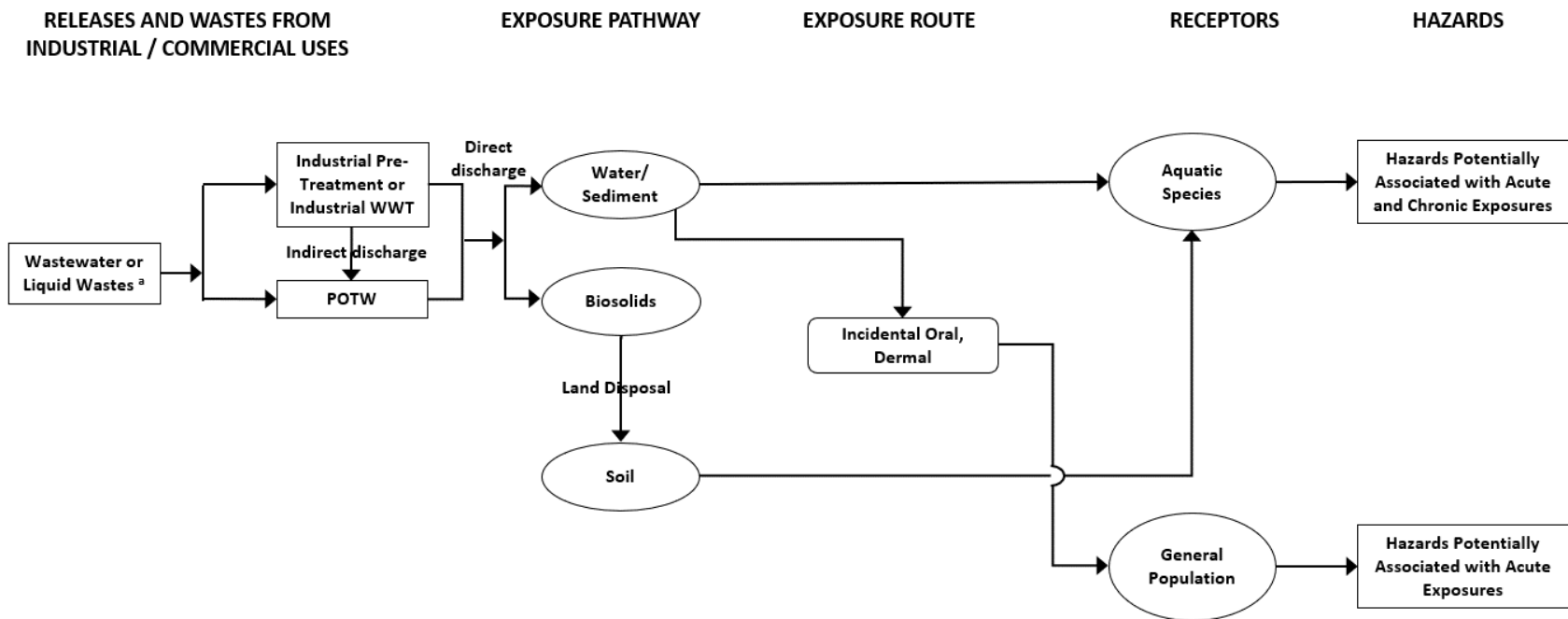


Figure 1-4. 1,4-Dioxane Conceptual Model for Environmental Releases and Wastes: Potential Exposures and Hazards

The conceptual model presents the major exposure pathways, exposure routes and hazards to human and environmental receptors from environmental releases and wastes of 1,4-dioxane that EPA analyzed in the draft risk evaluation and draft supplemental analysis to the draft risk evaluation. During problem formulation, EPA made refinements to the conceptual models resulting in no further analysis of the terrestrial exposure pathway following problem formulation. Analyses were conducted using physical and chemical properties, fate information and surface water modeling during problem formulation. EPA has included the results of the analyses in Section 2.3.1, and Appendix E) and risk characterizations based on these analyses are included in the risk characterization (Section 4.1).

^a Industrial wastewater or liquid wastes could be treated on-site and then released to surface water (direct discharge), or pre-treated and released to POTW (indirect discharge).

1.5 Systematic Review

TSCA requires EPA to use scientific information, technical procedures, measures, methods, protocols, methodologies and models consistent with the best available science and base decisions on the weight of the scientific evidence. Within the TSCA risk evaluation context, the weight of the scientific evidence is defined as “*a systematic review method, applied in a manner suited to the nature of the evidence or decision, that uses a pre-established protocol to comprehensively, objectively, transparently, and consistently identify and evaluate each stream of evidence, including strengths, limitations, and relevance of each study and to integrate evidence as necessary and appropriate based upon strengths, limitations, and relevance*” (40 C.F.R. 702.33).

To meet the TSCA § 26(h) science standards, EPA used the TSCA systematic review process described in the *Application of Systematic Review in TSCA Risk Evaluations* document ([U.S. EPA, 2018b](#)). The process complements the risk evaluation process in that the data collection, data evaluation and data integration stages of the systematic review process are used to develop the exposure and hazard assessments based on reasonably available information. EPA defines “reasonably available information” to mean information that EPA possesses, or can reasonably obtain and synthesize for use in risk evaluations, considering the deadlines for completing the evaluation (40 CFR 702.33).

EPA is implementing systematic review methods and approaches within the regulatory context of the amended TSCA. Although EPA is adopting as many best practices as practicable from the systematic review community, EPA expects modifications to the process to ensure that the identification, screening, evaluation and integration of data and information can support timely regulatory decision making under the aggressive timelines of the statute.

1.5.1 Data and Information Collection

EPA planned and conducted a comprehensive literature search based on chemical descriptors and key words related to the different discipline-specific evidence supporting the risk evaluation (*e.g.*, environmental fate and transport; engineering releases and occupational exposure; exposure to general population, consumers and environmental exposure; and environmental and human health hazard). EPA then developed and applied inclusion and exclusion criteria during the title and abstract screening to identify information potentially relevant for the risk evaluation process. The literature and screening strategy as specifically applied to 1,4-dioxane is described in the *Strategy for Conducting Literature Searches for 1,4-Dioxane: Supplemental File for the TSCA Scope Document* and the results of the title and abstract screening process were published in the *1, 4-Dioxane (CASRN 123-91-1) Bibliography: Supplemental File for the TSCA Scope Document* ([U.S. EPA, 2017a](#)). EPA subsequently conducted full-text screening using inclusion/exclusion criteria within population, exposure, comparator, outcome (PECO) or similar statements that are included in Appendix F of *Problem Formulation of the Risk Evaluation for 1,4-Dioxane* ([EPA, 2018b](#)).

For studies determined to be on-topic (or relevant) after title and abstract screening, EPA conducted a full text screening to further exclude references that were not relevant to the risk evaluation. Screening decisions were made based on eligibility criteria documented in the

form of the populations, exposures, comparators, and outcomes (PECO) framework or a modified framework.⁶ Data sources that met the criteria were carried forward to the data evaluation stage. The inclusion and exclusion criteria for full text screening for 1,4-dioxane are available in Appendix F of the *Problem Formulation of the Risk Evaluation for 1,4-Dioxane* (U.S. EPA, 2018c).

Although EPA conducted a comprehensive search and screening process as described above, EPA made the decision to leverage the literature published in previous assessments⁷ when identifying relevant key and supporting data⁸ and information for developing the 1,4-dioxane risk evaluation. This is discussed in the [Strategy for Conducting Literature Searches for 1,4-Dioxane: Supplemental Document to the TSCA Scope Document](#). In general, many of the key and supporting data sources were identified in the comprehensive [1,4-Dioxane \(123-91-1\) Bibliography: Supplemental File for the TSCA Scope Document](#) (U.S. EPA, 2017a). However, there were instances that EPA missed relevant references that were not captured in the initial categorization of the on-topic references. EPA found additional relevant data and information using backward reference searching, which was a technique that will be included in future search strategies. This issue was discussed in Section 4 of the [Application of Systematic Review for TSCA Risk Evaluations](#). Other relevant key and supporting references were identified through targeted supplemental searches to support the analytical approaches and methods in the 1,4-dioxane risk evaluation (e.g., to locate specific information for exposure modeling) or to identify new data and information published after the date limits of the initial search.

EPA used previous chemical assessments to quickly identify relevant key and supporting information as a pragmatic approach to expedite the quality evaluation of the data sources, but many of those data sources were already captured in the comprehensive literature as explained above. EPA also considered newer information not taken into account by previous chemical assessments as described in the [Strategy for Conducting Literature Searches for 1,4-Dioxane: Supplemental Document to the TSCA Scope Document](#). EPA then evaluated the confidence of the key and supporting data sources as well as newer information instead of evaluating the confidence of all the underlying evidence ever published on a chemical substance's fate and transport, environmental releases, environmental and human exposure and hazards. Such comprehensive evaluation of all of the data and information ever published for a chemical substance would be extremely labor intensive and could not be achieved under the TSCA statutory deadlines for most chemical substances especially those

⁶ A PESO statement was used during the full text screening of environmental fate and transport data sources. PESO stands for Pathways and Processes, Exposure, Setting or Scenario, and Outcomes. A RESO statement was used during the full text screening of the engineering and occupational exposure literature. RESO stands for Receptors, Exposure, Setting or Scenario, and Outcomes.

⁷ Examples of existing assessments are EPA's chemical assessments (e.g., previous work plan risk assessments, problem formulation documents), ATSDR's Toxicological Profiles, and EPA's IRIS assessments. This is described in more detail in the [Strategy for Conducting Literature Searches for 1,4-Dioxane: Supplemental File for the TSCA Scope Document](#).

⁸ Key and supporting data and information are those that support key analyses, arguments, and/or conclusions in the risk evaluation.

that have a data rich database. Furthermore, EPA determined how EPA’s evaluation of the key and supporting data and information and newer information would change the previous conclusions presented in the previous assessments.

Using this pragmatic approach, EPA evaluated the confidence of the key and supporting data sources as well as newer information instead of evaluating the confidence of all the underlying evidence ever published on 1,4-dioxane’s fate and transport, environmental releases, environmental and human exposure and hazards. This allowed EPA to maximize the scientific and analytical efforts of other regulatory and non-regulatory agencies by accepting for the most part the relevant scientific knowledge gathered and analyzed by others except for influential information sources that may have an impact on the weight of the scientific evidence and ultimately the risk findings. The influential information (*i.e.*, key/supporting) came from a smaller pool of sources subject to the rigor of the TSCA systematic review process to ensure that the risk evaluation uses the best available science and the weight of the scientific evidence.

Figures 1-5, 1-6, 1-7, and 1-8 depict the literature flow diagrams illustrating the results of this process for the scientific discipline-specific evidence supporting the risk evaluation. Each diagram provides the total number of references at the start of each systematic review stage (*i.e.*, data search, data quality evaluation, data extraction/data integration) and those excluded based on criteria guiding the screening and data quality evaluation decisions.

EPA made the decision to bypass the data screening step for data sources that were highly relevant to the risk evaluation as described above. These data sources are depicted as “key/supporting data sources” in the literature flow diagrams. Note that the number of “key/supporting data sources” were excluded from the total count during the data screening stage and added, for the most part, to the data evaluation stage depending on the discipline-specific evidence. The exception was the engineering releases and occupational exposure data sources that were subject to a combined data extraction and evaluation step (Figure 1-6).

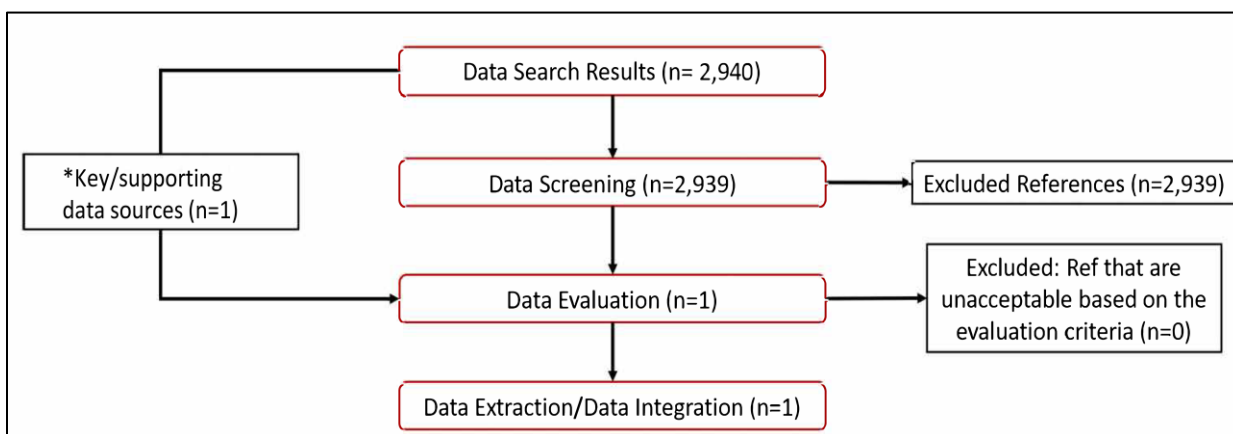


Figure 1-5. Literature Flow Diagram for Environmental Fate and Transport Data Sources

Following data screening, EPA determined during problem formulation that no environmental pathways would be further analyzed (U.S. EPA, 2018c). EPA evaluated a biodegradation study that was a key source in a previous EPA assessment (U.S. EPA, 2015) and is discussed in Section 2.1. Data sources identified relevant to physical-chemical properties were not included in this literature flow diagram. The data quality evaluation of physical-chemical properties studies can be found in the supplemental document, Data Quality Evaluation of Physical-Chemical Properties Studies (Docket: EPA-HQ-OPPT-2019-0500) and the extracted data are presented in Table 1-1..

* These are key and supporting studies from existing assessments (e.g., EPA IRIS assessments or ATSDR assessments) that were considered highly relevant for the TSCA risk evaluation. These studies bypassed the data screening step and moved directly to the data evaluation step.

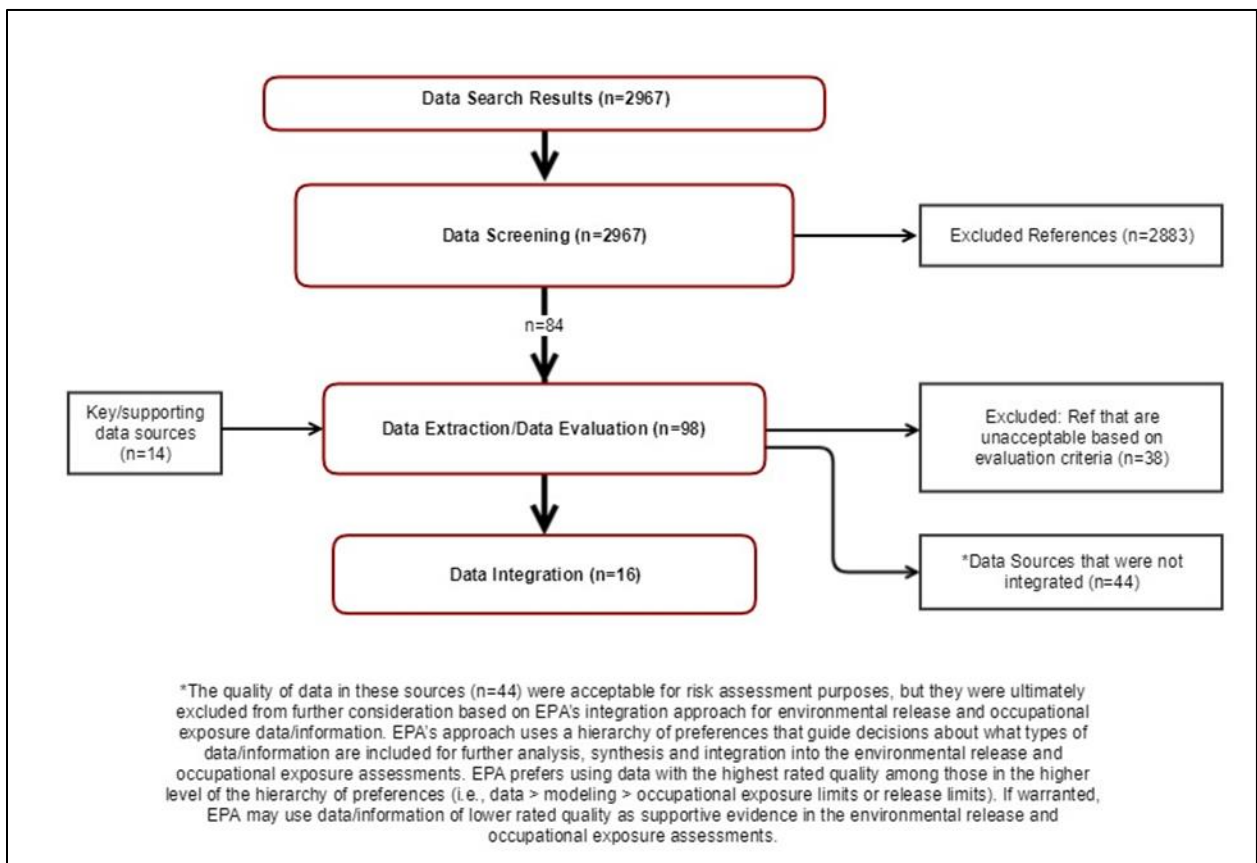


Figure 1-6. 1,4-Dioxane Literature Flow Diagram for Engineering Releases and Occupational Exposures

Literature search results for environmental release and occupational exposure yielded 2,967 data sources. Of these data sources, 84 were determined to be relevant for the risk evaluation through the data screening process. These relevant data sources were entered into the data extraction/evaluation phase. After data extraction/evaluation, EPA identified several data gaps and performed a supplemental, targeted search to evaluate these gaps (e.g., to locate information needed for exposure modeling). The supplemental search yielded 14 relevant data sources that bypassed the data screening step and were evaluated and extracted in accordance with *Appendix D: Data Quality Criteria for Occupational Exposure and Release Data of the Application of Systematic Review for TSCA Risk Evaluations* document.

EPA’s problem formulation laid out the scope of the evaluation and used reasonably available sources of information to evaluate potential exposures to environmental receptors (aquatic) pathways from 1,4-dioxane. The confidence of these data sources was considered acceptable for risk evaluation purposes and thus they were used to support the analyses during scoping and problem formulation. EPA determined during problem formulation that certain environmental pathways were within scope but would not be further analyzed based on quantitative and qualitative analyses covering ecological pathways (U.S. EPA, 2018c). In support of this evaluation, EPA undertook an additional literature search to identify, screen, and evaluate literature relevant for a consumer exposure assessment of 1,4-dioxane.

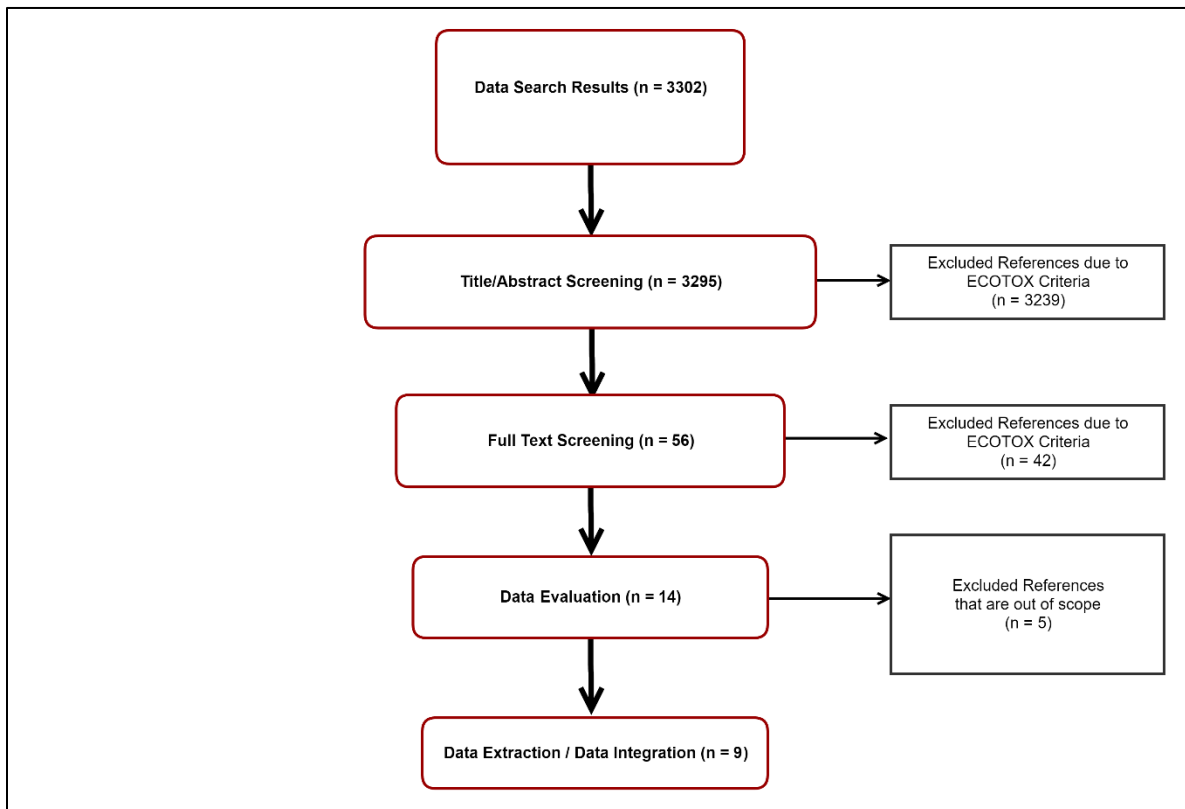


Figure 1-7. Literature Flow Diagram for Environmental Hazard Data Sources

The environmental hazard data sources were identified through literature searches and screening strategies using the ECOTOX Standard Operating Procedures. Additional details about the process can be found in the Strategy for Conducting Literature Searches for 1,4-Dioxane: Supplemental File for the TSCA Scope Document, EPA-HQ-OPPT-2016-0723. During problem formulation, EPA made refinements to the conceptual models resulting in no further analysis of the terrestrial exposure pathway following problem formulation. Such qualitative analyses can be conducted with limited data during problem formulation to identify which exposure pathways warrant more analysis. Thus, environmental hazard data sources on terrestrial organisms were excluded from data quality evaluation.

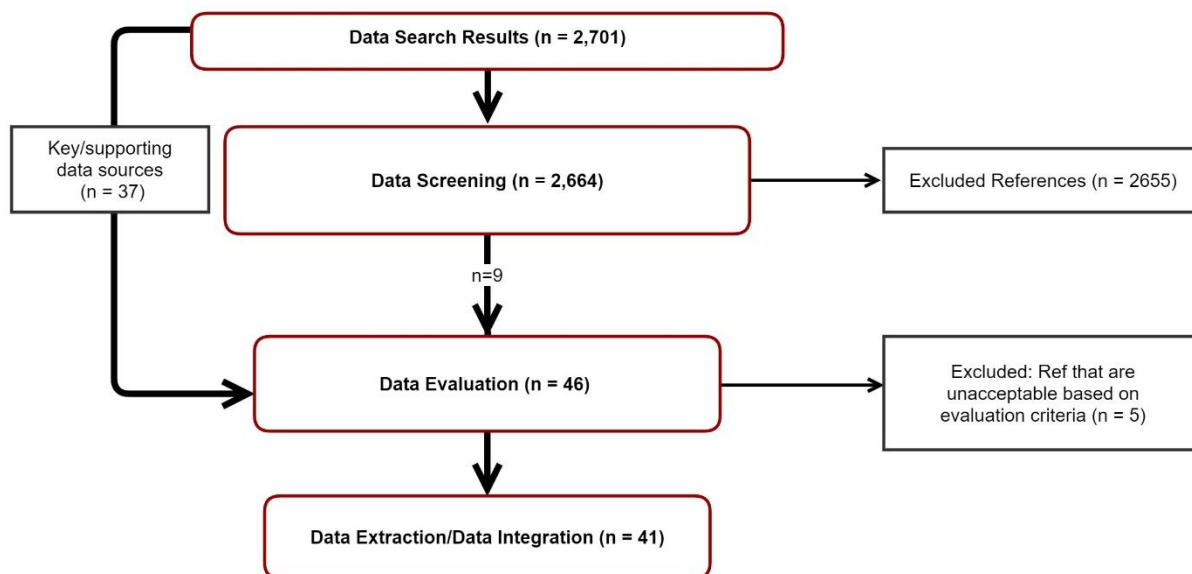


Figure 1-8. Literature Flow Diagram for Human Health Hazard Data Sources

Key and supporting studies (n=37) were identified from existing assessments (e.g., EPA IRIS assessments, ATSDR assessments) and considered highly relevant for the TSCA risk evaluation. These studies bypassed the data screening step and moved directly to the data evaluation step.

Supplemental Literature Search for Consumer Exposure

EPA performed a supplemental literature search of peer databases to identify studies related to consumer exposure. EPA conducted a new comprehensive literature search of databases of peer reviewed literature based on chemical name and CAS registry number related to exposure to general population, consumers and environmental exposure. EPA filtered the new literature search results of 1,4-dioxane for consumer specific references using Structured Query Language (SQL) querying shown in Table 1-5.

Table 1-5 Categorical Term Sets used in SQL Querying for 1,4-Dioxane consumer assessment

Term Sets
carpet Drapery curtain upholstery furniture rug Suede cleaner leather water proofing starch
anti-static candle matches bleach laundry detergent Insect repellent litter Charcoal briquettes lighter fluid Drain cleaner Dishwasher dishwashing dishes soap Fabric
dye softener Oven cleaner home pet collar Fertilizer garden Fire extinguisher floor metal silver Food packaging packaged food
deodorizer freshener disinfectant spot remover stain remover Scouring pad Toilet Herbicide patio Water treatment chemicals Insecticide swimming pool Paint varnish remover thinner interior spray house
exterior polyurethane stain Ceiling tile patching plaster caulk sealer filler Dry wall Roofing Refinishing wall wallpaper Insulation automobile car truck cycle van

Antifreeze|Motor oil|Radiator|additives|Automotive paint|Gasoline|diesel fuel|vehicle|Windshield|washer|Clothes|clothing|shoe|Sheets|towels|diaper|games|toys|chew|ingest|jewelry|colorprint|newsprint|newspaper|photograph|consumer|emission

Categorical term sets were derived from the Exposure Factors Handbook. This included Household Furnishings, Garment Conditioning Products, Household Maintenance Products, Home Building & Improvement Products, Automobile-Related Products, and Personal Materials. Cosmetic Hygiene Products, insecticide, food packaging terminology was excluded for the purposes of this assessment per TSCA section 3(2).

Next, a machine learning model was employed to rank how similar the filtered references were to a pre-determined set of consumer references (positive seeds), and how unsimilar the filtered references were to a pre-determined set of non-consumer references (negative seeds). More information about the machine learning model, the positive and negative seeds are provided in the Supplemental Analysis File [*Consumer References, Data Screening*]. References that ranked above a relevancy cut-off (0.1 for all references) were included for data screening. These approaches reduced the number of references from 21,373 to 239. The revised literature flow diagram (Table 3) includes the additional SQL querying and machine learning steps that were used for the consumer assessment.

In addition to the peer database search, EPA utilized previous assessments and performed an additional gray literature search for the supplemental consumer analysis. Previous assessments that were identified in support of the development of EPA's 2015 *TSCA Work Plan Chemical Problem Formulation and Initial Assessment of 1,4-Dioxane* ([U.S. EPA, 2015](#)), were screened and evaluated for use in the supplemental consumer assessment. EPA conducted an additional consumer gray literature search to identify references with consumer information related to 1,4-dioxane. Previous assessments and results of the additional gray literature search for consumer uses resulted in 34 data sources. The revised literature flow diagram (Table 3) includes the previous assessments, as well as the additional gray literature results that were used for the consumer assessment.

The 239 references as a result of the machine learning efforts and the 34 references from previous assessments and the additional gray literature search underwent data screening. These sources are listed in the Supplemental Analysis File [*Consumer References, Data Screening*].

For the consumer supplemental analysis, EPA modified the inclusion and exclusion criteria for title and abstract screening and full text screening to identify consumer information potentially relevant for the risk evaluation process. The revised PECO is presented in 1-6Table .

Table 1-6 PECO Statement 1,4-Dioxane Consumer Exposure Assessment (September 2020)

PECO Element	Evidence
<u>P</u> opulation	Human: Consumers and bystanders, including children. Targeted human population groups may be exposed to 1,4-dioxane.
	Ecological: None.
<u>E</u> xposure	<p>Expected Primary Exposure Sources, Pathways, Routes</p> <p><u>Source:</u> Consumer use of products containing 1,4 dioxane as a byproduct, and associated air emissions and dermal contact.</p> <p><u>Pathway:</u> Indoor air, contact with products.</p> <p><u>Routes:</u> Indoor (inhalation), dermal (contact with products)</p>
Comparator (Scenario)	Human: Consider use/source specific exposure scenarios as well as which receptors are and are not reasonably exposed across the projected exposure scenarios.
	Ecological: None.
<u>O</u> utcomes for Exposure Concentration or Dose	Human: A wide range of effects following acute and chronic exposure doses mg/kg/day and concentrations mg/m ³ .
	Ecological: None.

The results of the data screening efforts resulted in 37 references that were sent to data evaluation, and 17 references that were evaluated qualitatively. The results of the data evaluation are included in the Supplemental File [*Data Quality Evaluation of Consumer Exposure Studies*] and the list of references evaluated qualitatively are included in the Supplemental File [*Consumer References, Data Screening*]. Following data evaluation, 30 references were sent forward for data extraction/integration. The process is depicted below in Figure 1-9.

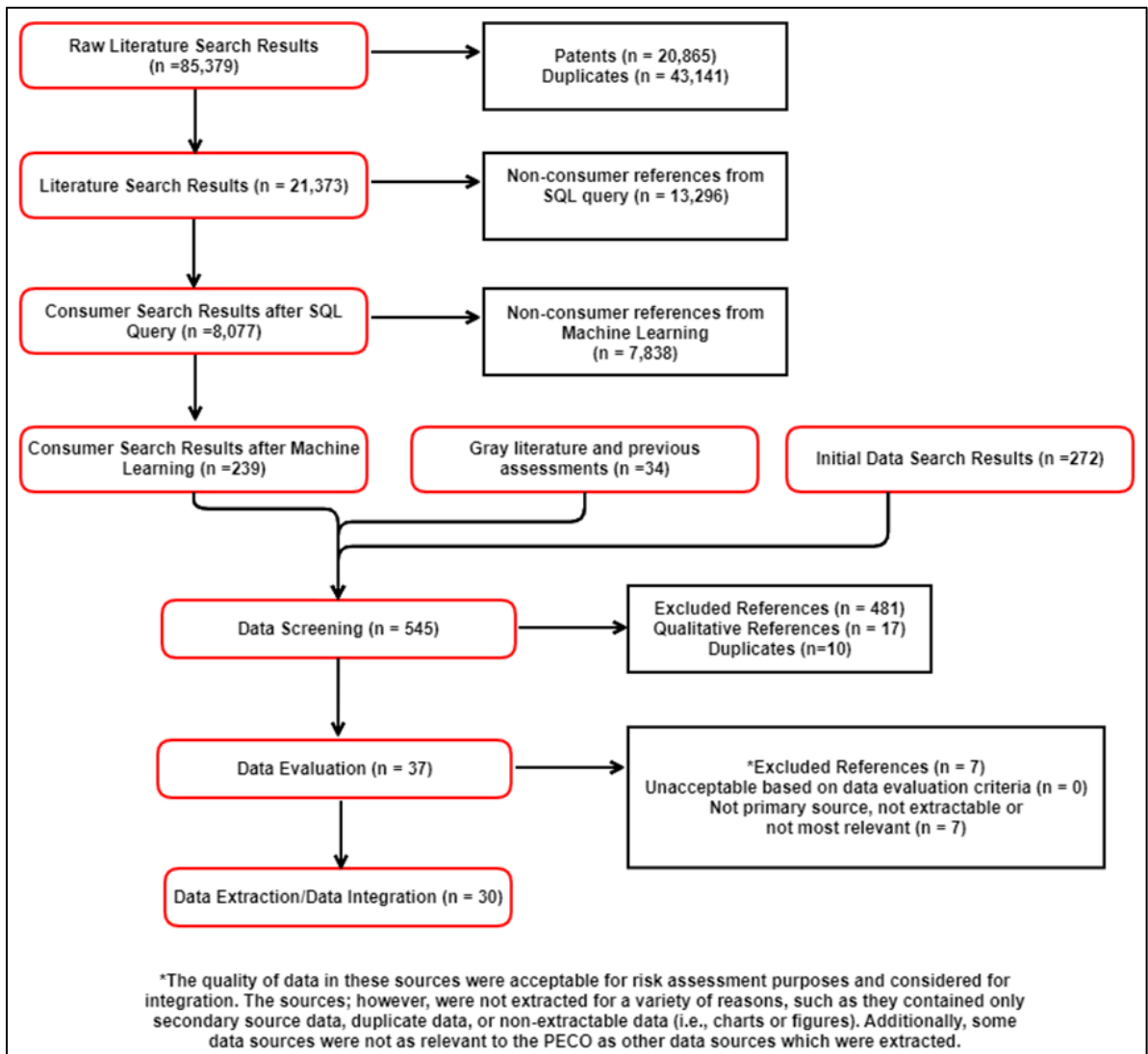


Figure 1-9. Literature Flow Diagram for General Population, Consumer and Environmental Exposure Data Sources

In support of this evaluation, EPA undertook an additional raw literature search (n=85,379) to identify, screen, and evaluate literature relevant for a consumer exposure assessment of 1,4-dioxane. Deduplication, SQL querying, and machine learning were employed to reduce the number of references for data screening. The Consumer Supplemental Search Results after Machine Learning (n=239) and the gray literature and previous assessments (n=34) represent the additional sources that were considered for the consumer supplemental analysis, whereas the initial data search results (n=272) refer to the references that were considered in the draft risk evaluation.

1.5.2 Data Evaluation

During the data evaluation stage, EPA assesses the quality of the data sources using the evaluation strategies and criteria described in the *Application of Systematic Review in TSCA Risk Evaluations* (U.S. EPA, 2018b). For the data sources that passed full-text screening and the key and supporting data sources, EPA evaluated their quality and each data source received an overall data quality rating of high, medium, low or unacceptable.

The results of the data quality evaluations are summarized in Sections 2.1 (Fate and Transport), 2.2 (Releases to the Environment), 2.3 (Environmental Exposures), 2.4 (Human Exposures), 3.1 (Environmental Hazards) and 3.2 (Human Health Hazards). Additional information is provided in the appendices of the main document. Supplemental files⁹ also provide details of the data evaluations including individual metric scores and the overall study score for each data source.

1.5.3 Data Integration

Data integration includes analysis, synthesis and integration of information for the risk evaluation. During data integration, EPA considers quality, consistency, relevancy, coherence and biological plausibility to make final conclusions regarding the weight of the scientific evidence. As stated in the *Application of Systematic Review in TSCA Risk Evaluations* (U.S. EPA, 2018b), data integration involves transparently discussing the significant issues, strengths, and limitations as well as the uncertainties of the reasonably available information and the major points of interpretation (U.S. EPA, 2018e). EPA defines “reasonably available information” to mean information that EPA possesses, or can reasonably obtain and synthesize for use in risk evaluations, considering the deadlines for completing the evaluation (*Procedures for Chemical Risk Evaluation Under the Amended Toxic Substances Control Act* (82 FR 33726)).

EPA used previous assessments (see Table 1-3.) to identify key and supporting information and then analyzed and synthesized available evidence regarding 1,4-dioxane’s chemical properties, environmental fate and transport properties and its potential for exposure and hazard. EPA’s analysis also considered recent data sources that were not considered in the previous assessments (Section 1.3) as well as reasonably available information on potentially exposed or susceptible subpopulations.

The exposures and hazards sections describe EPA’s analysis of the influential information (*i.e.*, key and supporting data) that were found acceptable based on the data quality reviews as well as discussion of other scientific knowledge using the approaches described in Sections 2.4.1, 3.1.1, and 3.2.1. The exposure section also describes whether aggregate or

⁹ There are various systematic review supplemental files accompanying the risk evaluation:
Final Risk Evaluation for 1,4-Dioxane, Systematic Review Supplemental File: Updates to the Data Quality Criteria for Epidemiological Studies
Final Risk Evaluation for 1,4-Dioxane, Systematic Review Supplemental File: Data Quality Evaluation for Engineering Releases and Occupational Exposure Data Sources
Final Risk Evaluation for 1,4-Dioxane, Systematic Review Supplemental File: Data Quality Evaluation of Environmental Hazard Studies
Final Risk Evaluation for 1,4-Dioxane, Systematic Review Supplemental File: Data Quality Evaluation of Environmental Fate and Transport Studies
Final Risk Evaluation for 1,4-Dioxane, Systematic Review Supplemental File: Data Quality Evaluation of Human Health Hazard Studies, Animal and *In Vitro* Studies
Final Risk Evaluation for 1,4-Dioxane, Systematic Review Supplemental File: Data Quality Evaluation of Epidemiological Studies
Final Risk Evaluation for 1,4-Dioxane, Systematic Review Supplemental File: Data Quality Evaluation of Consumer Exposure Studies
Final Risk Evaluation for 1,4-Dioxane, Systematic Review Supplemental File: Data Quality Evaluation of Physical-Chemical Properties Studies

sentinel exposures to a chemical substance were considered under the conditions of use within the scope of the risk evaluation, and the basis for that consideration.

2 EXPOSURES

2.1 Fate and Transport

EPA gathered and evaluated environmental fate information according to the process described in the *Application of Systematic Review in TSCA Risk Evaluations* ([U.S. EPA, 2018b](#)). Reasonably available environmental fate data were selected for use in the current evaluation. Furthermore, EPA used previous regulatory and non-regulatory 1,4-dioxane assessments to inform the environmental fate and transport information discussed in this section and Appendix D. EPA had confidence in the information used in the previous assessments of 1,4-dioxane (see Table 1-3.) to describe the environmental fate and transport of 1,4-dioxane and thus used it to make scoping decisions.

Because EPA determined during problem formulation that no environmental pathways would be further analyzed, EPA limited data extraction and evaluation to key data sources used in previous assessments (see Table 1-3.), as described in Section 1.5.2. Thus, EPA assessed the quality of a microcosm study on soil biodegradation ([Kelley et al., 2001](#)) based on the data quality criteria described in the *Application of Systematic Review in TSCA Risk Evaluations* ([U.S. EPA, 2018b](#)) and the study was rated ‘high’ quality. Data quality evaluation information for the sources used in this assessment can be found in the supplemental document, *Data Quality Evaluation of Environmental Fate and Transport Studies* ([U.S. EPA, 2019c](#)).

Other fate estimates were based on modeling results from [EPI Suite™](#) ([U.S. EPA, 2012c](#)), a predictive tool for physical/chemical and environmental fate properties. The inputs and setup of EPI Suite™ runs for 1,4-dioxane are described in Appendix D. EPI Suite™ was [reviewed by the EPA Science Advisory Board](#) and the individual models have been peer-reviewed in numerous articles published in technical journals. Citations for such articles are available in the EPI Suite™ help files.

The 1,4-dioxane environmental fate characteristics and physical-chemical properties used in fate assessment are presented in Table 2-1.. As part of problem formulation, EPA also analyzed the sediment and land-applied biosolids pathways. The results of the analyses are described in the 2018 problem formulation for 1,4-dioxane ([U.S. EPA, 2018c](#)) and presented again in Sections 4.1.3 and 4.1.4. Please note that this section and Sections 4.1.3 and 4.1.4 may also cite other data sources as part of the reasonably available information on the fate and transport properties of 1,4-dioxane. EPA did not subject these other data sources to the later phases of the systematic review process (*i.e.*, data evaluation and integration) based on the aforementioned approach.

Table 2-1. Environmental Fate Characteristics of 1,4-Dioxane

Property or Endpoint	Value ^a	References	Data Quality Rating
Direct photodegradation	Not expected to undergo direct photolysis ^b	ToxNet Hazardous Substances Data Bank	Not applicable

Property or Endpoint	Value ^a	References	Data Quality Rating
		(2017) ; U.S. EPA (2015)	
Indirect photodegradation	4.6 hours (estimated for atmospheric degradation) ^c	U.S. EPA (2015, 2012c)	High
Hydrolysis half-life	Does not undergo hydrolysis ^b	U.S. EPA (2015) ; Wilbur et al. (2012)	Not applicable
Biodegradation	0% in 120 days, 60% in 300 days (aerobic in soil microcosm)	U.S. EPA (2015) ; Kelley et al. (2001)	High
Bioconcentration factor (BCF)	3 (estimated via linear regression from Log K _{ow}) ^c 0.9 (estimated via Arnot-Gobas quantitative structure-activity relationship [QSAR]) ^c	U.S. EPA (2012c)	High
Bioaccumulation factor (BAF)	0.9 (estimated via Arnot-Gobas QSAR) ^c	U.S. EPA (2015, 2012c)	High
Organic carbon:water partition coefficient (log K _{oc})	0.4 (estimated) ^c	U.S. EPA (2015, 2012c)	High
^a Measured unless otherwise noted.			
^b 1,4-Dioxane lacks functional groups susceptible to the degradation mechanism			
^c Information was estimated using EPI Suite™ (U.S. EPA, 2012c)			

The EPI Suite™ module that estimates chemical removal in sewage treatment plants (STPWIN) was run using default settings (details available in the STPWIN help file in EPI Suite™) and estimated that 0.3% of 1,4-dioxane in wastewater will be removed by volatilization while < 2% of 1,4-dioxane will be removed by adsorption. The organic carbon-water partition coefficient, log K_{oc}, reported in previous assessments of 1,4-dioxane were in the range of 0.4 – 1.23 ([U.S. EPA, 2013d](#); [ATSDR, 2012](#); [U.S. EPA, 2010](#); [ECJRC, 2002](#); [NICNAS, 1998](#)), and log K_{oc} values within this range are associated with low sorption to soil, sediment, and suspended solids. Aerobic biodegradation of 1,4-dioxane is slow or negligible ([U.S. EPA, 2015](#); [ATSDR, 2012](#); [NTP, 2011](#); [Health Canada, 2010](#); [ECJRC, 2002](#); [NICNAS, 1998](#)) and will not contribute significantly to removal of 1,4-dioxane in wastewater treatment. Thus, concentrations of 1,4-dioxane in pore water of biosolids will be essentially equal to concentrations in the associated wastewater, and the 1,4-dioxane contained in biosolids will almost all be in the aqueous phase rather than adsorbed to particles. Similarly, 1,4-dioxane concentrations in sediment are expected to be nearly equal to concentrations in overlying water, with 1,4-dioxane almost exclusively in the aqueous phase of sediment samples.

Due to its water solubility (>800 g/L; Table 1-1.) and Henry's Law constant (4.8×10^{-6} atm·m³/mole at 25°C; Table 1-1.), 1,4-dioxane is expected to demonstrate limited volatility from

water surfaces, moist soil, and other moist surfaces such as land-applied biosolids. Once it enters the environment, 1,4-dioxane has low potential to sorb to suspended solids and sediment based on its log K_{oc} and is therefore expected to migrate to surface waters and groundwater.

1,4-Dioxane is expected to volatilize from dry surfaces and dry soil due to its vapor pressure (40 mm Hg at 25°C). In the atmosphere, it is expected to react with hydroxyl radicals with an indirect photolysis half-life on the order of hours (U.S. EPA, 2012c).

The estimated bioconcentration and bioaccumulation factors are 3 or below (Table 2-1.) and measured bioconcentration factors for 1,4-dioxane are 0.7 or below (ECJRC, 2002). Therefore, 1,4-dioxane has low bioaccumulation potential.

Overall, 1,4-dioxane is not likely to accumulate in wastewater biosolids, sediment, soil, or biota. It is expected to persist in soil, sediment, and water, but may slowly biodegrade in aerobic environments or volatilize from surface water or soil and then degrade by indirect photolysis.

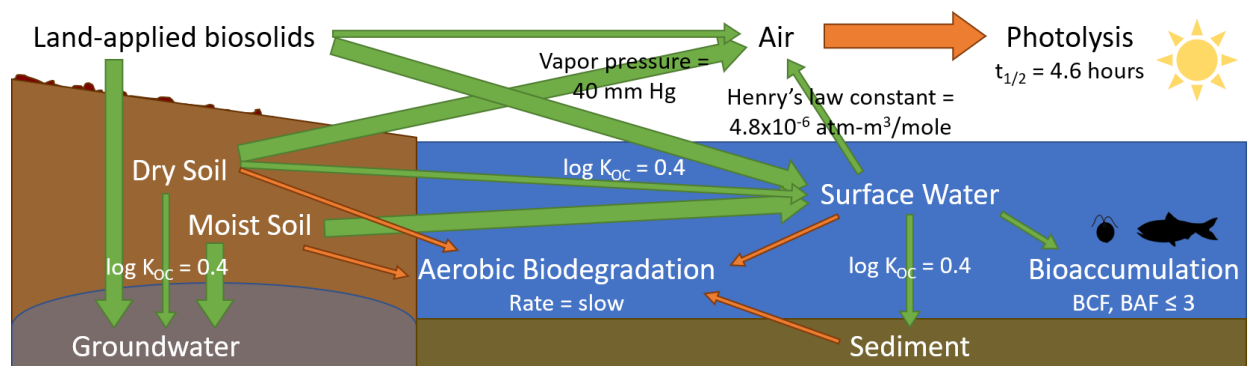


Figure 2-1 Environmental transport, partitioning, and degradation processes for 1,4-dioxane.

Figure 2-1 illustrates the transport and partitioning indicated by green arrows and degradation is indicated by orange arrows. The width of the arrow is a qualitative indication of the likelihood that the indicated partitioning will occur or the rate at which the indicated degradation will occur (*i.e.*, wider arrows indicate more likely partitioning or more rapid degradation). Although transport and partitioning processes (green arrows) can occur in both directions, the image illustrates the primary direction of transport indicated by partition coefficients. Figure 2-1 considers only transport, partitioning, and degradation within and among environmental media; sources to the environment such as discharge and disposal are not illustrated.

2.2 Environmental Releases

Releases to the environment from conditions of use (*e.g.*, industrial and commercial processes) are one component of potential exposure and may be derived from reported data that are obtained through direct measurement, calculations based on empirical data and/or assumptions and models.

Under the Emergency Planning and Community Right-to-Know Act (EPCRA) Section 313, 1,4-dioxane has been a Toxics Release Inventory (TRI)-reportable substance since 1987. The TRI

database includes information on disposal and other releases of 1,4-dioxane to air, water, and land, in addition to how it is being managed through recycling, treatment, and burning for energy recovery. Based on 2015 TRI reporting, an estimated 35,402 lbs. of 1,4-dioxane was released to surface water from industrial sources. See Table E-1 in Appendix E for a TRI summary table and further details on recent releases of 1,4-dioxane to various media.

2.2.1 Environmental Releases to Water

EPA categorized the conditions of use (COUs) listed in Table 1-4. into 12 Occupational Exposure Scenarios (OES). For each OES, a daily water release was estimated based on annual releases, release days, and the number of facilities (Figure 2-2). In this section, EPA describes its approach and methodology for estimating daily water releases, and for each OES provides a summary of release days, number of facilities, and daily water releases (Table 2-2.).

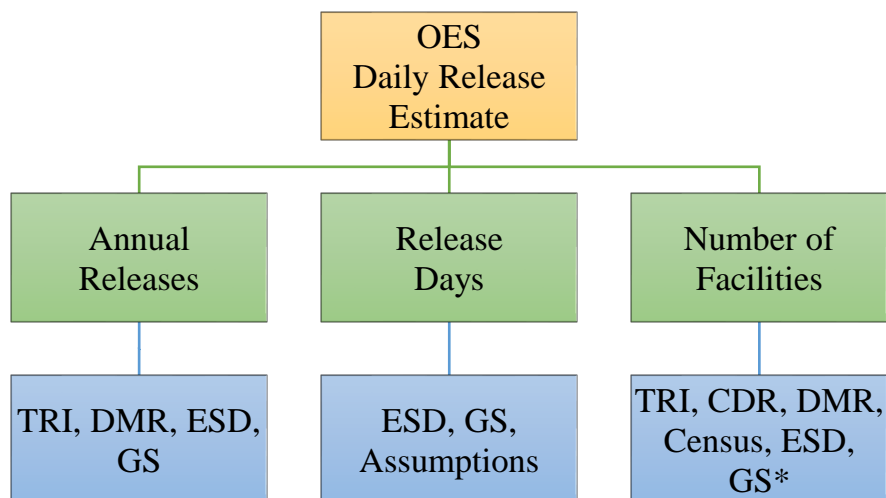


Figure 2-2. An Overview of How EPA Estimated Daily Water Releases for Each OES

* TRI: Toxics Release Inventory; DMR: Discharge Monitoring Report; ESD: Emission Scenario Document; GS: Generic Scenario

2.2.1.1 Results for Daily Release Estimate

EPA combined its estimates for annual releases, release days, and number of facilities to estimate a range for daily water releases for each OES. A summary of these ranges across facilities is presented in Table 2-2.. The examples of certain OES where water releases are not expected follows.

Laboratory Uses: EPA expects that releases of 1,4-dioxane from laboratory uses are to air (through volatile releases into the indoor laboratory air and/or through laboratory fume hoods to atmospheric air) and liquid wastes of 1,4-dioxane are handled as hazardous waste. EPA expects commercial and university laboratories to handle their wastes as hazardous waste and not discharge wastes to POTW via pouring the wastes down the drain.

Printing Inks (3D): EPA does not expect water releases from 3D printing ink uses. EPA expects spent printing ink containers, shavings or fragments, or waste scraps to be disposed of as solid waste. There is some uncertainty as to whether and how much 1,4-dioxane may remain in 3D printed products and waste scraps. However, due to the volatility of 1,4-dioxane, EPA expects 1,4-dioxane to evaporate from any printed object, shavings or fragments, or other printed material deposited to the floor or work surface prior to it being cleaned and disposed of as solid waste.

Film Cement: EPA assessed no wastewater discharges for this OES. EPA expects the small glue bottles to be disposed of as solid waste without rinsing them in a sink. There is some uncertainty as to whether and how much 1,4-dioxane may remain in the small glue bottles when disposed. However, due to the small quantities of the glue and high volatility of the 1,4-dioxane, EPA expects any residual 1,4-dioxane to evaporate to the air or remain in the solid waste stream.

Table 2-2. Summary of EPA’s Daily Water Release Estimates for Each OES and EPA’s Overall Confidence in these Estimates

Occupational Exposure Scenario (OES)	Estimated Daily Release Range Across Sites (kg/site-day)		Release Days per Year	Release Media	Overall Confidence	Notes
	Minimum	Maximum				
Manufacturing	0	2.48	250	Surface Water	M	Estimates based on TRI and DMR data.
Import and Repackaging	0	0	0	N/A	M	Estimates based on TRI and DMR data.
Recycling	-	-	-	-	-	EPA evaluated recycling as part of the industrial uses OES.
Industrial Uses	0	67.7	250	Surface Water, POTW, and Non-Public WWT	M	Estimates based on TRI and DMR data.
Functional Fluids (Open-System)	9.92E-4	3.79E-2	247	Surface Water and POTW	M	EPA estimates releases for three sites reported in DMR and for additional, unknown sites not captured in DMR or TRI using the Emission Scenario Document on the Use of Metalworking Fluids.
Laboratory Chemical Use	N/A	N/A	N/A	N/A	H	1,4-dioxane could be released to air; and wastes disposed of as hazardous waste for this OES.
Film Cement	N/A	N/A	N/A	N/A	H	EPA expects releases of 1,4-dioxane to be to air and wastes disposed of as solid waste for this OES.

Occupational Exposure Scenario (OES)	Estimated Daily Release Range Across Sites (kg/site-day)		Release Days per Year	Release Media	Overall Confidence	Notes
	Minimum	Maximum				
Spray Foam Application	3.59E-3		260	Surface Water or POTW	M	Modeled using the Application of Spray Polyurethane Foam Insulation Generic Scenario.
Printing Inks (3D)	N/A	N/A	N/A	N/A	H	EPA expects releases of 1,4-dioxane to be to air and wastes disposed of as solid waste for this OES.
Dry Film Lubricant	N/A	N/A	N/A	N/A	H	Based on conversations the with only known user, EPA expects wastes to be drummed and sent to a waste handler with residual wastes releasing to air or being disposed to landfill.
Disposal	0	0.12	250	Surface Water	M	Estimates based on TRI and DMR data.
N/A: Not applicable. EPA does not expect 1,4-dioxane releases to water from this OES. POTW = Publicly owned treatment works WWT = wastewater treatment						

2.2.1.2 Approach and Methodology

2.2.1.2.1 Water Release Estimates

Where available, EPA used 2018 TRI ([U.S. EPA, 2017f](#)) and 2018 DMR ([U.S. EPA, 2016a](#)) data to provide a basis for estimating releases. Facilities are only required to report to TRI if the facility has 10 or more full-time employees, is included in an applicable NAICS code, and manufactures, processes, or uses the chemical in quantities greater than a certain threshold (25,000 pounds for manufacturers and processors of 1,4-dioxane and 10,000 pounds for users of 1,4-dioxane). Due to these limitations, some sites that manufacture, process, or use 1,4-dioxane may not report to TRI and are therefore not included in these datasets.

For the 2018 Discharge Monitoring Report (DMR) ([U.S. EPA, 2016a](#)), EPA used the Water Pollutant Loading Tool within EPA's Enforcement and Compliance History Online (ECHO) to query all 1,4-dioxane point source water discharges in 2018. DMR data are submitted by National Pollutant Discharge Elimination System (NPDES) permit holders to states or directly to the EPA according to the monitoring requirements of the facility's permit. States are only required to load major discharger data into DMR and may or may not load minor discharger data. The definition of major versus minor discharger is set by each state and could be based on discharge volume or facility size. Due to these limitations, some sites that discharge 1,4-dioxane may not be included in the DMR dataset.

Where releases are expected but TRI and DMR data were not available or where EPA determined TRI and DMR data did not sufficiently represent releases of 1,4-dioxane to water for

a condition of use, releases were estimated using data from literature, relevant Emission Scenario Documents (ESDs), and Generic Scenarios (GSs).

2.2.1.2.2 Estimates of Number of Facilities

Where available, EPA used 2016 CDR ([U.S. EPA, 2016b](#)), 2018 TRI ([U.S. EPA, 2017f](#)), and 2018 DMR ([U.S. EPA, 2016a](#)) data to provide a basis to estimate the number of sites using 1,4-dioxane within a condition of use. Generally, information for reporting sites in CDR was sufficient to accurately characterize each reporting site's condition of use. However, information for determining the condition of use for reporting sites in TRI and DMR is typically more limited.

In TRI, sites submitting a Form R indicate whether they perform a variety of activities related to the chemical, including, but not limited to whether they: produce the chemical; import the chemical; use the chemical as a reactant; use the chemical as a chemical processing aid; and ancillary or other use. In TRI, sites submitting Form A are not required to designate an activity. For both Form R and Form A, TRI sites are also required to report the primary North American Industry Classification System (NAICS) code for their site. For each TRI site, EPA used the reported primary NAICS code and activity indicators to determine the condition of use at the site. For instances where EPA could not definitively determine the condition of use because: 1) the reported NAICS codes could include multiple conditions of use; 2) the site reported multiple activities; and/or 3) the site did not report activities due to submitting a Form A, EPA made an assumption on the condition of use to avoid double counting the site. For these sites, EPA supplemented the NAICS code and activity information with information from company websites, satellite images, and industry data to determine a "most likely" or "primary" condition of use.

In DMR, the only information reported on condition of use is each site's Standard Industrial Classification (SIC) code. EPA could not determine each reporting site's condition of use based on SIC code alone; therefore, EPA supplemented the SIC code information with the same supplementary information used for the TRI.

Where the number of sites could not be determined using CDR/TRI/DMR or where these data sources were determined to insufficiently capture the number of sites within a condition of use, EPA supplemented the available data with U.S. economic data using the following method:

- Identify the North American Industry Classification System (NAICS) codes for the industry sectors associated with these uses.
- Estimate total number of sites using the U.S. Census' Statistics of US Businesses (SUSB) ([U.S. Census Bureau, 2015](#)) data on total establishments by 6-digit NAICS.
- Review available ESDs and GSs for established facility estimates for each occupational exposure scenario.
- Combine the data generated in Steps 1 through 3 to produce an estimate of the number of sites using 1,4-dioxane in each 6-digit NAICS code, and sum across all applicable NAICS codes for the condition of use, augmenting as needed with data from the ESDs and GSs, to arrive at a total estimate of the number of sites within the condition of use.

Table 2-3. Summary of EPA’s Estimates for the Number of Facilities for Each OES

Occupational Exposure Scenario (OES)	Number of Facilities	Notes
Manufacturing	2	Based on CDR and TRI reporting (see Appendix G.6.1)
Import and Repackaging	3 to 18	Based on TRI and CDR reporting (see Appendix G.6.2)
Recycling	-	Evaluated as a part of Industrial Uses.
Industrial Uses	24	Based on TRI and DMR reporting (see Appendix G.6.3)
Functional Fluids (Open-System)	89,000	Based on TRI reporting and bounding estimate from the 2011 OECD <i>Emission Scenario Document on the Use of Metalworking Fluids</i> (see Appendix G.6.4)
Laboratory Chemicals	6,844	Bounding estimate based on CDR, and U.S. Census Bureau data for NAICS code 541380, Testing Laboratories (see Appendix G.6.5)
Film Cement	211	Bounding estimate based on U.S. Census Bureau data for NAICS code 512199, Other Motion Picture and Video Industries (see Appendix G.6.6)
Spray Foam Application	1,553,559	Bounding estimate based on U.S. Census Bureau data for NAICS code 238310, Drywall and Insulation Contractors and the 2018 EPA generic scenario <i>Application of Spray Polyurethane Foam Insulation</i> (see Appendix G.6.7)
Printing Inks (3D)	10,767	Bounding estimate based on U.S. Census Bureau data for NAICS code 339113, Surgical Appliance and Supplies Manufacturing (see Appendix G.6.8)
Dry Film Lubricant	8	Based on conversations with the Kansas City National Security Campus, a manufacturer and user (see Appendix G.6.9)
Disposal	14	Based on TRI and DMR reporting (see Appendix G.6.10)

2.2.1.2.3 Estimates of Release Days

EPA referenced Emission Scenario Documents (ESDs) or needed to make assumptions when estimating release days for each OES. A summary along with a brief explanation is presented in Table 2-4. below.

Table 2-4. Summary of EPA’s Estimates for Release Days Expected for Each OES

Occupational Exposure Scenario (OES)	Release Days	Notes
Manufacturing	250	Assumed five days per week and 50 weeks per year with two weeks per year for shutdown activities.
Import and Repackaging	250	Assumed five days per week and 50 weeks per year with two weeks per year for shutdown activities.
Recycling	-	Evaluated as a part of Industrial Uses.
Industrial Uses	250	Assumed five days per week and 50 weeks per year with two weeks per year for shutdown activities.
Functional Fluids (Open-System)	247	2011 OECD <i>Emission Scenario Document on the Use of Metalworking Fluids</i>
Laboratory Chemicals	250	Assumed five days per week and 50 weeks per year with two weeks per year for shutdown activities.
Film Cement	250	Assumed five days per week and 50 weeks per year with two weeks per year for shutdown activities.
Spray Foam Application	260	Based on the 2018 EPA generic scenario <i>Application of Spray Polyurethane Foam Insulation</i> , estimated average of 3 days spent/year at each work site.

Occupational Exposure Scenario (OES)	Release Days	Notes
Printing Inks (3D)	250	Assumed five days per week and 50 weeks per year with two weeks per year for shutdown activities.
Dry Film Lubricant	56	Facility provided dry film lubricant manufacture and application frequency.
Disposal	250	Assumed 5 days per week and 50 weeks per year.

Table 2-5 shows site-specific 1,4-dioxane releases as per 2018 TRI and DMR documents. For each Occupational Exposure Scenario (OES), annual releases, release media, the type of water body, and water use are also tabulated. These releases were reported to the 2018 TRI or DMR, and these data represent a snapshot in time. Several reported water releases to TRI and DMR are estimated only. Facilities below a requisite size are not required to report in TRI or DMR and therefore this map is likely not representative of all the releases in the U.S. for 2018. There were no releases reported to TRI or DMR for facilities in Alaska or Hawaii during this time period. Additional information available in the Supplemental File [*Exposure Modeling Inputs, Results, and Risk Estimates for Incidental Ambient Water Exposure*].

Table 2-5 1,4-Dioxane releases in TRI and DMR (2018)

Company Name	City, State	OES	Annual Release (kg/yr)	NPDES Permit Number ¹	Release Media	Sub-Watershed or Waterbody Name ¹	Recreational / Aquatic Life Use ¹
BASF Corp.	Zachary, LA	Manufacturing	620.06	LA0004057	Surface Water	Tchefuncta River: Savannah Branch	Yes / Yes
INEOS Oxide	Plaquemine, LA	Industrial Uses	721.70	LA0115100	Non-POTW WWT	Bayou Bourbeaux	No / No
Microdyn-Nadir Corp	Goleta, CA	Industrial Uses	24.04	CAZ482715	POTW	None Listed	No / No
Union Carbide Corp: St Charles Operations	Hahnville, LA	Industrial Uses	828.26	LA0000191	Surface Water	Bayou Fortier	No / No
Suez Wts Solutions USA Inc	Minnetonka, MN	Industrial Uses	16920.83	MN0059013	POTW	South Fork Ninemile Creek	No / No
The Dow Chemical Co - Louisiana Operations	Plaquemine, LA	Industrial Uses	647.73	LAG530436	Surface Water	Bayou Bourbeaux	No / No
Union Carbide Corp: Institute Facility	Institute, WV	Industrial Uses	3818.80	WVG611765	Surface Water	Rocky Fork	Yes / Yes
Union Carbide Corp: Seadrift Plant	Seadrift, TX	Industrial Uses	503.49	None	Surface Water	Private Surface Water	No / No
BASF Corp.	Monaca, PA	Industrial Uses	2.98	PA0092223	Surface Water	Sixmile Run-Ohio River -Raccoon Creek	No / No
Cherokee Pharmaceuticals LLC	Riverside, PA	Industrial Uses	1.66	PA0008419	Surface Water	Susquehanna River	No / No
Dak Americas LLC	Fayetteville, NC	Industrial Uses	7965.95	NC0003719	Surface Water	Locks Creek-Cape Fear River	Yes / Yes

Company Name	City, State	OES	Annual Release (kg/yr)	NPDES Permit Number ¹	Release Media	Sub-Watershed or Waterbody Name ¹	Recreational / Aquatic Life Use ¹
Institute Plant	Institute, WV	Industrial Uses	6132.57	WV0000086	Surface Water	Tyler Creek-Kanawha River - Rocky Fork	Yes / Yes
Kodak Park Division	Rochester, NY	Industrial Uses	63.88	NY0001643	Surface Water	Round Pond Creek, Paddy Hill Creek	Yes / Yes
Pharmacia & Upjohn (Former)	North Haven, CT	Industrial Uses	1.05	CT0001341	Surface Water	Quinnipiac River	No / No
Philips Electronics Plant	Parker County, TX	Industrial Uses	0.06	TX0113484	Surface Water	Rock Creek	No / No
Sanderson Gulch Drainage Improvements	Denver, CO	Industrial Uses	0.03	COG315474	Surface Water	Bolden Gulch-Muddy Creek	Yes / Yes
Ametek Inc. U.S. Gauge Division	Sellersville, PA	Open System Functional Fluid	2.64	PA0056014	Surface Water	East Branch Perkiomen Creek	No / No
Lake Reg Med/Collegeville	Collegeville, PA	Open System Functional Fluid	0.24	PA0042617	Surface Water	Lower Perkiomen Creek - Donny Brook	No / No
Pall Life Sciences Inc	Ann Arbor, MI	Open System Functional Fluid	5.42	MI0048453	Surface Water	Honey Creek	Yes / Yes
Beacon Heights Landfill	Beacon Falls, CT	Disposal	30.06	CTMIU0161	Surface Water	Bladens River-Naugatuck River	No / No
Ingersoll Rand/Torrington Facility	Walhalla, SC	Disposal	11.49	SC0049093	Surface Water	Cane Creek-Little River	No / No

¹Further detail on water releases and media of release are available at <https://echo.epa.gov/>.

2.2.1.3 Assumptions and Key Sources of Uncertainty for Environmental Releases

EPA estimated water releases using reported discharges from the 2018 TRI and the 2018 DMR. TRI and DMR data were determined to have a “medium” confidence rating through EPA’s systematic review process. Due to reporting requirements for TRI and DMR, the number of sites for a given OES may be underestimated. It is uncertain the extent to which sites not captured in these databases discharge wastewater containing 1,4-dioxane and whether any such discharges would be to surface water, POTW, or non-POTW WWT.

In addition, information on the use of 1,4-dioxane at facilities in TRI and DMR is limited; therefore, there is uncertainty as to whether the number of facilities estimated for a given OES do in fact represent that specific OES. If sites were categorized under a different OES, the annual wastewater discharges for each site would remain unchanged; however, average daily discharges may change depending on the release days expected for the different OES.

Facilities reporting to TRI and DMR only report annual discharges; to assess daily discharges, EPA estimated the release days and averaged the annual releases over these days. There is uncertainty that all sites for a given OES operate for the assumed duration; therefore, the average daily discharges may be higher if sites have fewer release days or lower if they have greater

release days. TRI-reporting facilities are required to submit their “best available data” to EPA for TRI reporting purposes. Some facilities are required to measure or monitor emissions or other waste management quantities due to regulations unrelated to the TRI Program (*e.g.*, permitting requirements), or due to company policies. These existing, readily available data are often used by facilities for TRI reporting purposes, as they represent the best available data. When monitoring or direct measurement data are not readily available or are known to be non-representative for TRI reporting purposes, the TRI regulations require that facilities determine release and other waste management quantities of TRI-listed chemicals by making reasonable estimates. These reasonable estimates may be obtained through various Release Estimation Techniques, including mass-balance calculations, the use of emission factors, and engineering calculations. There may be greater uncertainty in data resulting from estimates compared to monitoring measurements.

Furthermore, 1,4-dioxane concentrations in wastewater discharges at each site may vary from day-to-day such that on any given day the actual daily discharges may be higher or lower than the estimated average daily discharge.

In some cases, the number of facilities for a given OES was estimated using data from the U.S. Census. In such cases, the average daily release calculated from sites reporting to TRI or DMR was applied to the total number of sites reported in ([U.S. Census Bureau, 2015](#)). It is uncertain how accurate this average release is to actual releases at these sites; therefore, releases may be higher or lower than the calculated amount.

2.2.1.3.1 Summary of Overall Confidence in Release Estimates

Table 2-6. provides a summary of EPA’s overall confidence in its release estimates for each of the Occupational Exposure Scenarios assessed.

Table 2-6. Summary of Overall Confidence in Release Estimates by OES

Occupational Exposure Scenario (OES)	Overall Confidence in Release Estimates
Manufacturing	Wastewater discharges are assessed using reported discharges from the 2018 TRI for two sites. TRI data were determined to have a “medium” confidence rating through EPA’s systematic review process. Facilities reporting to TRI only report annual discharges; to assess daily discharges, EPA assumed 250 days/yr. of operation and averaged the annual discharges over the operating days. There is some uncertainty that all sites manufacturing 1,4-dioxane will operate for this duration; therefore, the average daily discharges may be higher if sites operate for fewer than 250 days/yr. or lower if they operate for greater than 250 days/yr. Furthermore, 1,4-dioxane concentrations in wastewater discharges at each site may vary from day-to-day such that on any given day the actual daily discharges may be higher or lower than the estimated average daily discharge. Based

Occupational Exposure Scenario (OES)	Overall Confidence in Release Estimates
	on this information, EPA has a medium confidence in the wastewater discharge estimates for the two sites in the 2018 TRI.
Import and Repackaging	<p>Wastewater discharges are assessed using reported discharges from the 2018 TRI and the 2018 DMR. TRI and DMR data were determined to have a “medium” confidence rating through EPA’s systematic review process. Due to reporting requirements for TRI and DMR, the number of sites in this OES may be underestimated. It is uncertain the extent that sites not captured in these databases discharge wastewater containing 1,4-dioxane and whether any such discharges would be to surface water, POTW, or non-POTW WWT. Additionally, information on the conditions of use of 1,4-dioxane at facilities in TRI and DMR is limited; therefore, there is some uncertainty as to whether all the sites assessed in this section are performing repackaging (of imported or domestically manufactured volumes) rather than a different OES. If the sites were categorized under a different OES, the annual wastewater discharges for each site would remain unchanged; however, average daily discharges may change depending on the number of operating days expected for the OES.</p> <p>Facilities reporting to TRI and DMR only report annual discharges; to assess daily discharges, EPA assumed 250 days/year of operation and averaged the annual discharges over the operating days. There is some uncertainty that all sites importing or repackaging 1,4-dioxane will operate for this duration; therefore, the average daily discharges may be higher if sites operate for fewer than 250 days/yr. or lower if they operate for greater than 250 days/yr. Furthermore, 1,4-dioxane concentrations in wastewater discharges at each site may vary from day-to-day such that on any given day the actual daily discharges may be higher or lower than the estimated average daily discharge. Based on this information, EPA has a medium confidence in the wastewater discharge estimates.</p>
Recycling	Assessed as part of industrial uses.
Industrial Uses	Wastewater discharges are assessed using reported discharges from the 2018 TRI and the 2018 DMR. TRI and DMR data were determined to have a “medium” confidence rating through EPA’s systematic review process. Due to reporting requirements for TRI and DMR, the number of sites in this OES may be underestimated. It is uncertain the extent that sites not captured in these databases discharge wastewater containing 1,4-dioxane and whether any such discharges would be to surface water, POTW, or non-POTW WWT. Additionally, information on the conditions of use of 1,4-dioxane at facilities in TRI and DMR is limited; therefore,

Occupational Exposure Scenario (OES)	Overall Confidence in Release Estimates
	<p>there is some uncertainty as to whether all the sites assessed in this section are using 1,4-dioxane in an industrial use capacity rather than a different OES. If the sites were categorized under a different OES, the annual wastewater discharges for each site would remain unchanged; however, average daily discharges may change depending on the number of operating days expected for the OES.</p> <p>Facilities reporting to TRI and DMR only report annual discharges; to assess daily discharges, EPA assumed 250 days/yr. of operation and averaged the annual discharges over the operating days. There is some uncertainty that all sites using 1,4-dioxane for industrial uses will operate for this duration; therefore, the average daily discharges may be higher if sites operate for fewer than 250 days/yr. or lower if they operate for greater than 250 days/yr. Furthermore, 1,4-dioxane concentrations in wastewater discharges at each site may vary from day-to-day such that on any given day the actual daily discharges may be higher or lower than the estimated average daily discharge. Based on this information, EPA has a medium confidence in the wastewater discharge estimates.</p>
Functional Fluids (Open-System)	<p>Wastewater discharges are assessed using reported discharges from the 2018 TRI and the 2018 DMR. TRI and DMR data were determined to have a “medium” confidence rating through EPA’s systematic review process. Due to reporting requirements, the number of sites reflected in TRI and DMR is assessed as an underestimate. EPA included the estimated 89,000 metal products and machinery facilities estimated by the ESD on the Use of Metalworking Fluids as a conservative bounding estimate for the possible range of sites. It is uncertain the extent that sites not captured in the TRI and DMR databases discharge wastewater containing 1,4-dioxane and whether any such discharges would be to surface water, POTW, or non-POTW WWT. Additionally, information on the conditions of use of 1,4-dioxane at facilities in TRI and DMR is limited; therefore, there is some uncertainty as to whether all the sites assessed in this section are using 1,4-dioxane in an open system functional fluids capacity rather than a different OES. If the sites were categorized under a different OES, the annual wastewater discharges for each site would remain unchanged; however, average daily discharges may change depending on the number of operating days expected for the OES.</p> <p>Facilities reporting to TRI and DMR only report annual discharges; to assess daily discharges, EPA assumed 247 days/yr. of operation and averaged the annual discharges over the operating days. There is some uncertainty that all sites using 1,4-dioxane for open system functional</p>

Occupational Exposure Scenario (OES)	Overall Confidence in Release Estimates
	<p>fluids will operate for this duration; therefore, the average daily discharges may be higher if sites operate for fewer than 247 days/yr. or lower if they operate for greater than 247 days/yr. Furthermore, 1,4-dioxane concentrations in wastewater discharges at each site may vary from day-to-day such that on any given day the actual daily discharges may be higher or lower than the estimated average daily discharge. Based on this information, EPA has a medium confidence in the wastewater discharge estimates.</p>
Laboratory Chemicals	<p>Water releases from laboratory uses are unlikely as laboratories collect and track spent and unspent chemicals prior to hazardous waste disposal. The releases of 1,4-dioxane from laboratory uses are to air (through volatile releases into the indoor laboratory air and/or through laboratory fume hoods to atmospheric air) and liquid wastes of 1,4-dioxane are handled as hazardous waste. The commercial analytical laboratories and university laboratories handle their wastes as hazardous waste and they are not allowed to discharge wastes to POTW via pouring the wastes down the drain. Small volume of 1,4-dioxane could be inadvertently spilled inside a laboratory and fractional amount may not be properly captured through spill containment techniques, resulting in 1,4-dioxane being discharged to POTW (through floor or sink drains). EPA does not evaluate exposures due to spills. Due to the high volatility of 1,4-dioxane, any spilled 1,4-dioxane not captured by spill containment materials could release to air.</p> <p>The number of laboratories assessed is based on the U.S. Census Bureau data for NAICS code 541380, Testing Laboratories. This NAICS code was chosen based on the main use of 1,4-dioxane in the laboratory setting: as a reference standard for determination of analytes in bulk pharmaceuticals. There are other types of laboratories, such as university laboratories and analytical laboratories, that may use 1,4-dioxane that are not represented in this NAICS code. However, it is unknown how many of laboratories within each of these categories use 1,4-dioxane. Thus, it is possible that the inclusion of only NAICS code 541380 could overrepresent the number of laboratories that use 1,4-dioxane. The direction of bias, whether the 6,844 number of sites is an underestimate or overestimate of the number of laboratories using 1,4-dioxane, is unknown. However, EPA has high confidence in the assessment of no or negligible releases to water or POTWs. This high confidence in no releases of water mitigates the uncertainties in the estimate of number of sites. Based on this information, EPA has a high confidence in the wastewater discharge estimates.</p>

Occupational Exposure Scenario (OES)	Overall Confidence in Release Estimates
Film Cement	<p>EPA assessed no wastewater discharges for this OES. The small glue bottles could be disposed of as solid waste without rinsing them in a sink. There is some uncertainty as to whether and what quantity of 1,4-dioxane could remain in the small glue bottles when disposed. However, due to the small quantities of the glue and high volatility of the 1,4-dioxane, EPA expects any residual 1,4-dioxane to evaporate to the air or remain in the solid waste stream. Small amount of film cement could inadvertently be spilled inside a facility, but due to the higher viscosity and small quantities of the substance, it will likely be cleaned up via wiping and disposed of as solid waste. However, EPA has not identified any data on the quantities or frequencies of accidental spills and does not evaluate exposures due to water releases resulting from such spills. Based on this information, EPA has a high confidence in the release assessment.</p>
Spray Foam Application	<p>Wastewater discharges are assessed using EPA’s container residual model. EPA defined operating days, operating days per site, foam thickness, and mass fraction of B-side in final formulation from the Generic Scenario for Application of Spray Polyurethane Foam Insulation. The parameters for average roofing area were defined from homeadvisor.com and houselogic.com. The parameters for density and mass fraction of the 1,4-dioxane in the B-side formulation were defined from a spray foam producer’s technical fact sheet. This EPA model addresses residual spray polyurethane foam in the container only and is based on industry averages, such as roof size. As a result of the model limitations and uncertainties due to various activities including container cleaning and product handling could vary dramatically on a site-by-site basis. It is uncertain to the extent these water releases are over- or underestimated.</p> <p>EPA determined that there were 17,857 establishments that fell into NAICS code 238310, for Drywall and Insulation Contractors. The GS estimates that a contractor spends three days at a job site before moving to the next job site and further estimates that a contractor works 260 days per year. Assuming a contractor works at only a single job site at a time, EPA calculates that a contractor works at approximately 87 job sites per year (260 working days divided by three days per job site). EPA multiplied the number of contractors by 87 to determine a bounding limit for the number of job sites in a year at which all contractors could potentially discharge container residuals down a drain to a POTW or directly on the ground, which could eventually reach surface waters. Based on this information, EPA has a low confidence in the release assessment.</p>

Occupational Exposure Scenario (OES)	Overall Confidence in Release Estimates
Printing Inks (3D)	<p>EPA assessed no wastewater discharges for this OES. EPA expects spent printing ink containers, shavings or fragments, or waste scraps to be disposed of as solid waste. There is some uncertainty as to whether and how much 1,4-dioxane may remain in 3D printed products and waste scraps. However, due to the volatility of 1,4-dioxane, EPA expects 1,4-dioxane to evaporate from any printed object, shavings or fragments, or other printed material deposited to the floor or work surface prior to it being cleaned and disposed of. Based on this information, EPA has a high confidence in the release assessment.</p>
Dry Film Lubricant	<p>EPA assessed no wastewater discharges for this OES based on conversations with the only known facility to use the product. All dry film lubricant materials are mixed and handled in a laboratory setting underneath a fume hood. The material is sprayed onto components in a spray booth with ventilation. Wastes are containerized and handled as wastes for removal by a waste handler. There is some uncertainty as to whether and how much 1,4-dioxane may be deposited on the floor or other surfaces as a result of overspray or spills. However, due to the volatility of 1,4-dioxane and expected spill clean-up methods of the laboratory setting, EPA expects deposited overspray or spilled 1,4-dioxane to evaporate to the air or be contained in spill containment materials and handled as waste. EPA does not evaluate exposures due to spills. Based on this information, EPA has a high confidence in the release assessment.</p>
Disposal	<p>Wastewater discharges are assessed using reported discharges from the 2018 TRI and the 2018 DMR. TRI and DMR data were determined to have a “medium” confidence rating through EPA’s systematic review process. Due to reporting requirements for TRI and DMR, the number of sites in this OES may be underestimated. It is uncertain the extent that sites not captured in these databases discharge wastewater containing 1,4-dioxane and whether any such discharges would be to surface water, POTW, or non-POTW WWT. Additionally, information on the conditions of use of 1,4-dioxane at facilities in TRI and DMR is limited; therefore, there is some uncertainty as to whether all the sites assessed in this section are using 1,4-dioxane in a disposal capacity rather than a different OES. If the sites were categorized under a different OES, the annual wastewater discharges for each site would remain unchanged; however, average daily discharges may change depending on the number of operating days expected for the OES.</p> <p>Facilities reporting to TRI and DMR only report annual discharges; to assess daily discharges, EPA assumed 250 days/yr. of operation and</p>

Occupational Exposure Scenario (OES)	Overall Confidence in Release Estimates
	<p>averaged the annual discharges over the operating days. There is some uncertainty that all sites using 1,4-dioxane for disposal will operate for this duration; therefore, the average daily discharges may be higher if sites operate for fewer than 250 days/yr. or lower if they operate for greater than 250 days/yr. Furthermore, 1,4-dioxane concentrations in wastewater discharges at each site may vary from day-to-day such that on any given day the actual daily discharges may be higher or lower than the estimated average daily discharge. Based on this information, EPA has a medium confidence in the wastewater discharge estimates.</p>

2.3 Environmental Exposures

EPA presents an analysis on environmental exposures to aquatic species based on releases to surface water. The 2014-2015 TRI dataset used as the basis for TRI releases in the first-tier aquatic exposure modeling was updated using data from [TRI Explorer](#). In response to public comment, the TRI analysis was also augmented to include indirect discharge sites, *i.e.*, those reporting off-site waste transfers to POTWs for treatment. 1,4-dioxane is present in environmental media such as groundwater, surface water, and air. EPA conducted analysis of the environmental release pathways based on a qualitative assessment of the physical-chemical properties and fate of 1,4-dioxane in the environment (described in Section 2.1), and a quantitative comparison of hazards and exposures for aquatic organisms as described in Section 4.1.

2.3.1 Environmental Exposures – Aquatic Pathway

An aquatic exposure assessment was conducted using TRI and DMR release information to model predicted surface water concentrations near discharging facilities. To examine whether near-facility surface water concentrations could approach 1,4-dioxane’s concentrations of concern, EPA employed a conservative approach, using available modeling tools and data to estimate near-facility surface water concentrations resulting from reported releases of 1,4-dioxane to surface water. High-end surface water concentrations (*i.e.*, those obtained assuming low receiving water body stream flows) from all [E-FAST 2014](#) ([U.S. EPA, 2014c](#)) runs ranged from 2.37E-08 µg/L to 11,500 µg/L. See Appendix E for results of this first-tier analysis, including the site-specific discharges modeled. Facility-specific release information is shown in the supplemental file [*Aquatic Exposure Screen Facility Information*].

In Section 2.2, more recent 2018 TRI and DMR data were used to estimate surface water releases for Occupational Exposure Scenarios (OES) within the scope of this evaluation. These estimated releases were as high as 67.7 kg/site/day for 250 days – for the Industrial Uses OES. The releases modeled as part of this first-tier aquatic exposure assessment (see Appendix E) were generally of greater magnitude, as they were based on top dischargers (per DMR and TRI), irrespective of scoped conditions of use or OES. Modeling the maximum water releases from the Industrial Use OES through E-FAST using conservative assumptions (*i.e.*, 67.7 kg/site/day for 250 days, 24

unspecified sites, generic SIC code with conservative stream flow assumptions, and 0% removal during wastewater treatment) results in a high-end surface water concentration of 8,724 µg/L, which is still less than the chronic COC of 14,500 µg/L. Therefore, the incorporation of the more recent OES release estimates would not have altered the conclusions of the screening-level assessment undertaken during problem formulation.

National-scale monitoring data from EPA's STorage and RETreival (STORET) and National Water Information System (NWIS) for the past ten years, shows that 1,4-dioxane is detected in surface water. The data points show a detection rate of approximately 6% for this media, with detections ranging from 0.568 to 100 µg/L.

2.4 Human Exposures

2.4.1 Occupational Exposures

Occupational exposures could be direct or indirect and the magnitude of exposure for an occupational worker could be a function of timeframe of exposures. The duration of exposure, which depends on occupational mobility, could vary for different population groups. ONUs are workers at the facility who neither directly perform activities near the 1,4-dioxane source area nor regularly handle 1,4-dioxane. Workers that are directly handling 1,4-dioxane and/or perform activities near sources of 1,4-dioxane are in the near field and are called workers throughout this risk evaluation. The near-field is defined as a volume of air within one-meter in any direction of the worker's head and the far-field comprises the remainder of the room ([Tielemans et al., 2008](#)). The source areas/exposure zones are determined by several factors such as the quantity of 1,4-dioxane releases, ventilation of the facility, vapor pressure and emission potential of the chemical, process temperature, size of the room, job tasks, and modes of chemical dispersal from activities ([Leblanc et al., 2018](#)). Corn and Esmen ([1979](#)) indicated that the assignment of zones is a professional judgment and not a scientific exercise. The job classifications for occupational users and non-occupational users are also dependent on the conditions of use of 1,4-dioxane, size and type of facility, and operation practice. The activities performed by occupational users and non-occupational users could overlap depending on conditions of use and facility. A large manufacturing facility includes supervisors, managers, and tradesmen, who may be co-located in the manufacturing floor, do not perform tasks that result in the same level of exposures as workers. However, a small or medium facility may have employees who perform activities as occupational users and non-occupational users throughout the workday. Occupational users and non-occupational users would not be able to be distinguished in groupings of employees due to overlapping tasks they typically perform.

EPA evaluated acute and chronic inhalation exposures to workers and ONUs in association with 1,4-dioxane manufacturing, import and repackaging, its use in industrial applications, open system functional fluids, spray polyurethane foam insulation, laboratory chemicals, film cement, printing inks (3D), dry film lubricant, and disposal. Appendix G.6 provides additional detail on the mapping of the conditions of use to the Occupational Exposure Scenario (OES) groups used in this risk evaluation. EPA used inhalation monitoring data from literature sources where available and that met data evaluation criteria (see Section 1.5); and modeling approaches to estimate potential inhalation exposures where inhalation monitoring data were not available. EPA modeled inhalation exposures using the following models: the *EPA AP-42 Loading Model*, the *EPA Mass Balance Inhalation Model*, and the *EPA Total PNOR PEL-Limiting Model*. More

information about these models may be found in Section 2.4.1.1. EPA also estimated dermal doses for workers in these scenarios since dermal monitoring data were not reasonably available. EPA modeled dermal doses using the *EPA Dermal Exposure to Volatile Liquids Model* which improves upon the existing *EPA 2-Hand Dermal Exposure* model by accounting for the effect of evaporation on dermal absorption for volatile chemicals and the potential exposure reduction due to glove use. More information about this model and how it was used may be found in Section 2.4.1.1.13 and Appendix G.7. EPA does not expect dermal exposures for occupational non-users due to no direct contact with the chemical.

Components of the Occupational Exposure Assessment

The occupational exposure assessment for each condition of use comprises the following components:

- **Process Description** of the condition of use, including the role of the chemical in the use; process vessels, equipment, and tools used during the condition of use; and descriptions of the worker activities, including an assessment for potential points of worker exposure.
- **Number of Sites** that use the chemical for the given condition of use.
- **Number of Workers and ONUs** potentially exposed to the chemical for the given condition of use. CDR data to identify the number of sites where exposure may occur and approximate workers who may be exposed to the chemicals. Unless mentioned otherwise in this report, the total number of workers and ONUs are number of personnel per site per day. The details on estimation of the number of workers and ONUs are discussed in Sections 2.4.1.1 for each condition of use, and Appendix G.5.
- **Central tendency and high-end estimates of inhalation exposure** to workers and occupational non-users. See Section 2.4.1.1 for a discussion of EPA's statistical analysis approach for assessing inhalation exposure.
- **Dermal Exposure** estimates for multiple scenarios, accounting for simultaneous absorption and evaporation, and different protection factors of glove use.
- **Users** include female and male adult workers (>16 years old) exposed to 1,4-dioxane for 8-hour exposure
- **ONUs** include female and male adult workers (>16 years old) exposed to 1,4-dioxane indirectly by being in the same work area of the building.

The OSHA respiratory protection standard, 29 CFR § 1910.134(a)(1), requires employers to utilize the hierarchy of controls for reducing or removing chemical hazards. The hierarchy of controls indicates that the most effective control is elimination, followed by substitution, and then engineering controls. These are followed by administrative controls and the use of PPE. The respiratory protection standard requires the use of feasible engineering controls as the primary means to control air contaminants. Respirators are required when effective engineering controls are not feasible. They are the last means of worker protection in the hierarchy of controls. When effective engineering and administrative controls are not feasible to adequately protect workers and maintain compliance with other OSHA statutory and regulatory requirements under 29 CFR § 1910.1000, employers should utilize respiratory protective equipment (29 CFR § 1910.134).

If information and data indicate that use or handling of a chemical cannot, under worst-case conditions, release concentrations of a respiratory hazard above a level that would trigger the need for a respirator or require use of a more protective respirator, employees would not be

assumed to wear them. Employers also use engineering or administrative controls to bring employee exposures below permissible exposure limits for airborne contaminants. Respirators would be used to supplement engineering and administrative controls only when these controls cannot be feasibly implemented to reduce employee exposure to permissible levels.

2.4.1.1 Occupational Exposures Approach and Methodology

EPA performed a literature search to find descriptions of processes involving 1,4-dioxane and worker activities that could potentially result in occupational exposures. The on-topic sources were then screened against inclusion criteria in the RESO (Receptors, Exposures, Setting/Scenario, Outcomes) statement and the relevant sources were further evaluated using the data quality criteria in the *Application of Systematic Review in TSCA Risk Evaluations* ([U.S. EPA, 2018b](#)). EPA identified 98 potentially useful sources based on literature search, of which 65 sources were determined to have potentially useful exposure information (see Figure 1-6). Sources with an overall confidence score of less than 4 were considered acceptable in the systematic review. Of these 65 sources, 27 were deemed to be acceptable. Sixteen of the acceptable sources were determined to have exposure data relevant to the conditions of use and were therefore used in this evaluation. A summary of the data quality evaluation results for the 1,4-dioxane occupational exposure sources are presented in Appendix G.1 (“*Systematic Review Supplemental File for the TSCA Risk Evaluation: Data Quality Evaluation for Occupational Exposure and Release Data*”).

For the integration of occupational exposure data/information, EPA considered any relevant data that it determined to be acceptable for use. The hierarchy found later in this section under “*General Inhalation Exposures Approach and Methodology*” presents the preferences among the primary types of data/information to be analyzed, synthesized and integrated for the occupational exposure assessments in this risk evaluation.

Additional Data Sources

EPA used a variety of sources to supplement the data found through the Systematic Review process. The additional sources included relevant NIOSH Health Hazard Evaluations, Generic Scenarios, and Emission Scenario Documents. These sources were sometimes used to provide process descriptions of the conditions of use as well as estimates for the number of sites and worker counts. An example is shown below.

CDR data were used to provide a basis to estimate the numbers of sites, workers, and ONUs. EPA supplemented the available CDR data with U.S. economic data using the following methods:

- Identification of the North American Industry Classification System (NAICS) codes for the industry sectors associated with the uses;
- Estimation of total employment by industry/occupation combination using the Bureau of Labor Statistics’ Occupational Employment Statistics (OES) data ([BLS, 2016](#));
- Refinement of the OES estimates where they are not sufficiently detailed by using the U.S. Census’ Statistics of US Businesses (SUSB) ([U.S. Census Bureau, 2016a](#)) data on total employment by 6-digit NAICS;
- Use market penetration data (where available) to estimate the percentage of employees likely to be using 1,4-dioxane instead of other chemicals;

- Combine the data generated in previous four bullets to produce an estimate of the number of establishments and employees using 1,4-dioxane in each industry/occupation combination, and sum these to arrive at a total estimate of the number of employees with exposure.

Market penetration data for 1,4-dioxane were not available for any condition of use. Without these data, it is unknown what portion of a given set of sites use 1,4-dioxane. In absence of this information, EPA generally assumes that all sites involve 1,4-dioxane. Therefore, site, worker, and ONU numbers considered could be overestimated.

EPA developed occupational exposure values representative of *central tendency* conditions and *high-end* conditions. A central tendency was assumed to be representative of occupational exposures in the center of the distribution for a given condition of use. EPA used the 50th percentile (median), mean (arithmetic or geometric), or mode of a distribution as representative of the central tendency scenario. EPA's preference was to provide the 50th percentile of the distribution. However, if the full distribution was not known, EPA assumed that the mean, mode, or midpoint of the distribution represented the central tendency depending on the statistics available for the distribution ([U.S. EPA, 1992](#)).

A high-end exposure estimate was defined to be representative of occupational exposures that occur at probabilities above the 90th percentile but below the 99.9th percentile, the exposure of the individual with the highest exposure ([U.S. EPA, 1992](#)). EPA considered high-end results at the 95th percentile. If the 95th percentile was not available, EPA used a different percentile greater than or equal to the 90th percentile but less than or equal to the 99th percentile, depending on the statistics available for the distribution. If the full distribution was not known and the preferred statistics were not available, EPA estimated a maximum or bounding estimate in lieu of the high-end occupational exposure estimates. In each case, EPA makes clear the actual percentile that was used.

For occupational exposures, EPA used measured or modeled air concentrations to calculate exposure concentration metrics essential for risk assessment. These exposures are presented as 8-hour time weighted averages (TWAs) and used to calculate acute exposure concentrations (AECs), average daily concentrations (ADCs), and lifetime average daily concentrations (LADCs). The ADC is used to estimate chronic, non-cancer risks and the LADC is used to estimate chronic, cancer risks. These calculations required additional parameter inputs, such as years of exposure, exposure duration and frequency, and lifetime years. See Appendix G.2 for more information about parameters and equations used to calculate acute and chronic exposures.

For the final exposure result metrics, each of the input parameters (*e.g.*, air concentrations, working years, exposure frequency, lifetime years) were *point estimates* (*i.e.*, a single descriptor or statistic, such as central tendency or high-end). EPA estimated a central tendency and high-end for each final exposure result metric using deterministic calculations and combinations of point estimates of each parameter. EPA documented the method and rationale for selecting parametric combinations to be representative of central tendency and high-end. A probabilistic approach was generally not used in cases where monitoring-based data were available, but models for that condition of use were not.

For occupational exposures, EPA used measured or estimated air concentrations to calculate exposure concentration metrics required for risk assessment, such as average daily concentration and lifetime average daily concentration. These calculations required additional parameter inputs, such as years of exposure, exposure duration and frequency, and lifetime years. EPA estimated exposure concentrations from monitoring data, modeling, or occupational exposure limits, and used each of these in its evidence integration to assess the strength of the evidence. For each use, EPA considered the assessment approach, the quality of the data and models, and uncertainties in assessment results to determine an overall level of confidence for the full shift data and modeled estimates. For the inhalation concentration monitoring data, strength of confidence is improved by the following factors: a) larger number of sites monitored, b) worker population groups included in monitoring, and c) higher systematic review data quality ratings. The strength of confidence in monitoring data is reduced by uncertainty of the representativeness of these data toward the true distribution of inhalation concentrations for the industries and sites covered by the use. For modeled air concentrations, strength of confidence is improved by the following factors: a) model validation, and b) full distributions of input parameters. The strength of confidence in modeled air concentration estimates is reduced by the uncertainty of the representativeness of the model or parameter inputs toward the true distribution of inhalation concentrations for the industries and sites covered by the use. For dermal dose rate estimates, strength of confidence is improved by the use of actual data rather than assumptions for input parameters. The strength of confidence in dermal potential dose rates is reduced by the uncertainty of the representativeness of the of the model or parameter inputs toward the true distribution of dermal doses for the industries and sites covered by the use.

Monitoring data of 1,4-dioxane considered from various types and key sources including the following:

- Personal sample monitoring data from directly applicable scenarios (*e.g.*, personal breathing zone (PBZ); non-CBI data from the Manufacturing scenario (such as BASF);
- Area sample monitoring data from directly applicable scenarios (*e.g.*, NIOSH HHE for the Film Cement scenario);
- Personal sample monitoring data from potentially applicable or similar scenarios (*e.g.*, PBZ data from a manufacturing site that makes a chemical that has physical properties similar to 1,4-dioxane);
- Area samples monitoring data from potentially applicable or similar scenarios (*e.g.*, area data from a site that processes a chemical that has physical properties similar to 1,4-dioxane)

Modeling approaches include the following monitoring data and key mathematical methodologies:

- Surrogate monitoring data from chemicals with similar properties. Surrogate data were used to estimate the inhalation exposure from the thickness verification step in the Spray Foam Application condition of use. Appendix G.6.7 provides additional details on this use of surrogate data.
- Fundamental modeling approaches (*e.g.*, modeling of the Spray Foam Application scenario); and
- Statistical regression modeling approaches

Occupational exposure limits considered include, but are not limited to, the following:

- Company-specific OELs (for site-specific exposure assessments, *e.g.*, there is only one manufacturer who provides to EPA their internal OEL but does not provide monitoring data)
- OSHA PEL
- Other occupational exposure limits (ACGIH TLV, NIOSH REL, Occupational Alliance for Risk Science (OARS) workplace environmental exposure level (WEEL) [formerly by AIHA])

EPA reviewed workplace inhalation monitoring data collected by government agencies such as OSHA and NIOSH, and monitoring data found in published literature (*i.e.*, personal exposure monitoring data and area monitoring data). Studies were evaluated using the evaluation strategies laid out in the *Application of Systematic Review in TSCA Risk Evaluations* ([U.S. EPA, 2018b](#)). The supplemental file provides details of the data evaluations, including scores for each metric and the overall study score for each information source.

Exposure values were calculated from the datasets provided in the sources depending on the size of the dataset. For datasets with six or more data points ([U.S. EPA, 1994a](#); [Hawkins et al., 1992](#)), central tendency and high-end exposures were estimated using the 50th percentile and 95th percentile, respectively. For datasets with three to five data points, central tendency exposure was calculated using the 50th percentile and the maximum was presented as the high-end exposure estimate. These data sets are considered to have relatively more uncertainty than datasets with more datapoints. For datasets with two data points, the midpoint was presented as a midpoint value and the higher of the two values was presented as a higher value. These data sets are generally considered to have high uncertainty. Finally, data sets with only one data point are considered indicating appropriate rationale, but EPA cannot determine the statistical representativeness of the values given the small sample size. Existing monitoring data such as worker breathing zone data may have been collected at areas or facilities where 1,4-dioxane releases have not occurred. As such these data sets are considered to have uncertainty associated with them.

EPA estimated exposures using the following models when exposure monitoring data were unavailable:

- *EPA AP-42 Loading Model* estimates vapor releases that occur when vapor is displaced by liquid during container loading. It calculates a vapor generation rate (G) using the physio-chemical properties of the chemical ([U.S. EPA, 2013b](#)).
- *EPA Mass Balance Inhalation Model* estimates occupational inhalation exposures assuming the air immediately around the source of exposure behaves as a well-mixed zone. EPA used the vapor generation rate (G), calculated using the *EPA AP-42 Loading Model*, in conjunction with this model to develop estimates of inhalation exposure ([U.S. EPA, 2013b](#)).
- *EPA Total PNOR PEL-Limiting Model* estimates occupational inhalation exposures to particulates containing the chemical. The estimate assumes that the worker exposure is equal to the OSHA Permissible Exposure Limit (PEL) for Particulates, Not Otherwise Regulated (PNOR), total particulate ([U.S. EPA, 2013b](#)).

Specific descriptions of the use of these models for each condition of use can be found in

Sections 2.4.1.1.1 - 2.4.1.1.12.

Respiratory Protection

OSHA’s Respiratory Protection Standard (29 CFR § 1910.134) provides a summary of respirator types by their assigned protection factor (APF). OSHA defines the APF to mean: the workplace level of respiratory protection that a respirator or class of respirators is expected to provide to employees when the employer implements a continuing, effective respiratory protection program according to the requirements of the OSHA Respiratory Protection Standard. OSHA recommends employers utilize the hierarchy of controls for reducing or removing hazardous exposures. The most effective controls are elimination, substitution, or engineering controls. Respirators, and any other personal protective equipment, are the last means of worker protection in the hierarchy of controls and should only be considered when process design and engineering controls cannot reduce workplace exposure to levels within regulation.

The United States has several regulatory and non-regulatory exposure limits for 1,4-dioxane: an OSHA PEL of 100 ppm 8-hour TWA (360 mg/m³) with a skin notation, a NIOSH Recommended Exposure Limit (REL) of 1 ppm (3.6 mg/m³) as a 30-minute ceiling and an American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Value (TLV) of 20 ppm TWA (72 mg/m³) (OSHA, 2005). If respirators are necessary in atmospheres that are not immediately dangerous to life or health, workers must use NIOSH-certified air-purifying respirators or NIOSH-approved supplied-air respirators with the appropriate APF. Respirators that meet these criteria include air-purifying respirators with organic vapor cartridges. Respirators must meet or exceed the required level of protection listed in Table 2-7. to meet NIOSH recommended a 1 ppm (3.6 mg/m³, 30 minute) ceiling because 1,4-dioxane is a potential human carcinogen (29 CFR § 1990).

The respirators should be used when effective engineering controls are not feasible as per OSHA’s 29 CFR § 1910.134. The knowledge of the range of respirator APFs is intended to assist employers in selecting the appropriate type of respirator that could provide a level of protection needed for a specific exposure scenario. Table 2-7. lists the range of APFs for respirators. The complexity and burden of wearing respirators increases with increasing APF. The APFs are not to be assumed to be interchangeable for any conditions of use, any workplace, or any worker or ONU.

Table 2-7. Assigned Protection Factors for Respirators in OSHA Standard 29 CFR § 1910.134

Type of Respirator	Quarter Mask	Half Mask	Full Facepiece	Helmet/Hood	Loose-fitting Facepiece
1. Air-Purifying Respirator	5	10	50		
2. Power Air-Purifying Respirator (PAPR)		50	1,000	25/1,000	25
3. Supplied-Air Respirator (SAR) or Airline Respirator					
Demand mode		10	50		
Continuous flow mode		50	1,000	25/1,000	25

Pressure-demand or other positive-pressure mode		50	1,000		
4. Self-Contained Breathing Apparatus (SCBA)					
Demand mode		10	50	50	
Pressure-demand or other positive-pressure mode (<i>e.g.</i> , open/closed circuit)			10,000	10,000	
Source: 29 CFR § 1910.134					

The performance of respiratory protective equipment programs varied across industry. The National Institute for Occupational Safety and Health (NIOSH) and the U.S. Department of Labor’s Bureau of Labor Statistics (BLS) conducted a voluntary survey of U.S. employers regarding the use of respiratory protective devices between August 2001 and January 2002. The survey had a 75.5% response rate ([NIOSH, 2003](#)). A voluntary survey may not be representative of all private industry respirator use patterns as some establishments with low or no respirator use could have chosen to not respond to the survey. Therefore, results of the survey could potentially be biased towards higher respirator use. NIOSH and BLS estimated about 619,400 establishments used respirators for voluntary or required purposes (including emergency and non-emergency uses). About 281,800 establishments (45%) were estimated to have had respirator use for required purposes in the 12 months prior to the survey. The 281,800 establishments estimated to have had respirator use for required purposes were estimated to be approximately 4.5% of all private industry establishments in the U.S. at the time ([NIOSH, 2003](#)). In a more recent article, Bell et al. ([2012](#)) reported cross-industry analysis for 20 companies, the majority representing small- or medium-sized enterprises, across a number of different sectors. Four distinct groups emerged from the 20 sites, ranging from learners (low theoretical competence and practical control - 4 sites), developers (acceptable theoretical competence and low practical control - 5 sites), and fortuitous (low theoretical competence and acceptable practical control - two sites), to proficient (acceptable theoretical competence and practical control - nine sites). None of the companies were achieving optimal control using the respiratory protective equipment. Widespread inadequacies were found with program implementation, particularly training, supervision, and maintenance. In a separate study, the University of Pittsburgh, CDC, and RAND Corporation used the OSHA data base to examine all inspections in manufacturing in 47 states from 1999 through 2006 ([Mendeloff et al., 2013](#)); the examination starts with 1999 because an expanded OSHA respiratory program standard became effective in late 1998. The article identified inspections and establishments at which respiratory protection violations were cited, and it compares the prevalence of violations by industry with the prevalence reported in the BLS survey of respirator use. The pattern of noncompliance across industries mostly mirrored the survey findings about the prevalence of requirements for respirator use. The probability of citing a respiratory protection violation was similar across establishment size categories, except for a large drop for establishments with over 200 workers. The presence of a worker accompanying the inspector increased the probability that a respiratory program violation could be cited; the presence of a union slightly decreased it. OSHA’s fatality reports from 1990 to 2012 were analyzed by [Cowan et al. \(2017\)](#) to characterize historical trends in fatalities associated with respirators. Industry- and time-specific trends were evaluated to determine the effect on respirator-related fatalities. Cowan et al. ([2017](#)) reported 174 respirator related deaths, and 79% of the fatalities were associated with asphyxia associated with improper employee use or lack of employer compliance.

Estimating the Number of Workers and Occupational Non-Users (ONUs)

EPA used the following steps to estimate the number of workers and ONUs who may be potentially exposed to 1,4-dioxane in each condition of use: 1) identified the North American Industry Classification System (NAICS) codes for the industry sectors associated with each condition of use; 2) estimated total employment by industry/occupation combination using the Bureau of Labor Statistics' Occupational Employment Statistics (OES) data ([BLS, 2016](#)); 3) refined the OES estimates where they are not sufficiently granular by using the U.S. Census' ([2016b](#)) Statistics of U.S. Businesses (SUSB) data on total employment by 6-digit NAICS; 4) estimated the percentage of employees likely to be using 1,4-dioxane instead of other chemicals (*i.e.*, the market penetration of 1,4-dioxane in the condition of use); 5) estimated the number of sites and number of potentially exposed employees per site; and 6) estimated the number of potentially exposed employees within the condition of use.

See Appendix G.5 for more information about the approach used to estimate potentially exposed workers and ONUs.

2.4.1.1.1 Manufacturing

1,4-Dioxane is commercially manufactured by the acid-catalyzed dehydration of diethylene glycol, which in turn is obtained from the hydrolysis of ethylene oxide. The information and data quality evaluation to assess occupational exposures during manufacturing is listed in Table 2-8.. See Appendix G.1 for additional details.

Table 2-8. Manufacturing Worker Exposure Data Evaluation

Worker Activity or Sampling Location	Data Type	Number of Samples	Data Quality Rating	Source Reference
Unknown	PBZ Monitoring	28	High	BASF (2016)
Routine duties, neutralization, evaporator dump	PBZ Monitoring	4	High	BASF (2017)
N/A	CDR Data – Number of sites and workers	N/A	High	U.S. EPA (2016c)

Occupational exposures to 1,4-dioxane during manufacturing were estimated by evaluating full-shift, personal breathing zone (PBZ) monitoring data obtained by BASF during internal industrial hygiene (IH) studies. BASF monitoring data were selected as it is more relevant and recent compared to the manufacturing data cited in other sources [such as [ECJRC \(2002\)](#)] and lack of availability of monitoring data from other U.S. manufacturer. For example, the data cited in the 2002 EU Risk Assessment ranges from 1976 to 1998 while the data provided by BASF ranged from 2006 to 2017 ([BASF, 2017, 2016](#); [ECJRC, 2002](#)). The BASF data had limitations including lack of descriptions of worker tasks, exposure sources, and possible engineering controls. The BASF ([2016](#)) workplace monitoring data were real-time PBZ exposure measurements. The data were assumed to be relevant to worker activities and were 8-hour TWA measurements. EPA estimated the total number of workers who could be potentially exposed as 78 and the number occupational non-users as 36 ([U.S. EPA, 2016c](#)).

Acute and chronic occupational inhalation exposures during manufacturing of 1,4-dioxane are summarized in Table 2-9.. EPA calculated the 95th percentile and 50th percentile of the available 30 data points for inhalation exposure monitoring data to assess the high-end and central tendency exposures, respectively. Using these 8-hour TWA exposure concentrations, EPA calculated the ADC and LADC using the equations in Appendix G.2. Additional information regarding the calculations is provided in Appendix G.6.1.

Table 2-9. Acute and Chronic Inhalation Exposures of Worker for Manufacturing Based on Monitoring Data

Exposure Type	Central Tendency (50 th percentile) (mg/m ³)	High-end (95 th Percentile) (mg/m ³)	Data Quality Rating of Associated Source ^a
15-minute TWA (Evaporator Dump)	N/A	137*	High
8-hour TWA Exposure Concentrations	0.42	7.7	High
8-hour TWA Acute Exposure Concentration (AEC)	0.42	7.7	High
Average Daily Concentration (ADC)	0.40	7.4	High
Lifetime Average Daily Concentration (LADC)	0.16	3.8	High

N/A = not applicable. *: The higher of the two reported ([BASF, 2017](#)) 15-minute short-term exposures values (137 mg/m³ from the evaporator dump step), considered as high-end, short-term exposure.
^a See Table 2-8. for corresponding references.

EPA estimated that 78 workers and 36 ONUs could be exposed at sites that manufacture 1,4-dioxane in the U.S. EPA used worker number estimates reported in CDR and refined them using BLS and SUSB data for the applicable NAICS codes. Additional information about the steps used to estimate the number of potentially exposed workers and ONUs are available in Appendix G.5. Exposure data for ONUs were not available. ONUs are likely to have lower exposures than workers. ONUs for manufacturing include supervisors, managers, and tradesmen that may be in the manufacturing area, but do not perform tasks that result in the same level of exposures as production workers.

Key Uncertainties

The data sets lacked specific descriptions of worker tasks, exposure sources, and possible engineering controls to provide context. EPA assumed that the 2016 BASF data are PBZ measurements relevant to worker activities and are 8-hour TWA measurements. This assumption could underestimate exposures. The sampling rate was missing for some of the 2016 data, so EPA assumed the same sampling rate was applied for other data in the set. It is uncertain to what extent the limited monitoring data used to estimate inhalation exposures for this scenario is representative of occupational exposures in other manufacturing facility of 1,4-dioxane.

2.4.1.1.2 Import and Repackaging

The import of chemicals, such as 1,4-dioxane, involves chemical handling during storage, transportation, distribution, and packaging and processing. In addition, 1,4-dioxane shipped in bulk containers could be repackaged into smaller containers for resale, such as drums or bottles

using automatic, semi-automatic, or manual filling, sealing, labeling, and wrapping. The shipment methods and regulations of 1,4-dioxane require the material to be properly classed, described, packaged, marked, labeled, and in condition for shipment (49 CFR § 171-177). To avoid spilling, 1,4-dioxane needs to be transported in securely sealed glass bottles or equivalent containers that should themselves be placed inside strong screw-cap or snap-top containers that will not open when dropped. Both the bottle and the outside container should be appropriately labelled. Airtight packaging is required by the International Labor Organization’s (ILO) International Chemical Safety Cards (ICSC).

The information and data quality evaluation to assess occupational exposures from import and repackaging is listed in Table 2-10.. See Appendix G.1 for more details about the data quality evaluation.

Table 2-10. Import and Repackaging Data Source Evaluation

Worker Activity or Sampling Location	Data Type	Number of Samples	Data Quality Rating	Source Reference
N/A	CDR Data – Number of sites and workers	N/A	High	U.S. EPA (2016c)

EPA modeled central tendency and high-end occupational inhalation exposures for this scenario using the *EPA AP-42 Loading Model* and the *EPA Mass Balance Inhalation Model* ([U.S. EPA, 2013b](#)) and the values listed in Appendix G.2. EPA used a Monte Carlo simulation to vary the saturation factor (f), ventilation rate (Q), and mixing factor (k) and calculated the 95th percentile and 50th percentile exposures during unloading directly in the simulation to assess the high-end and central tendency exposures, respectively. See Appendix G.4 for more information about the Monte Carlo simulation. Since some sites may only repackage into either bottles or drums and some sites may use both types of containers, EPA estimated exposures for both bottles and drums. EPA used these values to calculate acute and chronic inhalation exposures in the Monte Carlo simulation, varying working years (WY) and the number of days, using the equations in Appendix G.2. EPA determined once per day short-term exposures of 170 to 610 mg/m³ with a duration of 30 minutes may occur during drum unloading as central tendency and high-end short-term exposures, respectively. These estimates are presented in Table 2-10.

EPA estimated that the total number of potentially exposed workers could be between 50 to 198 workers, and occupational non-users could be between 12 to 49. EPA used worker number estimates reported in CDR and refined them using BLS and SUSB data for the applicable NAICS codes. See Appendix G.5 for more information about the steps used to estimate the number of potentially exposed workers and ONUs. Additional information including specific methodology and assumptions for modeling exposures are described in Appendix G.6.2.

Table 2-11. Acute and Chronic Inhalation Exposures of Workers for Import and Repackaging Based on Modeling

Exposure Type	Central Tendency (50 th Percentile) (mg/m ³)	High-end (95 th Percentile) (mg/m ³)	Data Quality Rating of Associated Source ^a
Short-Term Exposure (0.5-hour TWA)	170	610	N/A - Modeled Data
Bottle 8-hour TWA Exposure Concentration	9.3	33	N/A - Modeled Data
Drum 8-hour TWA Exposure	11	38	N/A - Modeled Data
Bottle 8-hour Acute Exposure Concentration (AEC)	9.3	33	N/A - Modeled Data
Drum 8-hour Acute Exposure Concentration (AEC)	11	38	N/A - Modeled Data
Average Daily Concentration (ADC)	0.46	3.4	N/A - Modeled Data
Lifetime Average Daily Concentration (LADC)	0.18	1.3	N/A - Modeled Data
^a See Table 2-10. for corresponding references.			

Exposure data for ONUs were not available. The ONU exposures are anticipated to be lower than worker exposures, since ONUs do not typically directly handle the chemical. Only inhalation exposures to vapors or incidental dermal exposures could be applicable to ONUs, which will likely be less than worker exposures.

Key Uncertainties

EPA modeled inhalation exposures using the *EPA AP-42 Loading Model* and the *EPA Mass Balance Inhalation Model*. Process specifics for import and repackaging at these sites were not available, therefore, EPA assumed certain process details, such as container sizes and loading and unloading frequency. Additionally, EPA assumed that the process steps associated with this scenario occur indoors, without engineering controls, and in an open-system environment where vapors freely escape. In the absence of industry-specific information, these assumptions provide for conservative estimates for exposures during this operation. Actual exposures may be less due to various factors including closed-system loading and unloading, the use of vapor recovery systems, or the automation of various process steps.

2.4.1.1.3 Recycling

In the *Problem Formulation of the Risk Evaluation for 1,4-Dioxane* (U.S. EPA, 2018c), EPA identified recycling as a separate occupational exposure scenario. EPA assessed the exposure profile and activities of the recycling process to be more equivalent, and in many cases synonymous with the Industrial Uses group, described in Section 2.4.1.1.4. Operations at dedicated recycling facilities often mirror the activities performed at industrial use sites as they receive much of the spent 1,4-dioxane in smaller containers such as 55-gallon drums rather than the bulk containers that a traditional processing site would receive. Any exposures from worker activities, such as unloading, maintenance, and drumming spent 1,4-dioxane for disposal are

assessed in Section 2.4.1.1.4.

2.4.1.1.4 Industrial Uses

1,4-Dioxane is used as a process solvent, an intermediate, and a catalyst in several industrial applications. For this assessment, these uses have been grouped into a broad category called “industrial uses.” The relevant industries and uses include the following:

- Process solvent in basic organic chemical manufacturing;
- Wetting and dispersing agent in textile processing¹⁰;
- Wood pulping¹⁰;
- Extraction of animal and vegetable oils¹⁰;
- Purification of process intermediates;
- Etching of fluoropolymers;
- Agricultural chemical intermediate;
- Polymerization catalyst;
- Plasticizer intermediate;
- Plastics modeling (thermoforming); and
- Catalysts and reagents for anhydrous acid reactions, brominations, and sulfonations.

EPA did not find specific details for most of these processes, but typical operations are expected to be similar across these uses. For uses grouped in this “industrial uses” category, it is expected that 1,4-dioxane is received as a solvent, intermediate, or catalyst in its final formulation and requires no further processing. The 1,4-dioxane is unloaded and fed to intermediate storage or directly used in the process. If it is being used as an intermediate, it will likely be consumed during the reaction. For solvents or catalysts, spent 1,4-dioxane will be collected at the end of the process for reuse or disposal.

The information and data quality evaluation to assess occupational exposures from industrial uses is listed in Table 2-12.. See Appendix G.1 for more details about the data quality evaluation.

¹⁰ These uses were evaluated but are likely not current uses of 1,4-dioxane.

Table 2-12. Industrial Uses Data Source Evaluation

Worker Activity or Sampling Location	Data Type	Number of Samples	Data Quality Rating	Source Reference
Medicine Manufacture	PBZ and Area Monitoring	20	High	ECJRC (2002)
Pharmaceutical Production	PBZ Monitoring	<30	High	ECJRC (2002)
Use (e.g., as solvent) in other productions	PBZ Monitoring	194	High	ECJRC (2002)
Use (e.g., as solvent) in other productions	PBZ Monitoring	49	High	ECJRC (2002)
Extractant in medicine manufacturing	EASE Modeling	N/A – estimates from modeling	High	ECJRC (2002)
N/A	CDR Data – Number of sites and workers	N/A	High	U.S. EPA (2016c)

N/A = Not Applicable.

Occupational exposure for 1,4-dioxane used as an industrial chemical was determined using estimates provided in the EU Risk Assessment for 1,4-dioxane ([ECJRC, 2002](#)). The report proposed a “typical concentration” of 5 mg/m³ and a “reasonable worst-case” concentration of 20 mg/m³ to estimate the inhalation exposures for various industrial uses. These estimates were based on full-shift monitoring data provided by other sources cited in the report, which covered use in the pharmaceutical industry and use as a solvent in industrial processes. However, the report did not provide details about how these values were calculated, therefore, it is unclear what percentile is represented when an exposure is described as “typical” or “reasonable worst case” (*i.e.*, 50th and 95th percentile).). These “typical” and “reasonable worst-case” full-shift estimates were assumed to be 8-hour TWA values and equivalent to central tendency and high-end values, respectively. Acute and chronic inhalation exposures for Industrial Uses are calculated using the equations in Appendix G.2. Results of these calculations are summarized below in Table 2-12.

EPA estimated a total of 768 workers and 312 occupational non-users may be exposed across all sites. EPA estimated the number of potentially exposed workers and ONUs per site using BLS and SUSB data for the applicable NAICS codes. EPA used the number of sites reported in the 2018 TRI and 2018 DMR to estimate the total number of workers and ONUs that may be exposed. Additional information including typical industrial use, monitoring data, and estimation of high-end inhalation values for 1,4-dioxane used as an industrial chemical are described in Appendix G.6.3.

Table 2-13. Acute and Chronic Inhalation Exposures of Worker for Industrial Uses Based on Monitoring Data

Exposure Type	Central Tendency ^a (EU RAR: Typical Concentration) (mg/m ³)	High-End ^a (EU RAR: Reasonable Worst Case Concentration) (mg/m ³)	Data quality rating of Associated Source ^b
8-hour TWA Exposure Concentrations	5.0	20	High
8-hour TWA Acute Exposure Concentration (AEC)	5.0	20	High
Average Daily Concentration (ADC)	4.8	19	High
Lifetime Average Daily Concentration (LADC)	1.9	9.9	High
^a The risk assessment did not provide details about how these values were calculated, therefore, it is unclear what percentile is represented when an exposure is described as “typical” or “reasonable worst case” (<i>i.e.</i> , 50 th and 95 th percentile). ^b See Table 2-12. for corresponding references.			

Exposure data for ONUs were not available. ONU exposures are lower than worker exposures, since ONUs do not typically directly handle the chemical. Only inhalation exposures to vapors are expected, which will likely be less than worker exposures.

Key Uncertainties

EPA used estimates based on exposure data from the 2002 EU Risk Assessment for 1,4-dioxane in order to estimate the inhalation exposures for this scenario. The data sets used are limited and mostly lacked specific descriptions of worker tasks, exposure sources, and possible engineering controls to provide context. Most of the datasets were only presented in ranges with key statistics (*i.e.*, median or average and 90th percentile), so EPA was unable to directly calculate final values from the raw data and relied on estimates provided in the 2002 EU Risk Assessment. The assessment also did not explain how the final 8-hour TWA exposure values of 5 and 20 mg/m³ were derived. These values were reported by the EU to be full-shift values, but EPA assumed them to be 8-hour TWA values.

2.4.1.1.5 Functional Fluids (Open System)

1,4-Dioxane may be a component of functional fluids that are used in open systems such as metalworking fluids and cutting and tapping fluids based on information safety data sheets (SDSs) listed in *Preliminary Information on Manufacturing, Processing, Distribution, Use, and Disposal: 1,4-Dioxane* ([U.S. EPA, 2017d](#)).

The information and data quality evaluation used to assess occupational exposures for functional fluids (open systems) are listed in Table 2-14.. See Appendix G.1 for more details about the data quality evaluation.

Table 2-14. Functional Fluids (Open System) Data Evaluation

Worker Activity or Sampling Location	Data Type ^a	Number of Samples	Data quality rating	Source Reference
Threader, Broaching, Apex Drill, and Lunch Tables	Area Monitoring	4	High	Burton and Driscoll (1997)
Transfer Lines, Roughing, Four-way, Multiple, Screw Machine-Lathing, and Apex Drill	PBZ Monitoring	6	High	Burton and Driscoll (1997)
a: PBZ monitoring data were superseded by Monte Carlo simulation. The area monitoring data were used to estimate ONU exposures.				

Occupational exposure for 1,4-dioxane use as an open system functional fluid was modeled using the *EPA AP-42 Loading Model* and the *EPA Mass Balance Inhalation Model*. EPA used a Monte Carlo simulation to vary the saturation factor (f), ventilation rate (Q), and mixing factor (k). See Appendix G.4 for more information about the Monte Carlo simulation. EPA calculated the 95th percentile and 50th percentile exposures during unloading directly in the simulation to assess the high-end and central tendency exposures, respectively. EPA used these values to calculate acute and chronic inhalation exposures in the Monte Carlo simulation, varying working years (WY), using the equations in Appendix G.2. These results are summarized in Table 2-15.. A 1997 NIOSH Health Hazard Evaluation (HHE) report provided personal breathing zone (PBZ) samples collected at a facility that manufactures axels for trucks and recreational vehicles ([Burton and Driscoll, 1997](#)). The NIOSH HHE sample results were within the 10th percentile of the distribution¹¹ from the Monte Carlo simulation and contributed a minor effect to the overall distribution.

Table 2-15. Acute and Chronic Inhalation Exposures of Worker for Open System Functional Fluids Based on Modeling

Exposure Type	Central Tendency (50 th Percentile) (mg/m ³)	High-End (95 th Percentile) (mg/m ³)	Confidence Rating of Associated Source ^a
Short-Term Exposure (Drum Unloading, 0.05 hr)	0.17	0.61	N/A - Modeled Data
8-hour TWA Exposure Concentrations	1.1E-03	3.8E-03	N/A - Modeled Data
8-hour TWA Acute Exposure Concentration (AEC)	1.1E-03	3.8E-03	N/A - Modeled Data
Average Daily Concentration (ADC)	1.0E-03	3.7E-03	N/A - Modeled Data
Lifetime Average Daily Concentration (LADC)	3.9E-04	1.5E-03	N/A - Modeled Data
^a See Table 2-14. for corresponding references.			

¹¹ All points, except one from the HHE study ([Burton and Driscoll, 1997](#)), were within the 5th percentile from the Monte Carlo simulation. Only one value was within the 10th percentile.

The above values could be influenced by 1,4-dioxane’s high vapor pressure (40 mm Hg at 25°C) causing evaporation from droplets in the air, ventilation rate at the work facility, mixing factor, vapor saturation factor and other working condition variables. The concentration of 1,4-dioxane in the formulation could vary from 0.01 to 0.1 wt% resulting in a partial pressure that likely represents an insignificant source of exposure ([U.S. EPA, 2017d](#)). EPA estimated acute and chronic inhalation exposures using these values directly in the Monte Carlo simulation. EPA defined bounding estimates of the total number of potentially exposed workers as 69 to 4,094,000, and ONUs as three to 178,000. This estimate is based on worker numbers provided in the ESD ([OECD, 2011](#)) and 2018 DMR. Additional information including typical use, modeling methodology, and monitoring data are described in Appendix G.6.4.

To assess ONU inhalation exposures, EPA combined the area measurements taken from a variety of locations in the manufacturing facility into a single sample set with five datapoints ([Burton and Driscoll, 1997](#)). EPA calculated the 50th percentile of this data set to assess the central tendency exposure and presents the maximum as the high-end exposure (see Section 2.4.1.1). These results are summarized in Table 2-16.. The ONU exposures were less than the estimated central tendency and high-end values for workers, as expected.

Table 2-16. Acute and Chronic ONU Inhalation Exposures for Open System Functional Fluids Based on Monitoring Data

Exposure Type	Central Tendency (50 th Percentile) (mg/m ³)	High-End (Maximum) (mg/m ³)	Data quality rating of Associated Source ^a
8-hour TWA Exposure Concentrations	1.5E-4	2.5E-4	N/A - Modeled Data
8-hour TWA Acute Exposure Concentration (AEC)	1.5E-4	2.5E-4	N/A - Modeled Data
Average Daily Concentration (ADC)	1.4E-04	2.4E-04	N/A - Modeled Data
Lifetime Average Daily Concentration (LADC)	5.7E-05	1.2E-04	N/A - Modeled Data
^a See Table 2-14. for corresponding references.			

Key Uncertainties

EPA used exposure data for metalworking fluids from the 2011 OECD ESD on the Use of Metalworking Fluids and from a 1997 NIOSH HHE. Neither dataset specifically addressed exposures to 1,4-dioxane. EPA used concentrations provided in relevant SDSs to estimate these exposures. In addition, the HHE was conducted to address concerns regarding adverse human health effects reported following exposures during use and therefore the measured exposures may be inherently biased high.

The data did not estimate exposures during chemical unloading; therefore, EPA estimated this exposure using the *EPA AP-42 Loading Model* and the *EPA Mass Balance Inhalation Model*. These models assume that the unloading of fluid containing 1,4-dioxane occurs indoors, without engineering controls, and in an open-system environment where vapors freely escape. In the

absence of industry-specific information, these assumptions provide for conservative estimates for exposures during this unloading operation. Actual exposures may be less due to various factors including closed-system unloading, the use of vapor recovery systems, or an automated unloading process.

2.4.1.1.6 Functional Fluids (Closed System)

EPA identified closed system functional fluids as a condition of use for 1,4-dioxane in the problem formulation ([U.S. EPA, 2018c](#)). The *Preliminary Information on Manufacturing, Processing, Distribution, Use, and Disposal: 1,4-Dioxane* presented three SDSs for closed system functional fluids (hydraulic fluids). These SDSs did not list content information for 1,4-dioxane, which suggests that it is not an intended component in these products ([U.S. EPA, 2017d](#)). BASF manufactures neat 1,4-dioxane (anhydrous, 99.8% minimum) as well as products that contain 1,4-dioxane. In a public comment from 2017, BASF provided a table of products that contain residual amounts of 1,4-dioxane. BASF specifically stated that the residual 1,4-dioxane is a byproduct of the ethoxylation process and is not an intended component. One of these products (Pluriol E 400™ or equivalent commercial polyethylene glycols) could be used as a hydraulic or heat transfer fluid and has a residual level of less than 25 ppm (0.0025%) ([BASF, 2017](#)). This concentration is lower than the concentration assessed for open system functional fluids in Section 2.4.1.1.5, which was 0.1%, or 1,000 ppm. Additionally, EPA reviewed 91 literature sources and performed targeted internet searches and did not find any references to the use of 1,4-dioxane in closed system functional fluids. A closed system precludes exposure as the transfer device could prohibit the escape of chemicals outside the system. Due to the lack of evidence supporting its intended use in closed system functional fluids, EPA did not assess occupational exposures for this use of 1,4-dioxane.

2.4.1.1.7 Laboratory Chemicals

1,4-Dioxane is used in a variety of laboratory applications, which include, but are not limited to, the following:

- Chemical reagent during lab scale reactions;
- Reference material for quality control or calibration;
- Medium for spectroscopic and photometric measurement;
- Liquid scintillation counting medium;
- Stable reaction medium;
- Cryoscopic solvent for molecular mass determinations; and
- Preparation of histological sections for microscopic examination.

Occupational exposure for 1,4-dioxane used as a laboratory chemical for research/development and analytical applications was determined by evaluating available monitoring data including short-term and 8-hour TWA exposures for workers in a laboratory setting ([ECJRC, 2002](#); [NICNAS, 1998](#)). The information and data evaluation for exposures to laboratory chemicals by the workers are listed in Table 2-17.. See Appendix G.1 for more details about the data quality evaluation.

Table 2-17. Laboratory Chemicals Data Evaluation

Worker Activity or Sampling Location	Data Type	Number of Samples	Data quality rating	Source Reference
Solvent extraction and TLC	PBZ Monitoring Data	Unknown	High	NICNAS (1998)
Laboratory Work (HPLC)	PBZ and Area Monitoring Data	1	High	ECJRC (2002)
Laboratory	PBZ and Area Monitoring Data	305	High	ECJRC (2002)
Laboratory	PBZ and Area Monitoring Data	29	High	ECJRC (2002)
N/A	CDR Data – Number of sites and workers	N/A	High	U.S. EPA (2016c)

N/A = Not Applicable.

From these monitoring data, EPA estimated concentrations representing central tendency and high-end estimates of potential occupational inhalation exposures based on the EU risk assessment monitoring data ([ECJRC, 2002](#)) of 1,4-dioxane as laboratory use (see Table 2-18.). EPA used a mean value to estimate the central tendency exposures. EPA calculated the high-end value by calculating an 8-hour TWA of the 15-minute short-term peak exposure and the highest 90th percentile value. This calculated value represents an exposure above the 90th percentile, which is equivalent to a high-end exposure. Using these 8-hour TWA exposure concentrations, EPA calculated the ADC and LADC. EPA determined a once per day short-term exposure of 166 mg/m³ may occur with a 15-minute duration during degassing of the high-performance liquid chromatography fluid based on occupational exposures for laboratory use ([ECJRC, 2002](#)). A submitter to the 2016 CDR reported 1,4-dioxane estimated that at least 50 but less than 100 laboratory workers could be potentially exposed ([U.S. EPA, 2016c](#)). EPA used U.S. Census and BLS data for the NAICS code 541380, Testing Laboratories, and relevant SOC codes to estimate a total of 6,844 sites, 6,610 workers, and 804 ONUs (see Appendix G.5), which corresponds to an estimated average of one worker and 0.12 ONUs per site. EPA used these data to calculate a ratio of 8:1 workers to ONUs. Additional information on various conditions of use including typical laboratory use, number of workers and ONUs, monitoring data, and estimation of high-end inhalation value for laboratory chemicals are described in Section 4.2 (Human Health Risk) and Appendix G.6.5.

Exposure data for ONUs were not available. ONU exposures could be lower than worker exposures, since ONUs do not typically directly handle the chemical. Only inhalation exposures to vapors are expected, which are anticipated to be less than worker exposures.

Table 2-18. Acute and Chronic Inhalation Exposures of Worker for Laboratory Chemicals Based on Monitoring Data

Exposure Type	Central Tendency (Mean Value) (mg/m ³)	High-end (90 th Percentile) (mg/m ³)	Data quality rating of Associated Source ^a
Short-Term Exposure (15-minutes)	N/A	166	High
8-hour TWA Exposure Concentrations	0.11	5.8*	High
Acute Exposure Concentration (AEC)	0.11	5.8	High
Average Daily Concentration (ADC)	0.11	5.5	High
Lifetime Average Daily Concentration (LADC)	0.042	2.8	High

N/A = not applicable.
 * NICNAS (1998) did not provide occupational exposure 1,4-dioxane data, however, cited studies where the highest 8-hour TWA value from personal monitoring was 1.8 ppm (approximately 6.5 mg/m³) ([Rimatori et al., 1994](#); [Hertlein, 1980](#))
^a See Table 2-17. for corresponding references.

Key Uncertainties

EPA used estimates based on exposure data from the 2002 EU Risk Assessment for 1,4-dioxane ([ECJRC, 2002](#)) to estimate the inhalation exposures for this scenario. The data sets used are limited, assumed to be 8-hour TWA values, and mostly lacked specific descriptions of worker tasks, exposure sources, and possible engineering controls to provide context. Most of the datasets were only presented in ranges with key statistics (*i.e.*, median or average and 90th percentile), so EPA was unable to directly calculate final values from the raw data and relied on the statistics provided in the report. Actual exposures could be less due to various factors in laboratory chemicals including variations with respect to number of workers and ONUs, scale of operations, and tasks performed for various process/analytical activities.

2.4.1.1.8 Film Cement

Film cement contains a mixture of solvents including 1,4-dioxane. Film cement is used in the film processing and archiving industries to splice celluloid movie film together ([U.S. EPA, 2017d](#)). Occupational exposure to 1,4-dioxane used in film cement was determined using monitoring data provided in a NIOSH HHE report ([Okawa and Coye, 1982](#)). The information and data evaluation for worker exposures during use of film cement are presented in Table 2-19.. See Appendix G.1 for more details about the data quality evaluation.

Table 2-19. Film Cement Data Evaluation

Worker Activity or Sampling Location	Data Type	Number of Samples	Data quality rating ^a	Source Reference / Hero ID
N/A	References data provided in NIOSH, 1982	N/A	High	NICNAS (1998)
MovieLab	Area Monitoring	1	High	Okawa and Coye (1982)
MovieLab	PBZ Monitoring	1	High	Okawa and Coye (1982)
Technicolor	PBZ Monitoring	4	High	Okawa and Coye (1982)

a: NIOSH (1982) reported six points that were relevant to 1,4-dioxane. Five were personal breathing zone points that were used to estimate worker inhalation exposures and one point was an area sample used to estimate the ONU exposure. Because of the data being a single data set, it was scored as such instead of viewing the two types of points each as their own data set. Thus, the sample size sub-score was “High” and that supported the overall score of “High”.

The NIOSH HHE report provided five PBZ samples and one area sample collected at two film laboratories that develop and clean film. Worker activities included film splicing and manual film cleaning. These values were used to calculate acute and chronic inhalation exposures using the equations in Appendix G.2. Results of these calculations are shown in Table 2-20.. EPA estimated a total of 30 workers and 10 ONUs could be exposed across all the sites. EPA estimated the number of potentially exposed workers and ONUs using BLS and SUSB data for the applicable NAICS codes. See Appendix G.5 for more information about the steps used to estimate workers and ONUs. Additional information including methodology for estimating the number of workers, typical film cement use, monitoring data, and estimation of high-end inhalation values for 1,4-dioxane used as a film cement are described in Appendix G.6.6.

Table 2-20. Acute and Chronic Inhalation Exposures of Worker for the Use of Film Cement Based on Monitoring Data

Exposure Type	Central Tendency (50 th percentile) (mg/m ^{3 a})	High-end (Maximum) (mg/m ^{3 a})	Data quality rating of Associated Source ^{bb}
8-hour TWA Exposure Concentrations	1.5	2.8	High
8-hour TWA Acute Exposure Concentration (AEC)	1.5	2.8	High
Average Daily Concentration (ADC)	1.5	2.7	High
Lifetime Average Daily Concentration (LADC)*	0.58	1.4	High

^a Analytical detection limits are lower than the concentrations shown in the table. The method detection limits of 1,4-dioxane in air are 530 ppt (1.9E-6 mg/m³) and 0.01 ppb (3.6E-5 mg/m³) by selected ion flow tube-mass spectrometry (SIFT-MS) and Gas Chromatography with Flame-Ionization detection (GC-FID), respectively. In

addition, NIOSH method 1602 could be used to determine the concentration of 1,4-dioxane in a 10-L air sample by GC-FID. Samples are collected by drawing air through a solid sorbent tube containing coconut shell charcoal. The flow rate is between 0.01 and 0.2 L/minute for a total sample size of 0.5–15 L. 1,4-Dioxane is eluted from the solid sorbent with agitation using carbon disulfide. The carbon disulfide eluent sample is then injected directly into the GC-FID. The detection limit is 0.01 mg per sample.

^b See Table 2-19. for corresponding references.

* Refer to Equation 5.2 and Appendix G.2 for additional information on estimation of LADC.

Three out of six NIOSH HHE samples have detectable concentrations and three values were non-detect ([Okawa and Coye, 1982](#)). The values of the three non-detects were considered as half the detection limit assuming that the average non-detect values could be between the detection limit and zero, and that the average value of non-detects could be as high as half the detection limit ([U.S. EPA, 1991](#)). EPA calculated an upper bound for these measurements and used it to calculate an 8-hour TWA value. EPA presented this as an 8-hour TWA inhalation exposure value for ONUs (Table 2-21.). This value was used to calculate acute and chronic inhalation exposures as per the equations in Appendix G.2. These values are plausible, but EPA cannot determine the statistical representativeness of the values given the small sample size. Dermal exposures are not expected for ONUs since they are not expected to directly handle the chemical.

Table 2-21. Acute and Chronic ONU Inhalation Exposures for the Use of Film Cement Based on Monitoring Data

Exposure Type	Central Tendency ^a (mg/m ³)	High-End ^a (mg/m ³)	Data quality rating of Associated Source ^b
8-hour TWA Exposure Concentrations	0.10		High
8-hour TWA Acute Exposure Concentration (AEC)	0.10		High
Average Daily Concentration (ADC)	0.10	0.10	High
Lifetime Average Daily Concentration (LADC)	0.040	0.051	High
^a These values are plausible, but EPA cannot determine the statistical representativeness of the values given the sample size of six data. High uncertainty is introduced given that these values are based on non-detects.			
^b See Table 2-19. for corresponding references.			

Key Uncertainties

Three of the NIOSH HHE reported values were non-detects and three were detectable. The values of the three non-detects were considered as half the detection limit as per the considerations indicated earlier. The estimated exposures could be overestimates due to the single area HHE study, lack of statistical representativeness of the values due to limited sample size, and typical operations that might not involve direct handling of 1,4-dioxane.

2.4.1.1.9 Spray Foam Application

1,4-Dioxane is present in two-component high-pressure, two-component low-pressure, and one component foam (OCF). The two-component, high-pressure spray polyurethane foams (SPFs), which are typically used for larger insulation applications, as an air sealant in hybrid insulations, and in roofing applications ([U.S. EPA, 2017c, d](#)). It is unclear how dependent 1,4-dioxane

emissions are on the specific SPF product or the way it is installed (such as compounds emitted from the spray foam specimens when they were fresh). (Naldzhiev et al., 2017) and Bayer MaterialScience (Karlovich et al., 2011a) indicated that 1,4-dioxane is not intentionally added as reactant and could be present in the foam as a contaminant. However, several technologies and researchers reported 1,4-dioxane’s presence as an ingredient. Polyester polyols are used for producing polyurethane, and amounts ranged from 0.8 g to 6 g of 1,4-dioxane generated per kg of polyester polyol formed in the esterification of aromatic phthalic acid depending on the technology used (2013). The United States Consumer Product Safety Commission (CPSC) and the National Institute of Standards and Technology (NIST) characterized and quantified 1,4-dioxane and other chemicals released from SPF after application (Poppendieck, 2017; Poppendieck et al., 2017). These authors reported 1,4-dioxane emission rates from SPF samples. Researchers from the NRC-Canada reported that tests on spray foam specimens detected 1,4-dioxane (Won, 2014). CDC/NIOSH reported presence of 1,4-dioxane in bulk sample analysis of component-B (a polyol blend with an amine catalyst) of the SPF formulation (Marlow, 2014).

Monitoring data for worker inhalation exposure to 1,4-dioxane from spray application of SPF was not identified. Instead, occupational exposure to 1,4-dioxane used in SPFs was estimated.

The information and data quality evaluation used to assess occupational exposures for spray foam application are listed in Table 2-22.. See Appendix G.1 for more details about the data quality evaluation.

Table 2-22. Spray Foam Application Data Source Evaluation

Worker Activity or Sampling Location	Data Type	Number of Samples	Data quality rating	Source Reference
A typical two-story, 2,300-square-foot house with a medium-pitch roof with a roof area of about 1,500 square feet	Parameters used in modeling	Not applicable – Monitoring data not provided	Medium	Huber (2018)
An average size house is 1,500 square feet of roofing	Parameters used in modeling	Not applicable – Monitoring data not provided	Medium	HomeAdvisor (2018)
Mix A-side and B-side in 1:1 ratio	Parameters used in modeling	Not applicable – Monitoring data not provided	High	OMG Roofing Products (2018)
0.1% 1,4-dioxane in B-Side	Parameters used in modeling	Not applicable – Monitoring data not provided	High	GAF (2014)

EPA used assumptions and values from the *GS on the Application of Spray Polyurethane Foam Insulation*, which used the *EPA AP-42 Loading Model*, the *EPA Mass Balance Inhalation Model*, the *EPA Total PNOR PEL-Limiting Model* (U.S. EPA, 2018a) and surrogate data to estimate inhalation exposures during container unloading, spray foam application, and thickness verification. EPA used a Monte Carlo simulation to vary the saturation factor (f), ventilation rate (Q), and mixing factor (k) and calculate 50th and 95th percentile 8-hour TWA exposures during container unloading. See Appendix G.4 for more information about the Monte Carlo simulation. The results from each activity were combined to construct an 8-hour TWA. EPA used these

values to calculate acute and chronic inhalation exposures in the Monte Carlo simulation, varying working years (WY), using the equations in Appendix G.2. These exposure results are shown in Table 2-23.

EPA estimated a total of 162,518 potentially exposed workers and 15,627 potentially exposed workers who are non-sprayers but could not be categorized as ONUs. EPA estimated the number of potentially exposed workers and non-sprayer workers using BLS and SUSB data for the applicable NAICS codes. EPA considered the total number of establishments and potentially exposed workers and non-sprayer workers in this NAICS code as bounding estimates of the number of establishments that use and the number of workers and non-sprayer workers that are potentially exposed to 1,4-dioxane-based spray polyurethane foam during insulation installation. These bounding estimates are likely underestimates of the actual number of establishments and employees potentially exposed to 1,4-dioxane during spray polyurethane foam insulation installation, since only a single spray polyurethane foam product that contains 1,4-dioxane was identified. See Appendix G.5 for more information about the steps used to estimate workers and non-sprayer workers. Additional information including specific methodology for estimating worker numbers, typical spray foam application methods, modeling assumptions, and estimation of high-end and central tendency inhalation values for 1,4-dioxane used in spray foam insulation are described in Appendix G.6.5.

Table 2-23. Acute and Chronic Inhalation Exposures of Worker for Spray Application Based on Modeling

Exposure Type	Central Tendency (50 th Percentile) (mg/m ³)	High-end (95 th Percentile) (mg/m ³)	Data quality rating of Associated Source ^a
8-hour TWA Exposure Concentrations	9.7E-03	1.2E-02	N/A - Modeled Data
8-hour TWA Acute Exposure Concentration (AEC)	9.7E-03	1.2E-02	N/A - Modeled Data
Average Daily Concentration (ADC)	9.4E-03	1.1E-02	N/A - Modeled Data
Lifetime Average Daily Concentration (LADC)	3.6E-03	5.3E-03	N/A - Modeled Data
^a See Table 2-22. for corresponding references.			

Exposure data from application of SPFs for non-sprayer workers were not available. Per the GS, it is assumed that some non-sprayer workers could perform tasks related to trimming the cured spray foam insulation. Exposures were estimated using the *EPA Total PNOR PEL-Limiting Model* with the OSHA PEL for total particulates (15 mg/m³). EPA multiplied the OSHA PEL by the expected concentration of 1,4-dioxane in the mixed SPF (0.0005) and averaged the exposure over 8 hours, assuming non-sprayer workers are exposed during trimming and not exposed during the remainder of the 8-hour period. Due to the small sample size of only one estimated value, EPA calculated an 8-hour TWA inhalation exposure value for non-sprayer workers and used this value to calculate acute and chronic inhalation exposures using the equations in Appendix G.2. These values are summarized in Table 2-24.. While these values may be plausible, due to the small sample size of only one estimated value, EPA could not determine the statistical representativeness.

Table 2-24. Acute and Chronic Non-Sprayer Workers Inhalation Exposures for Spray Applications Based on Modeling

Exposure Type	Central Tendency ^a (mg/m ³)	High-End ^a (mg/m ³)	Data quality rating of Associated Source ^b
8-hour TWA Exposure Concentrations	1.9E-03		N/A - Modeled Data
8-hour TWA Acute Exposure Concentration (AEC)	1.9E-03		N/A - Modeled Data
Average Daily Concentration (ADC)	1.8E-03		N/A - Modeled Data
Lifetime Average Daily Concentration (LADC)	7.2E-04	9.3E-04	N/A - Modeled Data
^a These values are plausible, but EPA cannot determine the statistical representativeness of the values given the small sample size. ^b See Table 2-22. for corresponding references.			

Key Uncertainties

Due to a lack of data specific to 1,4-dioxane for this use, EPA used assumptions and values from the *GS on the Application of Spray Polyurethane Foam Insulation*, which used the *EPA AP-42 Loading Model*, the *EPA Mass Balance Inhalation Model*, the *EPA Total PNOR PEL-Limiting Model* ([U.S. EPA, 2018a](#)) and surrogate data to estimate inhalation exposures during container unloading, spray foam application, thickness verification, and trimming. Values for the parameters listed in Table G-21 were assumed based on general industry data. These parameter values may not always be representative of applications specific to spray foam insulations containing 1,4-dioxane. The estimate for exposures during application did not account for the potential evaporation of 1,4-dioxane from the mist particulates and the potential inhalation exposure of the evaporated vapors. EPA assumed that this is not a significant exposure given that the partial pressure of 1,4-dioxane is likely very low due to the low concentration of 1,4-dioxane in the mixed spray foam. EPA also estimated exposures during thickness verification using surrogate data.

The *EPA AP-42 Loading Model* and the *EPA Mass Balance Inhalation Model* were used to estimate inhalation exposures during container unloading. These models assume that the unloading of fluid containing 1,4-dioxane occurs indoors, without engineering controls, and in an open-system environment where vapors freely escape. In the absence of industry-specific information, these assumptions provide for conservative estimates for exposures during this unloading operation. Actual exposures may be less due to various factors including closed-system unloading or the use of vapor recovery systems.

2.4.1.1.10 Printing Inks (3D)

1,4-Dioxane is used in solvent-based inks that are used in a type of additive manufacturing known as material jetting or 3D printing ([U.S. EPA, 2017d](#)). A published literature review and hazard assessment for material jetting measured exposures to a number of chemicals, including 1,4-dioxane, were reported during additive manufacturing. This report provided a single data point from an 8-hour sampling period for 1,4-dioxane exposure ([Ryan and Hubbard, 2016](#)). The sample was collected inside a commercial grade photopolymerization 3D printer enclosure. Ryan and Hubbard ([2016](#)) reported that the 1,4-dioxane concentrations could be higher than the

observed value in cases of lack of local exhaust ventilation and operation of multiple printers. Other researchers also supported the observations indicating that the releases of volatile organic carbons (VOCs) and particulate matters could increase to higher concentration levels depending on the temperature of the nozzle, extrusion temperature, the type of filament used, and type of 3D printer (2018); (Zhang et al., 2017). The information and data evaluation for worker exposures during use of printing inks are presented in Table 2-25.. See Appendix G.1 for more details about the data quality evaluation.

Table 2-25. Use of Printing Inks Data Evaluation

Worker Activity or Sampling Location	Data Type	Number of Samples	Data quality rating	Source Reference
3-D printing	Area Monitoring Data	1	High	Ryan and Hubbard (2016)

The scores for this source were assigned “High” and weighted higher than other sub-scores, including the sample size, which was scored “Medium.” The overall confidence score of this source was rated “High” despite single data set.

EPA used this sample value to calculate acute and chronic inhalation exposures (Table 2-26.) per the equations shown in Appendix G.2. EPA cannot determine the statistical representativeness of the values given the small sample size. It is estimated that a total of 59,970 workers, and 20,430 ONUs could be exposed across all the sites. EPA estimated the number of potentially exposed workers and ONUs using BLS and SUSB data for the applicable NAICS codes. See Appendix G.5 for more information about the steps used to estimate workers and ONUs. Additional information including specific methodology for estimating workers, ingredients of inks, use of 3_D printer, and details about the monitoring data for 1,4-dioxane used in printing inks (3D) are described in Appendix G.6.8.

Table 2-26. Acute and Chronic Inhalation Exposures of Worker for Use of Printing Inks Based on Monitoring Data

Exposure Type	Central Tendency ^a (mg/m ³)	High-End ^a (mg/m ³)	Data quality rating of Associated Source ^b
8-hour TWA Exposure Concentrations	0.097		High
8-hour TWA Acute Exposure Concentration (AEC)	0.097		High
Average Daily Concentration (ADC)	0.093		High
Lifetime Average Daily Concentration (LADC)	0.037	0.048	High

^a These values are plausible, but EPA cannot determine the variability and uncertainty of the values due to lack of data. High uncertainty is introduced given that these values are based on one point.

^b See Table 2-25. for corresponding references.

Exposure data for ONUs were not available. EPA expected that ONU exposures may be lower

than worker exposures, since ONUs do not typically directly handle the chemical. Only inhalation exposures to vapors are expected, which will likely be less than worker exposures to vapors.

Key Uncertainties

The data source used only provided one data point that was used to estimate the inhalation exposure of workers. EPA cannot determine the statistical representativeness due to limited data. The representativeness of this value to other 3D printing sites is unknown. Additionally, the sample provided is not a PBZ sample. Since the sample was taken within the 3D printing enclosure, the exposure value is likely higher than a worker would typically experience while operating the 3D printer. EPA considered the available monitoring data as no model is readily available to predict the release of 1,4-dioxane under this condition of use.

2.4.1.1.11 Dry Film Lubricant

1,4-Dioxane is used as a carrier in the manufacturing and application of a dry film lubricant. Occupational exposures to 1,4-dioxane during manufacturing and application were estimated by evaluating PBZ monitoring sample data provided by the U.S. Department of Defense, Kansas City National Security Campus (KCNSC) (DOE, 2018a). The information and data evaluation for worker exposures during use of dry film lubricant are presented in Table 2-27.. See Appendix G.1 for more details about the data quality evaluation.

Table 2-27. Dry Film Lubricant Data Source Evaluation

Worker Activity or Sampling Location	Data Type	Number of Samples	Data quality rating	Source Reference
Non-nuclear parts manufacturing for nuclear weapons.	PBZ and Area Monitoring Data	25	High	DOE (2018a)
Non-nuclear parts manufacturing for nuclear weapons.	Number of Workers	N/A – Monitoring data not provided	High	DOE (2018b)

These data were used to assess inhalation exposures to 1,4-dioxane for this condition of use. The PBZ samples included two full shift 8-hour TWA samples and five 8-hour TWAs that are derived from same-day task-based TWA samples, for a total of seven 8-hour TWA samples. These data are shown in Appendix G.6.9. EPA calculated the 95th percentile and 50th percentile of the available data. Acute and chronic inhalation exposures were calculated using the assumptions and equations listed in Appendix G.2. The dry film lubricant was manufactured six to eight days per year and the lubricant was applied about 48 days per year for a total exposure frequency of 56 days per year at the KCNSC-reported facility (DOE, 2018a). This assumption was used in place of the standard 250 days per year consideration as outlined in Appendix G.2. The results are summarized in Table 2-28.. Based on information provided by KCNSC, it is estimated that 16 workers and 64 ONUs could be exposed across all sites (DOE, 2018b). KCNSC provided monitoring data for workers but did not have monitoring data for ONUs. Additional information regarding this use, including monitoring data and assumptions made, are included in Appendix G.6.9.

Table 2-28. Acute and Chronic Inhalation Exposures of Workers for the Use of Dry Film Lubricant Based on Exposure Data

Exposure Type	Central Tendency (50 th Percentile) (mg/m ³)	High-end (95 th Percentile) (mg/m ³)	Data quality rating of Associated Source ^a
8-hour TWA Exposure Concentrations	0.47	1.6	High
Acute Exposure Concentration (AEC)	0.47	1.6	High
Average Daily Concentration (ADC)	0.10	0.35	High
Lifetime Average Daily Concentration (LADC)	0.040	0.18	High

^a See Table 2-27. for corresponding references.

Information was not available as to whether other Department of Energy (DOE) facilities within the National Nuclear Security Administration (NNSA) use 1,4-dioxane like the KCNSC. However, it was assumed the other seven facilities in the NNSA use 1,4-dioxane in the same manner and workers are exposed at the same levels as at the KCNSC.

Key Uncertainties

EPA confirmed with the KCNSC that the 8-hour TWAs from task samples were representative of the employee’s entire 1,4-dioxane exposure during their shift. EPA was not, however, able to confirm if other DOE facilities within the NNSA use 1,4-dioxane in addition to the KCNSC.

2.4.1.1.12 Disposal

Each of the conditions of use of 1,4-dioxane could generate waste streams containing 1,4-dioxane that are collected and transported to third-party sites for disposal, treatment, or recycling. Industrial sites that treat or dispose onsite generated wastes were assessed for the occupational exposure assessment for each condition of use in Sections 2.4.1.1.1 through 2.4.1.1.11 (except closed functional fluids). The information and data evaluation for worker exposures during disposal are presented in Table 2-29.. See Appendix G.1 for more details about the data quality evaluation.

Table 2-29. Disposal Data Source Evaluation

Worker Activity or Sampling Location	Data Type	Number of Samples	Data quality rating	Source Reference
N/A	TRI Data	N/A	Medium	U.S. EPA (2016d)
N/A	DMR Data	N/A	Medium	

EPA modeled occupational exposures using the *EPA AP-42 Loading Model* and the *EPA Mass Balance Inhalation Model* to estimate central tendency and high-end 8-hour TWA exposures. EPA used a Monte Carlo simulation to vary the saturation factor (f), ventilation rate (Q), and mixing factor (k). See Appendix G.4 for more information about the Monte Carlo simulation. EPA also estimated the 3.25-minute (0.06 hr) exposures from drum unloading as central tendency and high-end short-term exposures (see Table 2-30.). EPA used these values to

calculate acute and chronic inhalation exposures in the Monte Carlo simulation, varying working years (WY), using the equations in Appendix G.2.

A total of 177 workers and 53 ONUs could be exposed across all the sites. EPA estimated the number of potentially exposed workers and ONUs using BLS and SUSB data for the applicable NAICS codes. See Appendix G.5 for more information about the steps used to estimate workers and ONUs. Additional information including typical disposal methods, TRI data, and assumptions for estimating exposure values for the disposal of 1,4-dioxane are described in Appendix G.6.10.

Table 2-30. Acute and Chronic Inhalation Exposures of Worker for Disposal Based on Modeling

Exposure Type	Central Tendency (50 th Percentile) (mg/m ³)	High-end (95 th Percentile) (mg/m ³)	Data quality rating of Associated Source ^a
Short-Term Exposure Concentration (0.09 hrs)	170	610	N/A - Modeled Data
8-hour TWA Exposure Concentrations	1.9	6.6	N/A - Modeled Data
8-hour TWA Acute Exposure Concentration (AEC)	1.9	6.6	N/A - Modeled Data
Average Daily Concentration (ADC)	1.8	6.4	N/A - Modeled Data
Lifetime Average Daily Concentration (LADC)	0.68	2.5	N/A - Modeled Data
^a See Table 2-29. for corresponding references.			

Exposure data for ONUs were not available. EPA did not model exposures for ONUs, but EPA expects ONU exposures to be lower than worker exposures, since ONUs do not typically directly handle the chemical. Only inhalation exposures to vapors are expected, which will likely be less than worker exposures.

Key Uncertainties

EPA modeled inhalation exposures using the *EPA AP-42 Loading Model* and the *EPA Mass Balance Inhalation Model*. Process specifics for disposal sites were not available, therefore, EPA assumed certain process details, such as container sizes and unloading frequency. Additionally, EPA assumed that the process steps associated with this scenario occur indoors, without engineering controls, and in an open-system environment where vapors freely escape. In the absence of industry-specific information, these assumptions provide for conservative estimates for exposures during this operation. Actual exposures may be less due to various factors including closed-system loading and unloading, the use of vapor recovery systems, or the automation of various process steps.

2.4.1.1.13 Dermal Exposure Assessment

EPA estimated workers' dermal exposure to 1,4-dioxane for the industrial and commercial use scenarios considering evaporation of liquid from the surface of the hands and conditions of use

with and without gloves. OSHA requires employers to utilize the hierarchy of controls, except under limited circumstances, as a general concept that OSHA accepts as good industrial hygiene practice for reducing or removing hazardous exposures. OSHA's hierarchy of controls indicate that the most effective control is elimination, followed by substitution, and then engineering controls. Gloves are the last course of worker protection in the hierarchy of controls and should only be considered when process design and engineering controls cannot reduce workplace exposure to levels within regulation.

General Approach and Methods

Dermal exposure is the absorption and transport of 1,4-dioxane from the outer surface of the skin to the inner layers of the skin (Figure 2-1). The relatively thin epidermis lacks vascularization and is generally considered the primary barrier to uptake of chemicals encountered in the workplace or general environment. The dermis is vascularized and contains the sweat glands and hair follicles. Dermal absorption 1,4-dioxane through the skin could occur with or without being noticed by the worker. The rate of dermal absorption depends largely on the outer layer of the skin called the stratum corneum. The stratum corneum serves an important barrier function by keeping molecules from passing into and out of the skin, thus protecting the deeper layers of skin. Theoretical equations and models have been developed to describe the transport of a diffusing chemical through the skin. 1,4-Dioxane could permeate the skin's diffusional barriers and enter the systemic circulation via capillaries at the dermo-epidermal junction. The process begins with diffusion through the stratum corneum and could involve metabolic processes during traversal of the living epidermis. The released 1,4-dioxane that encounters skin could undergo many processes including:

- a) evaporation from the surface of the skin;
- b) uptake (absorption) into the stratum corneum, followed by reversible or irreversible binding; and
- c) penetration into the viable epidermis, followed by metabolism.

Several factors that influence the dermal absorption of 1,4-dioxane are shown in Figure 2-3 ([Eleftheriadou et al., 2019](#); [WHO, 2006](#); [Semple, 2004](#)). The factors affecting dermal exposure could vary based on working conditions, process operations and work practices, type and conditions of chemical releases, and other site-specific conditions. Various models have been developed to address various factors impacted by risk assessors; chemicals, and other industries ([Almeida et al., 2019](#); [Eleftheriadou et al., 2019](#); [Kissel et al., 2018](#); [Sugibayashi, 2017](#); [Chittenden and Riviere, 2015](#); [Frasch and Bunge, 2015](#); [Chittenden et al., 2014](#); [Gajjar and Kasting, 2014](#); [Nitsche and Kasting, 2013](#); [Mitragotri et al., 2011](#)).

IHSkinPerm©, developed by the American Industrial Hygiene Association (AIHA), is one of the available tools that estimates dermal absorption using the dermal loading, the exposure duration, and physical-chemical properties of chemicals. This model has taken into account losses to evaporation and estimates the mass that is absorbed. IH SkinPerm© computes dermal risk assessment for four types of occupational skin exposures found in work environments: a) deposition over time (*e.g.*, from repeated or continuous emission); b) instantaneous deposition (*e.g.*, from a splash); c) skin absorption from airborne vapors, and d) estimating absorption of 1,4-dioxane in water. The scenario output parameters are shown in Table 2-31.

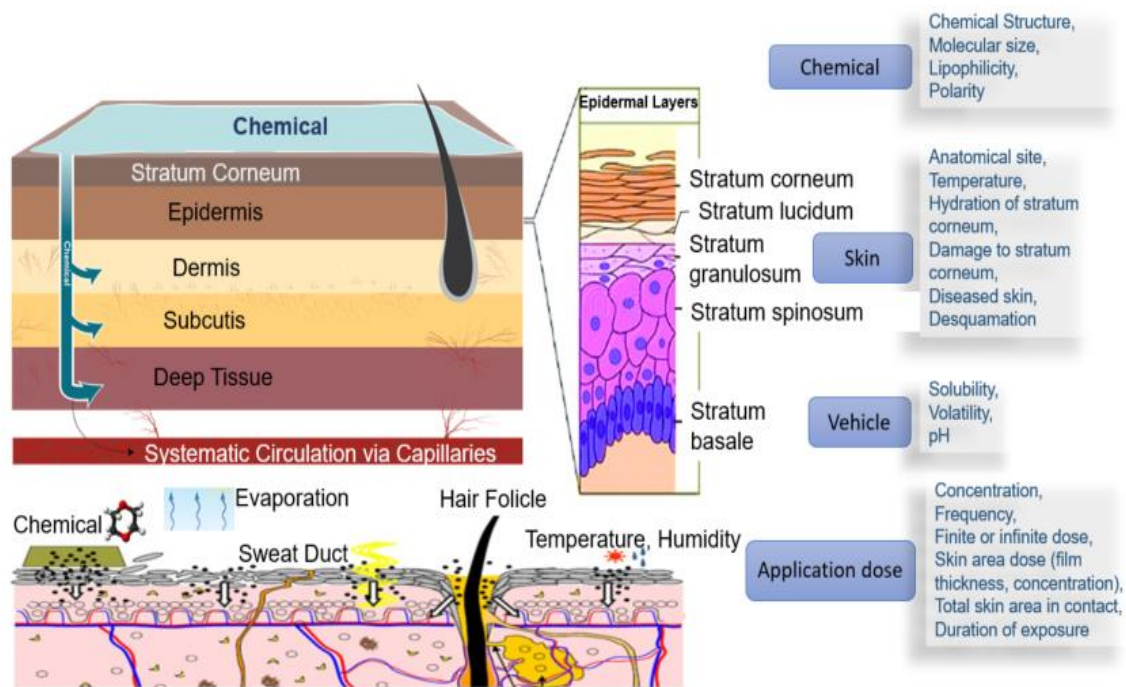


Figure 2-3 Conceptual diagram showing various key factors that influence dermal exposures in the event of 1,4-dioxane releases (modified after [Chattopadhyay and Taft, 2018](#)).

Table 2-31 IHSkinPerm© Output Data for Various Dermal Exposure Scenarios of 1,4-Dioxane

Scenario	Unit	Deposition over time (8hr)	Instantaneous	Vapor to skin	Water solution
Total deposition	mg	8560	100	0.19	3560
Fraction absorbed	%	1.05	5.51E-01	96.9	96.9
Amount absorbed	mg	8.99E+01	5.51E-01	1.81E-01	3.45E+3
Kp-lipids (vehicle water) ¹	cm/hr	4.08E-04			
Kp-lipids (vehicle air) ²	cm/hr	1.7			
Kp-keratins (vehicle water) ³	cm/hr	9.69E-05			
Kp-keratins (vehicle air) ⁴	cm/hr	4.05E-01			
Diffusivity through stratum corneum ⁵	cm ² /hr	1.83E-06			
Kp-stagnant air ⁶	cm/hr	3.34E+02			
Skin/water partition ratio	dimensionless	0.55			
Skin/air partition ratio	dimensionless	2300			
Permeation coefficient water ⁷	cm/hr	5.05E-04			
Permeation coefficient air ⁸	cm/hr	2.09			
<p>1: Kp-lipids (vehicle water) = permeability coefficient is a constant that describes the speed at which 1,4-dioxane diffuses through the lipid mortar between skin cells.</p> <p>2: Kp-lipids (vehicle air) = the estimated permeation coefficient of 1,4-dioxane as vapor in air, valid for the stratum corneum lipid mortar.</p> <p>3: Kp-keratins (vehicle water) = permeability coefficient is a constant that describes the speed at 1,4-dioxane diffuses through the dead skin cells. Keratins are a group of tough, fibrous proteins that form the structural framework of epithelial cells that make up tissues such as the hair, skin, and nails.</p> <p>4: Kp-keratins (vehicle air) = the estimated permeation coefficient of 1,4-dioxane as vapor in air, valid for the dead corneocytes of the stratum corneum.</p> <p>5: Diffusivity through stratum corneum is a dependent variable describing the effective diffusion of 1,4-dioxane through the stratum corneum.</p> <p>6: Kp-stagnant air layer = permeability coefficient of 1,4-dioxane through air boundary layer at the skin.</p> <p>7: Permeation coefficient water = an estimate of 1,4-dioxane dermally absorbed into the stratum corneum from water.</p> <p>8: Permeation coefficient air = an estimate of the 1,4-dioxane dermally absorbed from vapor in air.</p>					

A tiered approach has been used for dermal exposure assessment. As a first step, dermal exposures were estimated using methodologies as described in Appendix G.7. Though the fixed fractional dermal absorption¹² has commonly been used, the shortcomings of this practice have

¹² After the estimation of chemical contact rates, the absorbed dose has been assumed by researchers (Sahmel and Boeniger, 2006) to be a fixed fraction of the material encountered, irrespective of load conditions.

been reported ([Frasch et al., 2014](#); [Kissel et al., 2018](#)). Thus, in the second step, a sensitivity analysis was performed by varying the fraction absorbed (F_{abs}) from 0.3% to 100% of dermal absorption. The third step was a consideration of dermal absorption test data that included in vitro and ex vivo studies.

Dermal Test Data Interpretations

The results of dermal absorption parameters and/or flux¹³ values for 1,4-dioxane obtained from empirical studies or tests have been varied. [Mahdi \(2014\)](#) performed in vitro dermal absorption study of dioxane across human skin from the abdominal region that was obtained from white-skinned females who had undergone tummy tuck surgery (Manhattan Surgical Hospital, Manhattan, Kansas). The skin was dermatomed to 0.5 mm thickness and stored at -20°C for two months. The dermatomed skins were thawed at room temperature for 30 min and cut into disks that were mounted in the flow-through diffusion cell system with exposed skin surface areas of 1 cm^2 . [Mahdi \(2014\)](#) reported steady state flux of dioxane ranged between 12.157 ± 0.907 and $12.805 \pm 1.125\ \mu\text{g}/\text{cm}^2/\text{hr}$. [Bronaugh \(1982\)](#) showed that the fluxes of dioxane from water in human skin were low ($0.36 \pm 0.03\ \mu\text{g}/\text{cm}^2/\text{hr}$) while the flux was high (freshly excised = $1483.4 \pm 311.8\ \mu\text{g}/\text{cm}^2/\text{hr}$; 4 days stored skin = $1263.8 \pm 448\ \mu\text{g}/\text{cm}^2/\text{hr}$; 30 days stored skin = $1116.8 \pm 109.9\ \mu\text{g}/\text{cm}^2/\text{hr}$) in 4-hr tests performed by [Dennerlein et al. \(2013\)](#) at the Friedrich-Alexander University, Erlangen-Nürnberg, Germany.

The percutaneous penetration of 1,4-dioxane was investigated by [Dennerlein et al. \(2013\)](#) using the diffusion cell technique for freshly excised as well as for 4 and 30 days at -20°C stored human skin (four anonymous female donors, aged 30–59 years after surgical reduction abdominoplasty). The National Industrial Chemicals Notification and Assessment Scheme (NICNAS) used the empirical formula ([Potts Ro., 1992](#)) to calculate the 1,4-dioxane flux value to be approximately $300\ \mu\text{g}/\text{cm}^2/\text{hr}$ ([NICNAS, 1998](#)). The fractional absorption for 1,4-dioxane as estimated following a theoretical framework provided by Kasting and Miller ([2006](#)) and other transdermal flux parameters for 1,4-dioxane obtained from test studies are shown in the Figure 2-4.

¹³ Flux is the rate of mass accumulation per unit area of exposed surface (mass/area/time).

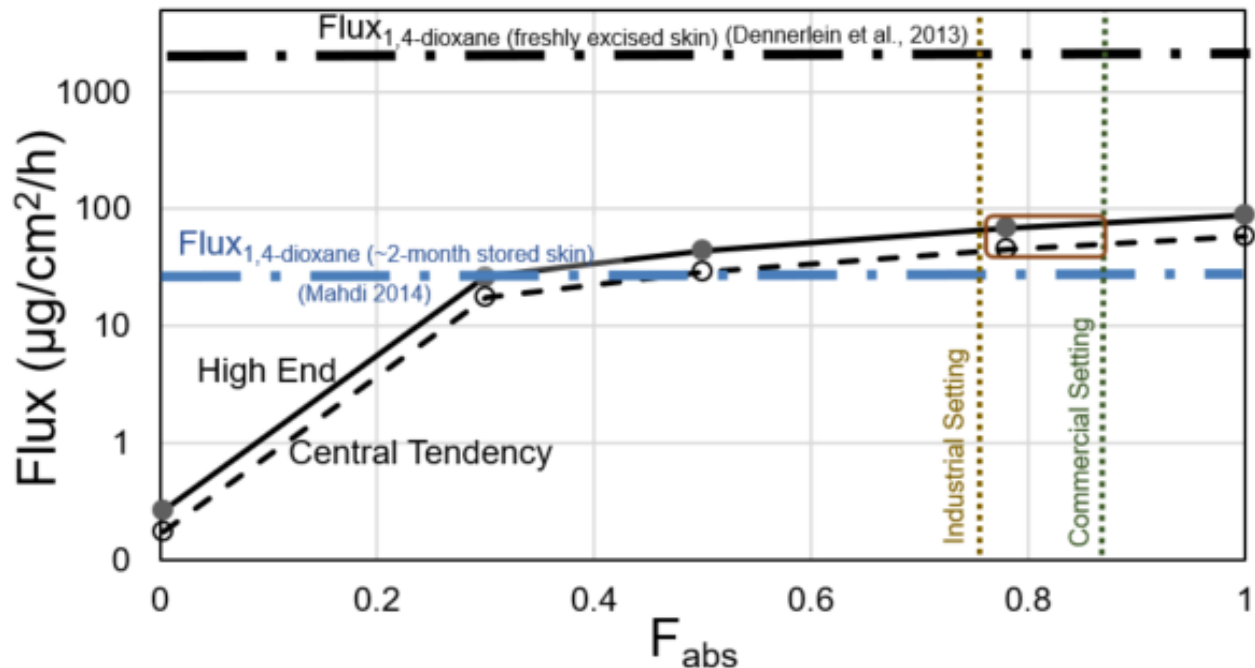


Figure 2-4 Flux of 1,4-dioxane across human skin at various exposure conditions

Dermal Exposure Estimation

Vapor absorption during dermal exposure requires that 1,4-dioxane be capable of achieving concentration in the media at the temperature and atmospheric pressure of the scenario under evaluation to provide a significant driving force for skin penetration. Because 1,4-dioxane is a volatile liquid (VP = 40 mmHg and 25°C) the dermal absorption of 1,4-dioxane depends on the type and duration of exposure. Only a fraction of 1,4-dioxane that contacts the skin will be absorbed as the chemical readily evaporates from the skin. Dermal absorption may be significant in cases of repeated contacts or dermal immersion. See Appendix G.7 for more information about the incorporation of gloves in the dermal exposure assessment. EPA collected and reviewed available SDSs to inform the evaluation of gloves used in the following conditions of use:

- Manufacturing;
- Import and Repackaging;
- Spray Foam Application;
- Laboratory Chemicals; and
- Film Cement.

Except for spray foam use, the SDSs recommended the use of protective or chemical resistant gloves during the handling of 1,4-dioxane or film cement. The spray foam related SDS indicated that the selection of specific PPE depends on the operation. However, a specific glove material or protection factor rating was not provided ([BASF, 2018b](#); [GAF, 2014](#); [Tedia, 2014](#); [Kodak, 2011](#)). For operations involving the use of larger amounts of 1,4-dioxane (for example, transferring dioxane from one container to another) or for other potential extended contact, butyl rubber or double nitrile gloves could be used. It should be noted that Viton™ or equivalent gloves need to be avoided as 1,4-dioxane degrades synthetic fluoropolymer product.

To assess dermal exposure, EPA used the *EPA Dermal Exposure to Volatile Liquids* model (See Equation 2.4.1-1) to calculate the dermal retained dose. The equation modifies the *EPA 2-Hand Dermal Exposure to Liquids Model* by incorporating a “fraction absorbed (f_{abs})” parameter to account for the evaporation of volatile chemicals and a “protection factor (PF)” to account for glove use. Default PF values, which vary depending on the type of glove used and the presence of employee training program, are shown in Table 2-32.. The additional details to calculate dermal exposures are described in Sections 4.2.2.4 and 4.2.2.5, and Appendix G.7.

Equation 2.4.1-1. Dermal Dose Equation

$$D_{exp} = S \times \frac{(Q_u \times f_{abs})}{PF} \times Y_{derm} \times FT$$

Where:

- S** = surface area of contact (cm²)
- Q_u** = quantity remaining on the skin after bulk liquid has been wiped away (mg/cm²-event)
- Y_{derm}** = weight fraction of the chemical of interest in the liquid (0 ≤ Y_{derm} ≤ 1)
- FT** = frequency of events (integer number per day)
- f_{abs}** = fraction of applied mass that is retained and absorbed systemically (Defaults for 1,4-dioxane: 0.78 for industrial use and 0.86 for commercial use)
- PF** = glove protection factor (Default: see Table 2-32..)

The fractional absorption (f_{abs}) for 1,4-dioxane is estimated to be 0.86 in commercial settings with lower indoor wind speeds and 0.78 in industrial settings with higher indoor wind flows based on a theoretical framework provided by Kasting and Miller (2006), meaning that 86% or 78% of the applied dose is retained by the stratum corneum, the outermost layer of the epidermis skin, and absorbed systemically.

Table 2-32. Exposure Control Efficiencies and Protection Factors for Different Dermal Protection Strategies

Dermal Protection Characteristics	Affected User Group	Efficiency (%)	Protection Factor, PF
a. No gloves used, or any glove / gauntlet without permeation data and without employee training	Industrial and Commercial Uses	0	1
b. Gloves with available permeation data indicating that the material of construction offers good protection for the substance		80	5
c. Chemically resistant gloves (<i>i.e.</i> , as “b” above) with “basic” employee training		90	10
d. Chemically resistant gloves in combination with specific activity training (<i>e.g.</i> , procedure for glove removal and disposal) for tasks where dermal exposure can be expected to occur	Industrial Uses Only	95	20

Table 2-33. presents the estimated dermal absorbed dose for *workers* in various exposure scenarios. The dose estimates assume one exposure event (applied dose) per work day and that

approximately seventy-eight to eighty-six percent¹⁴ of the applied dose is absorbed through the skin. The exposure estimates are provided for each condition of use, where the conditions of use are “binned” based on the maximum possible exposure concentration (Y_{derm}), the likely level of exposure. The exposure concentration is determined based on EPA’s review of currently available products and formulations containing 1,4-dioxane. For example, EPA found that 1,4-dioxane concentration in film cements can be as high as 50 percent ([Kodak, 2011](#)).

To streamline the dermal exposure assessment, the conditions of use were grouped based on characteristics known to effect dermal exposure such as the maximum weight fraction of 1,4-dioxane that could be present in that condition of use, open or closed system use of 1,4-dioxane, and large or small-scale use. Six different groups or “bins” were created to group conditions of use based on this analysis.

Bin 1 covers large-scale industrial uses that typically occur in a closed system. For these uses, dermal exposure is likely limited to chemical loading/unloading activities (*e.g.*, connecting hoses).

No gloves used: Operators in these industrial uses, while working around closed-system equipment, may not wear gloves or may wear gloves for abrasion protection or gripping that are not chemical resistant.

Gloves used with a protection factor of 5, 10, and 20: Operators may wear chemical-resistant gloves when taking quality control samples or when connecting and disconnecting hoses during loading/unloading activities.

Bin 2 covers open system functional fluids, which includes metalworking fluids and cutting and tapping fluids. During these types of open-system operations, workers are expected to be exposed during chemical loading/unloading; container cleaning; diluting water-based metalworking fluids; metal shaping operations; rinsing, wiping, and/or transferring the completed part; changing filters; transferring spent fluids; and cleaning equipment.

No gloves used: Due to the variety of shop types in these uses the actual use of gloves is uncertain. EPA assumes workers may not wear gloves or may wear gloves for abrasion protection or gripping that are not chemical resistant during routine operations.

Gloves used with a protection factor of 5, 10, and 20: Workers may wear chemical-resistant gloves when charging and draining metal shaping equipment, drumming spent metalworking fluid, and changing filters. EPA assumes gloves may offer a range of protection, depending on the type of glove and employee training provided.

Bin 3 covers the use of 1,4-dioxane in small-scale industrial uses. Workers may unload small volumes of nearly pure 1,4-dioxane and directly handle small quantities in research labs.

¹⁴ The absorbed fraction (f_{abs}) is a function of indoor air flow rate, which differs for industrial and commercial settings.

No gloves used: Operators in these small-scale industrial uses, while working around small amounts of the chemical, may not wear gloves or may wear gloves for abrasion protection or gripping that are not chemical resistant.

Gloves used with a protection factor of 5, 10, and 20: Operators may wear chemical-resistant gloves when taking quality control samples or when transferring small quantities of the chemical. EPA assumes gloves may offer a range of protection, depending on the type of glove and employee training provided.

Bin 4 covers the use of 1,4-dioxane in polyurethane spray foam insulation. Workers are expected to be exposed during chemical unloading, spray application, and trimming activities.

No gloves used: Actual use of gloves in this use is uncertain. EPA assumes workers may not wear gloves or may wear gloves for abrasion protection or gripping that are not chemical resistant during routine operations.

Gloves used with a protection factor of 5, 10, and 20: Workers may wear chemical-resistant gloves when charging application equipment, applying the foam, and trimming cured spray foam insulation. EPA assumes gloves may offer a range of protection, depending on the type of glove and employee training provided.

Bin 5 covers the use of 1,4-dioxane in film cements. Workers are exposed during manual application of the film cement with a small brush. The NIOSH HHE observed splicer operators had skin contact with 1,4-dioxane and recommended that employees wear neoprene or other appropriate chemical resistant gloves when handling solvents, including 1,4-dioxane ([Okawa and Coye, 1982](#)). The NICNAS report concludes that exposures to skin are likely insignificant in comparison to inhalation exposures for this use ([NICNAS, 1998](#)).

No gloves used: Operators in these small-scale photo shops, while working around small amounts of the chemical, may not wear gloves or may wear gloves for gripping that are not chemical resistant.

Gloves used with a protection factor of 5, 10, and 20: Operators may wear chemical-resistant gloves when transferring small quantities of the chemical, applying the film cement, or trimming film coated with cured film cement. EPA assumes gloves may offer a range of protection, depending on the type of glove and employee training provided.

Bin 6 covers the use of 1,4-dioxane in the manufacture and application of dry film lubricants. Workers are expected to unload and handle small volumes of pure 1,4-dioxane during dry film lubricant manufacture, mixing, and spray application. Although the process is small-scale and involved handling of purity of 1,4-dioxane similar to Bin 3, Bin 6 is considered a separate industrial application as it is part of a larger manufacturing process.

Gloves used with a protection factor of 5, 10, and 20: Operators may wear chemical-resistant gloves when taking quality control samples, when transferring small quantities of the chemical, mixing, or spray applying. EPA assumes gloves may offer a range of protection, depending on the type of glove and employee training provided.

Scenarios not assessed: The “no gloves” exposure scenario is not included in Bin 6 because Kansas City National Security Campus, the only known manufacturer, reports that their workers use gloves in their operation.

As shown in the Table 2-33., the calculated absorbed dose is high, which is due to high absorption characteristics, miscibility with water, and a lower octanol-water coefficient (-0.27) ([U.S. EPA, 2014g](#)). Dermal exposure to liquid is not assumed for ONUs, as they do not directly handle 1,4-dioxane.

Table 2-33. Estimated Dermal Absorbed Dose¹ (mg/day) for Workers in Various Conditions of Use

Condition of Use	Bin	Weight Fraction (Max Y _{derm})	Exposures due to Glove Permeation/Chemical Breakthrough (mg/day)			
			No Gloves (PF = 1)	Protective Gloves ² (PF = 5)	Protective Gloves ² (Commercial uses, PF = 10)	Protective Gloves ² (Industrial uses, PF = 20)
Manufacture	Bin 1	1.00	586 (CT) 1,759 (HE)	N/A	N/A	29 (CT) 88 (HE)
Import and Repackaging						
Industrial Use						
Disposal						
Functional Fluids (Open System)	Bin 2	0.001	0.59 (CT) 1.76 (HE)	N/A	N/A	0.02 (CT) 0.09 (HE)
Laboratory Chemicals	Bin 3	1.00	641 (CT) 1,924 (HE)	128 (CT) 385 (HE)	64 (CT) 192 (HE)	N/A
Use of Printing Inks (3D)						
Spray Foam Application	Bin 4	0.001	0.64 (CT) 1.92 (HE)	0.13 (CT) 0.39 (HE)	0.06 (CT) 0.19 (HE)	N/A
Film Cement	Bin 5	0.50	321 (CT) 962 (HE)	64 (CT) 192 (HE)	32 (CT) 96 (HE)	N/A
Dry Film Lubricant	Bin 6	1.00	N/A	N/A	N/A	29 (CT) 88 (HE)

CT = Central Tendency, HE = High End, N/A = not applicable.

¹The identified amounts are assumed to be retained by the stratum corneum, the outermost layer of the epidermis skin, and absorbed systemically. The resistance of viable tissue layers underlying the stratum corneum may reduce further absorption. ²Additional information available in Appendix G-27 and ([Marquart et al., 2017](#)).

2.4.2 General Population Exposure

1,4-Dioxane does not currently have established water quality criteria to protect human health under the CWA Section 304(a). Therefore, in this evaluation, EPA considers potential general population exposures via the ambient water pathway through evaluating incidental oral and dermal exposures related to recreational activities such as swimming. 1,4-Dioxane is not expected to accumulate in fish tissues; therefore, exposures to the general population via fish ingestion are not expected. The EPI Suite™ BCFBAF model estimates 1,4-dioxane’s bioaccumulation factor (BAF) to be 0.9. The BAF indicates the concentration in fish tissues relative to the surrounding water, with concentrations in fish tissues resulting from partitioning

from water and dietary sources and reduced by metabolism. A BAF < 1 indicates that concentrations in fish tissues are expected to be lower than aqueous concentrations and supports the expectation that fish ingestion is not a primary pathway of human exposure for 1,4-dioxane. This is consistent with human and rat toxicokinetic data suggesting a short half-life (approximately 1 hour) for 1,4-dioxane following uptake. Given its hydrophilic properties and short half-life, 1,4-dioxane is not expected to accumulate in tissue.

2.4.2.1 General Population Exposure Approach

Both estimated (*i.e.*, modeled) and measured levels of 1,4-dioxane in ambient water/surface water, were used to estimate incidental oral and dermal exposures during recreational activities such as swimming. Based on the incidental nature of such exposures, this supplemental analysis focuses on only acute exposures.

2.4.2.1.1 Modeling Surface Water Concentrations

In Section 2.2.1, Environmental Releases to Water, EPA estimates annual releases, release days, and number of facilities to provide a range of daily water releases for each OES based on 2018 TRI and DMR. Some OES had no predicted releases to surface water (see Table 2-2.). Therefore, included in this evaluation of general population exposures via ambient water include discharging sites involved in the following OES: manufacturing, industrial uses, functional fluids (open-system), spray foam application, and disposal. Table 2-2. shows the range of surface water release estimates across these OES; however, site-specific discharges are provided and used in this exposure analysis (see Supplemental File [*Exposure Modeling Inputs, Results, and Risk Estimates for Incidental Ambient Water Exposure*]).

Using the described site-specific water release information (kg/site/day) and days of release based on OES categories and assumptions, environmental modeling was conducted using EPA's Exposure and Fate Assessment Screening Tool (E-FAST 2014) to predict surface water concentrations in near-facility ambient water bodies ([U.S. EPA, 2014c](#)). For more on the operation and inputs of the E-FAST model, refer to the Estimating Surface Water Concentrations Section of Appendix E and the [E-FAST 2014 Documentation Manual \(U.S. EPA, 2007\)](#).

In this evaluation, site-specific stream flows were applied within E-FAST, where available, and no wastewater treatment removal was applied. E-FAST does not incorporate degradation or volatilization once released and estimates concentrations at the point of release (not downstream).

Modeled Surface Water Concentrations

Table 2-34 displays the modeled surface water concentrations obtained from E-FAST, as well as the site-specific water release inputs. Refer to the Supplemental Files [*Exposure Modeling Inputs, Results, and Risk Estimates for Incidental Ambient Water Exposure* and *Ambient Water Exposure Modeling Output from E-FAST*].

Table 2-34 Modeled Surface Water Concentrations

Occupational Exposure Scenario (OES)	Facility	SIC Code or NPDES¹	Daily Release (kg/site/day)	Days of Release	30Q5² Surface Water Concentration (µg/L)
Manufacturing	BASF	LA0004057	2.48	250	9.67E+01
Industrial Uses	Ineos Oxide	Industrial POTW	2.89	250	2.17E+02
	Microdyn-Nadir Corp	Industrial POTW	0.10	250	7.24E+00
	St Charles Operations (Taft/Star) Union Carbide Corp	LA0000191	3.31	250	1.11E-02
	SUEZ Water Technologies & Solutions	Industrial POTW	67.68	250	5.09E+03
	The Dow Chemical Co - Louisiana Operations	LA0003301	2.59	250	8.70E-03
	Union Carbide Corp Institute Facility	WV0000078	15.28	250	3.33E+00
	Union Carbide Corp Seadrift Plant	TX0002844	2.01	250	2.41E+01
	BASF Corp	PA0092223	0.01	250	3.40E-01
	Cherokee Pharmaceuticals LLC	PA0008419	0.01	250	2.63E-03
	DAK Americas LLC	NC0003719	31.86	250	2.78E+01
	Institute Plant	WV0000086	24.53	250	5.27E+00
	Kodak Park Division	NY0001643	0.256	250	1.70E-01
	Pharmacia & Upjohn (Former)	CT0001341	0.00	250	2.74E-02
	Philips Electronics Plant	TX0023779	0.00	250	1.00E-01
	Sanderson Gulch Drainage Improvements	Industrial POTW	0.00	250	1.00E-02
Open System Functional Fluids	Ametek Inc. U.S. Gauge Div	PA0020460	0.01	247	4.00E-01
	Lake Reg Med/Collegeville	PA0042617	0.00	247	1.31E-02

Occupational Exposure Scenario (OES)	Facility	SIC Code or NPDES ¹	Daily Release (kg/site/day)	Days of Release	30Q5 ² Surface Water Concentration (µg/L)
	Pall Life Sciences Inc	MI0024066	0.02	247	4.30E-02
	Modeled Release Estimates	Industrial POTW	0.038	247	2.85E+00
Spray Foam Application	Modeled Release Estimates	Industrial POTW	0.00	260	2.70E-01
Disposal	Beacon Heights Landfill	CT0101061	0.12	250	5.30E-01
	Ingersoll Rand/Torrington Fac	Industrial POTW	0.05	250	3.46E+00
<p>¹ Some of the site-specific OES release estimates were unable to be associated with a specific NPDES code and receiving water body within the E-FAST model. These sites were modeled using a generic, sector-specific SIC code.</p> <p>² Predicted 30Q5 surface water concentrations are the concentrations predicted using a 30Q5 stream flow. The 30Q5 stream flow is the lowest 30-day mean stream flow for a recurrence interval of five years. For sites modeled using a generic SIC code, the values in this column correspond to concentrations predicted using the low-end (<i>i.e.</i>, 10th percentile) of the 30Q5 stream flow distribution for that SIC code. Receiving stream flow distributions for direct discharges within a given SIC code are used to apply the 10th percentile flow. The 30Q5 concentrations are used in this evaluation over the mean or 7Q10 concentrations based on alignment with the E-FAST guidance for assessing acute drinking water exposures; this is noted to be consistent with EPA’s Office of Water Technical Support Document for Water Quality-Based Toxics Control (U.S. EPA, 2007).</p>					

2.4.2.1.2 Measured Surface Water Concentrations

Surface water monitoring data were discussed and submitted during the public comment for 1,4-dioxane. These submitted sources are briefly summarized below and were utilized in this evaluation of general population exposures via ambient water.

A report from the North Carolina Department of Environmental Quality identified 1,4-dioxane in surface water in the Deep, Haw, and Cape Fear Rivers at levels as high as 1,030 ug/L (mean 42.6-350.5 ug/L) ([EPA-HQ-OPPT-2019-0238-0042](#); [EPA-HQ-OPPT-2019-0238-0060](#); [EPA-HQ-OPPT-2019-0238-0061](#)). Sun et al. (2016) reported detections in North Carolina’s Cape Fear watershed of 154 to 1,405 µg/L. The Minnesota Department of Environmental Quality reported 1,4-dioxane in state surface waters at levels ranging from 0.05 to 4.4 µg/L ([EPA-HQ-OPPT-2019-0238-0043](#)). The upper ends of these ranges were also used to estimate incidental oral and dermal exposures from swimming.

2.4.2.1.3 Estimating Incidental Oral Exposures from Swimming

Predicted stream concentrations were used to estimate acute incidental oral exposure from swimming. Predicted surface water concentrations range from 2.63E-03 µg/L to 5.09E+03 µg/L

(see Table 2-34); this range of predicted concentrations encompasses the full range of the surface water monitoring data submitted during the public comment period.

Additional inputs/exposure factors used to estimate these acute oral exposures are included in Table 2-35. Supplemental File [*Exposure Modeling Inputs, Results, and Risk Estimates for Incidental Ambient Water Exposure*] for additional details on inputs and assumptions. This evaluation focused on children 11-15 years, as they present most conservative conditions when considering the age-specific ingestion rate, body weight, and duration of exposure.

Table 2-35 Incidental Oral Exposure Factors

Description	Value	Notes
Age Class	11-15	Selected based on having highest incidental oral ingestion rate during swimming from the Exposure Factors Handbook, Table 3-7 (EPA, 2019b)
Incidental Ingestion Rate	152 mL/hr	Upper-percentile hourly incidental ingestion rate from the Exposure Factors Handbook, Table 3-7 (EPA, 2019b)
Body Weight	56.8 kg	Recommended, mean body weight for children 11-15 from the Exposure Factors Handbook Table 8-1 (U.S. EPA, 2011a)
Duration of Exposure	2 hrs/day	High-end default short-term duration default from EPA Swimmer Exposure Assessment Model (SWIMODEL); based on competitive swimmers in the child 11-15 age class (EPA, 2015)
Daily Incidental Ingestion Rate	0.304 L/day	0.152 L/day * 2 hrs

The equation used to estimate the acute daily dose rate (ADR) for incidental oral ingestion is shown below ([U.S. EPA, 2007](#)):

$$ADR = \frac{SW \times IR \times CF}{BW}$$

Where,

SWC = Surface water concentration (µg/L)

IR = Daily ingestion rate (L/day)

CF = 0.001 mg/µg

BW = Body weight (kg)

2.4.2.1.4 Estimating Dermal Exposures from Swimming

Predicted stream concentrations were used to estimate incidental acute and incidental dermal exposure from swimming. Predicted surface water concentrations ranges from 2.63E-03 µg/L to 5.09E+03 µg/L (see Table 2-34). Additional inputs/exposure factors used to estimate these acute dermal exposures are included in Table 2-36. Supplemental File [*Exposure Modeling Inputs, Results, and Risk Estimates for Incidental Ambient Water Exposure*] for additional details on inputs and assumptions. This evaluation focused on the adult age class, as they present the most conservative exposure conditions when considering the age-specific surface area to body weight ratio and duration of exposure. Default parameterization from OPP's [SWIMODEL](#) were utilized for most inputs as shown in Table 2-36 ([EPA, 2015](#)).

Table 2-36 Dermal Exposure Factors

Description	Value	Notes
Age Class	Adult	Selected based on having highest dose based on permeability-based dermal exposure equation used in SWIMODEL , considering exposed surface area, duration, and body weight
Skin Surface Area	19,500 cm ²	Default dermal contact surface area for the adult age class in SWIMODEL (EPA, 2015)
Body Weight	80 kg	Recommended, mean body weight for adult age class (EFH , Table 8-1)
Exposure Duration	3 hrs/day	High-end, short-term default duration from EPA Swimmer Exposure Assessment Model (SWIMODEL); based on competitive swimmers in the adult age class (EPA, 2015)
Permeability Coefficient (Kp)	5.05E-04 cm/hr	Estimated using IHSkinPerm© for 1,4-dioxane dermally absorbed into the stratum corneum from water

The equation used to estimate the acute daily dose rate for dermal exposure from swimming shown below ([EPA, 2015](#)):

$$ADR = \frac{CW \times Kp \times SA \times ET \times CF}{BW}$$

Where,

- CW = Chemical concentration in water (mg/L)
- Kp = Permeability coefficient (cm/hr)
- SA = Skin surface area exposed (cm²)
- ET = Exposure time (hrs/day)
- CF = Conversion factor (0.001 L/cm³)
- BW = Body Weight (kg)

2.4.2.2 General Population Exposure Results

Estimated acute incidental oral exposures range from 1.41E-08 to 2.73E-02 mg/kg/day, while estimated acute dermal exposures range from 9.71E-10 to 1.88E-03 mg/kg/day. The highest exposures are associated with releases from the industrial uses OES. This range of exposure estimates cover acute oral and dermal doses estimated using both modeled and measured surface water concentrations. Refer to the Supplemental File [*Exposure Modeling Inputs, Results, and Risk Estimates for Incidental Ambient Water Exposure*] and 4.2.4 for the full set of results for all releasing sites and submitted monitoring data.

2.4.3 Consumer Exposures

As explained in the scope document, 1,4-dioxane may be found as a contaminant in consumer products that are readily available for public purchase.

2.4.3.1 Consumer Conditions of Use and Routes of Exposure Evaluated

Eight consumer conditions of use are evaluated based on the uses identified in EPA's 2015 TSCA Work Plan Chemical Problem Formulation and Initial Assessment of 1,4-Dioxane ([U.S. EPA, 2015](#)). An additional systematic review effort was undertaken for consumer exposures to identify, screen, and evaluate relevant data sources. These conditions of use include surface cleaner, antifreeze, dish soap, dishwasher detergent, laundry detergent, paint and floor lacquer, textile dye, and spray polyurethane foam (SPF). 1,4-Dioxane may be found in these products at

low levels (0.0009 to 0.02%) based on its presence as a byproduct of other formulation ingredients, *i.e.*, ethoxylated chemicals.

Inhalation exposures to 1,4-dioxane are estimated for household consumers (*i.e.*, product users – receptors who use a product directly) and bystanders (*i.e.*, receptors who are a non-user that may be incidentally exposed to the product). Acute inhalation exposures are presented for all conditions of use, while chronic inhalation exposures are only presented for conditions of use that are reasonably expected to involve daily use intervals (*i.e.*, surface cleaner, dish soap, dishwasher detergent, and laundry detergent). Other conditions of use (*i.e.*, SPF, antifreeze, textile dye, and paint and floor lacquer) are not evaluated over chronic exposure durations based on expected infrequent and intermittent use frequencies.

Dermal exposures to 1,4-dioxane are estimated for household consumers, or users. Users are assumed to include adults (21+ years) and children (11-20 years). As with inhalation, acute dermal exposures are presented for all conditions of use, while chronic inhalation exposures are only presented for conditions of use that are reasonably expected to involve daily use intervals (*i.e.*, surface cleaner, dish soap, dishwasher detergent, and laundry detergent). Other conditions of use (*i.e.*, SPD, antifreeze, textile dye, and paint and floor lacquer) are not evaluated over chronic exposure durations based on expected infrequent and intermittent use frequencies. Generally, individuals that have contact with liquid 1,4-dioxane would be users and not bystanders. Therefore, direct dermal exposures are not expected for bystanders and are only estimated for users.

2.4.3.2 Consumer Exposure Modeling Approach

Modeling was conducted to estimate exposure from the identified consumer conditions of use. Acute exposures via inhalation and acute and chronic exposures via dermal contact to consumer products were estimated using EPA’s Consumer Exposure Model (CEM) Version 2.1 ([U.S. EPA, 2019a](#)), along with consumer behavioral pattern data (*i.e.*, use patterns) and product-specific inputs. An older version of CEM, available within E-FAST 2014, was used to estimate chronic inhalation exposures and obtain lifetime average daily concentration outputs ([U.S. EPA, 2014c](#)). EPA’s Multi-Chamber Concentration and Exposure Model (MCCEM) was used to estimate inhalation exposures related to use of SPF based on the availability of measured emission rate data for that scenario ([EPA, 2010](#)). Table 2-37 displays the models used to estimate inhalation and dermal exposures across the consumer conditions of use.

Table 2-37 Models Used Across Consumer Conditions of Use and Routes of Exposure

Consumer Condition of Use	Acute Inhalation Exposure	Chronic Inhalation Exposure	Acute Dermal Exposure	Chronic Dermal Exposure
Surface Cleaner	CEM 2.1	CEM	CEM 2.1	CEM 2.1
Antifreeze	CEM 2.1	---	CEM 2.1	---
Dish Soap	CEM 2.1	CEM	CEM 2.1	CEM 2.1
Dishwasher Detergent	CEM 2.1	CEM	CEM 2.1	CEM 2.1
Laundry Detergent	CEM 2.1	CEM	CEM 2.1	CEM 2.1
Paint and Floor Lacquer	CEM 2.1	---	CEM 2.1	---
Textile Dye	CEM 2.1	---	CEM 2.1	---
SPF	MCCEM	---	CEM 2.1	---

Emission data were identified and evaluated through systematic review. For some conditions of use, emission data were used to support estimated exposures and to model emissions of SPF (see Appendix H.1.2.1).

2.4.3.2.1 Modeling Air Concentrations and Inhalation Exposure

Consumer Exposure Model

CEM 2.1 and CEM predict indoor air concentrations from consumer product use by implementing a deterministic, mass-balance calculation utilizing an emission profile determined by applying appropriate emission scenarios. The model uses a two-zone representation of the building of use (*e.g.*, residence, school, office), with Zone 1 representing the room where the consumer product is used (*e.g.*, a utility room) and Zone 2 being the remainder of the building. The product user is placed within Zone 1 for the duration of use, while a bystander is placed in Zone 2 during product use. Otherwise, product users and bystanders follow prescribed activity patterns throughout the simulated period.

For acute exposure scenarios, emissions from each incidence of product usage are estimated over a period of 72 hours using the following approach that accounts for how a product is used or applied, the total applied mass of the product, the weight fraction of the chemical in the product, and the molecular weight and vapor pressure of the chemical. Time weighted averages (TWAs) were then computed based on these user and bystander concentration time series per available human health hazard data. For 1,4-dioxane, 8-hour TWAs were quantified for use in risk evaluation based on alignment of relevant acute human health hazard endpoints. For additional details on CEM 2.1's underlying emission models, assumptions, and algorithms, please see the User Guide Section 3: Detailed Descriptions of Models within CEM 2.1 ([U.S. EPA, 2019a](#)), also summarized in Appendix H. The emission models used have been compared to other model results and measured data; see Appendix D: Model Corroboration of the User Guide Appendices for the results of these analyses ([U.S. EPA, 2019b](#)).

For chronic exposure scenarios, CEM within E-FAST 2014 was used to obtain lifetime average daily concentrations (LADCs) for the scenarios involving chronic exposures. Emissions are estimated over a period of 60 days. For cases where the evaporation time estimated exceeds 60 days, the model will truncate the emissions at 60 days. Conversely, for cases where the evaporation time is less than 60 days, emissions will be set to zero between the end of the evaporation time and 60 days. For more information on this version of CEM and its chronic inhalation estimates, refer to the [E-FAST 2014 Documentation Manual](#) ([U.S. EPA, 2007](#)).

The general steps of the calculation engine within the CEM 2.1 and CEM models include:

- Introduction of the chemical (*i.e.*, 1,4-dioxane into the room of use (Zone 1) through two possible pathways: (1) overspray of the product or (2) evaporation from a thin film;
- Transfer of the chemical to the rest of the house (Zone 2) due to exchange of air between the different rooms;
- Exchange of the house air with outdoor air; and
- Compilation of estimated air concentrations in each zone as the modeled occupant (*i.e.*, user or bystander) moves about the house per prescribed activity patterns.

Multi-Chamber Concentration and Exposure Model

The Multi-Chamber Concentration and Exposure Model (MCCEM) estimated indoor air concentrations of chemicals released from household products (EPA, 2010). It uses air infiltration and interzonal air flow rates with user-input emission rates to calculate time-varying concentrations in several zones or chambers within a residence. Four types of source models are available in MCCEM – constant, single exponential, incremental, and data entry. For additional details, see the MCCEM User Guide (EPA, 2019c).

Within MCCEM, the incremental source model is specifically designed for products that are applied to a surface (as SPF is) rather than products that are placed in an environment (*e.g.*, an air freshener). This distinction is important because the incremental source model considers the time or duration of application or use in its calculations of emissions and concentrations, while the single exponential source model does not. The incremental model assumes a constant application rate over time, coupled with an emission rate for each instantaneously applied segment that declines exponentially.

The incremental model can be populated using data derived from the experimental data and proposed model of emission rates in Karlovich et al. (2011b). See H.1.2.1 for details on the underlying equations and applying these data to estimate the emission rate for this scenario.

2.4.3.2.2 Modeling Dermal Exposure

CEM 2.1 contains dermal modeling components that estimate absorbed dermal doses resulting from dermal contact with chemicals found in consumer products: P_DER2a: Dermal Dose from a Product Applied to Skin, Fraction Absorbed Model and P_DER2b: Dermal Dose from Product Applied to Skin, Permeability Model. The selection of the appropriate dermal model was based on whether an evaluated condition of use is expected to involve dermal contact with impeded or unimpeded evaporation. For scenarios that are more likely to involve dermal contact with impeded evaporation (*e.g.*, wiping or cleaning with a chemical soaked rag), the permeability model is applied. In contrast, for scenarios less likely to involve impeded evaporation, the fraction absorbed model is applied. For acute exposure scenarios, dermal acute dose rates (ADRs) are estimated and, for chronic exposure scenarios, lifetime average daily doses (LADDs) are estimated. See H.2 for a more detailed comparison of these dermal models.

The permeability model estimates the mass of a chemical absorbed and dermal flux based on a permeability coefficient (K_p) and is based on the ability of a chemical to penetrate the skin layer once contact occurs. It assumes a constant supply of chemical directly in contact with the skin throughout the exposure duration. K_p is a measure of the rate of chemical flux through the skin. The parameter can either be specified by the user (if measured data are reasonably available) or be estimated within CEM using a chemical's molecular weight and octanol-water partition coefficient (K_{ow}). The permeability model does not inherently account for evaporative losses (unless the available flux or K_p values are based on non-occluded, evaporative conditions), which can be considerable for volatile chemicals in scenarios where evaporation is not impeded. While the permeability model does not explicitly represent exposures involving such impeded evaporation, the model assumptions make it the preferred model for an such a scenario. For 1,4-dioxane, an estimated aqueous dermal permeability coefficient (K_p , 5.05E-04 cm/hr) is used, based on IHSkinPerm© predictions. For additional details on this model, please see Appendix

H.2 and the CEM User Guide Section 3: Detailed Descriptions of Models within CEM ([U.S. EPA, 2019a](#)).

The fraction absorbed model estimates the mass of a chemical absorbed through the application of a fractional absorption factor to the mass of chemical present on or in the skin following a use event. The initial dose or amount retained on the skin is determined using a film thickness approach. A fractional absorption factor is then applied to the initial dose to estimate absorbed dose. The fraction absorbed is essentially the measure of two competing processes, evaporation of the chemical from the skin surface and penetration deeper into the skin. It can be estimated using an empirical relationship based on Fransch and Bunge ([2015](#)). Due to the model's consideration of evaporative processes, it was considered more representative of dermal exposure under unimpeded exposure conditions. For additional details on this model, please see Appendix H.2 and the CEM User Guide Section 3: Detailed Descriptions of Models within CEM ([U.S. EPA, 2019a](#)).

2.4.3.3 Consumer Exposure Scenarios and Modeling Inputs

Based on the combination of high-end and central tendency inputs, modeling results are presented for “high-intensity users” or “moderate-intensity users.” High-intensity user scenarios are characterized by high-end (*i.e.*, 95th percentile or maximum) inputs governing key user behavior pattern inputs (duration of use, mass of product used). Moderate-intensity user scenarios are characterized by central tendency (*i.e.*, 50th percentile) inputs governing the key user behavior pattern inputs of duration of use and mass of product used. Although key inputs represent high-end or central tendencies, this was a deterministic assessment and exposure results are not reflective of a distribution.

For acute exposure scenarios, only high-intensity user scenarios that incorporate high-end mass, duration, and weight fraction inputs are presented. For chronic exposure scenarios, both high-end and moderate-intensity user scenarios are presented based on model documentation and the understanding that central tendency parameters may more accurately represent lifetime exposures. CEM and CEM 2.1 are designed to use central tendency inputs for mass, duration, use frequency, and weight fraction when estimating lifetime exposures ([U.S. EPA, 2007](#); [U.S. EPA, 2019a](#)). Chronic high-intensity user scenarios, unlike the acute high-intensity user scenarios, utilize central tendency weight fraction inputs, where possible.

Some modeling inputs such as the room of use (*i.e.*, Zone 1 volume) and surface area to body weight ratio exposed in dermal exposure scenarios were held constant across the multiple iterations of a single product scenario but differed across product scenarios based on their product-specific nature. Other parameters such as chemical properties, building volume, air exchange rate, interzonal ventilation rate, and user and bystander activity patterns (*i.e.*, movements around the home) were held constant across all exposure scenarios and reflect central tendency inputs (*i.e.*, median or mean values; see Table 2-38).

For details on default modeling inputs and a sensitivity analysis, see Appendix B and Appendix C, respectively, of the CEM 2.1 user guide appendices ([U.S. EPA, 2019b](#)). The sensitivity analysis is also summarized in Appendix H.4.

Table 2-38 Default Modeling Input Parameters

Parameter Type	Modeling Parameter	Default Value Modeled	Value Characterization	Reference	
Building Characteristic ¹	Building Volume (m ³)	492	Central Tendency (Mean)	U.S. EPA (2011a)	
	Air Exchange Rate (hr ⁻¹)	0.45	Central Tendency (Median)	U.S. EPA (2011a)	
	Interzonal Ventilation Rate ² (m ³ /hr)	107	NA	Defaults U.S. EPA (2019a, b)	
Emission Characteristics	Background Air Concentration (mg/m ³)	0	Minimum		
	Gas Phase Mass Transfer Coefficient (m/hr)	Based on chemical properties and estimated within CEM (for SPF scenario modeled with MCCEM, see H.1.2.1)			
	Emission Factor (ug/m ² /hr)				
	Saturation Concentration in Air (mg/m ³)	1.89E+05	Based on chemical properties and estimated within CEM		
Use Patterns and Exposure Factors	Receptor Activity Pattern	Stay at home ³	NA	Default U.S. EPA (2019a, b)	
	Use Start Time	9 AM ⁴		NA	
	Frequency of Use	1 event per day		Defaults U.S. EPA (2019a, b)	
	Acute Exposure Duration	1 day			
	Acute Averaging Time	1 day			
	Chronic Exposure Duration	57 years			
	Chronic Averaging Time	78 years			
	Surface Area to Body Weight Ratio	Face, Hands, Arms			Central tendency (mean)
		Adult (21+): 15.8			
		Children (16-20): 14.9			
		Both Hands		Central tendency (mean)	
		Adult (21+): 12.4			
		Children (16-20): 11.6			
		Children (11-15): 12.7			
		Inside of One Hand		Central tendency (mean)	
		Adult (21+): 3.10			
		Children (16-20): 2.90			
		Children (11-15): 3.17			
		10% of Hands		Central tendency (mean)	
Adult (21+): 1.24					
Children (16-20): 1.16					
Children (11-15): 1.27					

NA = not applicable

¹ An overall residential building volume of 492 m³ is used to calculate air concentrations in Zone 2 and room volume is used to calculate air concentrations in Zone 1. The volume of the near-field bubble in Zone 1 was assumed to be 1 m³ in all cases, with the remaining volume of Zone 1 comprising the far-field volume.

² The default interzonal air flows are a function of the overall air exchange rate and volume of the building, as well as the “openness” of the room itself. Kitchens, living rooms, garages, schools, and offices are considered more open to the rest of the home or building of use; bedrooms, bathrooms, laundry rooms, and utility rooms are usually accessed through one door and are considered more closed.

³ The activity pattern (*i.e.*, zone location throughout the simulated exposure period) for user and bystander was the default “stay-at-home” resident, which assumes the receptors are primarily in the home (in either Zone 1 or 2) throughout the day. These activity patterns in CEM were developed based on Consolidated Human Activity Database (CHAD) data of activity patterns (Isaacs, 2014).

⁴ Product use was assumed to start at 9 AM in the morning; as such, the user was assumed to be in the room of use (Zone 1) at that time, regardless of the default activity pattern at 9 AM.

Key product scenario-specific modeling inputs for inhalation modeling are shown in Table 2-39. For scenarios with both acute and chronic exposure estimates, the table includes both high-end and central tendency inputs for duration, mass, and frequency of use. Please refer to the Supplemental File [*Consumer Exposure Assessment Modeling Input Parameters*] for a detailed listing of all inputs and associated sources.

Table 2-39 Key Product-Specific Inputs for Inhalation Modeling

Consumer Product Scenario	Form	Range of Product Conc. (ppm)	Max ¹ Weight Fraction	Room of Use (volume, m ³)	Duration of Use (min)	Mass of Product Used (g)	Frequency of Use (days/year)
Surface Cleaner	Liquid	0.36 – 9	9.00E-06	Bathroom (15)	30	300	365
					15	200	300
Antifreeze	Liquid	0.01 – 86	8.60E-05	Garage (90)	15	150	NA
Dish Soap	Liquid	0.7 – 204	2.04E-04	Kitchen (24)	20	84	365
					10	48	300
Dishwasher Detergent	Liquid/ Gel	0.86 – 9.7	9.70E-06		50	40	365
					45	20	300
Laundry Detergent	Liquid	0.05 – 14	1.40E-05	Utility Room (20)	50	60	365
					45	40	300
Paint and Floor Lacquer	Liquid	0.02 – 30	3.00E-05	Bedroom (36)	810	26025	NA
Textile Dye	Aqueous	NA	4.70E-06	Utility Room (20)	20	100	NA
SPF ²	Foam	500 ³	5.00E-04	Attic (123)	360	4.5 ⁴	NA
				Basement (246)		4.5 ⁴	
				Garage (118)	180	2.2 ⁴	

Consumer Product Scenario	Form	Range of Product Conc. (ppm)	Max ¹ Weight Fraction	Room of Use (volume, m ³)	Duration of Use (min)	Mass of Product Used (g)	Frequency of Use (days/year)
NA = not applicable							
¹ The use of “Max” (<i>i.e.</i> , maximum) here does not indicate use of a theoretical maximum or upper limit but refers to the highest identified weight fraction for a given product type based on the available data. Mean weight fractions were used, where possible, for chronic exposure estimates. See the Supplemental File [<i>Consumer Exposure Assessment Modeling Input Parameters</i>].							
² The SPF scenario was modeled using MCCEM to estimate inhalation exposures. Please refer to the Supplemental File [<i>Consumer Exposure Assessment Modeling Input Parameters</i>] for additional, distinct modeling inputs for this scenario.							
³ The applied 500 ppm concentration aligns with the related OES, which assumed 50% blending (parts A and B).							
⁴ Mass of use was not an input in MCCEM as it was in the CEM model. These masses instead reflect the total mass of chemical released in each exposure setting. These were estimated using loading ratios, application surface areas, emission rate per square inch, and decay rate per hour. Please refer to the Supplemental File [<i>Consumer Exposure Assessment Modeling Input Parameters</i>] and Appendix H.1.2 for more details.							

Key product scenario-specific modeling inputs for dermal modeling are shown in Table 2-40. For scenarios with both acute and chronic exposure estimates, the table includes both high-end and central tendency inputs for duration, mass, and frequency of use. Please refer to the Supplemental File [*Consumer Exposure Assessment Modeling Input Parameters*] for a detailed listing of all inputs and associated sources.

Table 2-40 Key Product-Specific Inputs for Dermal Modeling

Consumer Product Scenario	Form	Max ¹ Weight Fraction	Exposed Surface Area	Duration of Use ² (min)	Absorption Fraction ³	Film Thickness (cm)	Permeability Coefficient (Kp, cm/hr)	Frequency of Use (days/year)
Surface Cleaner	Liquid	9.00E-06	Inside of one hand	30	0.32	0.00214	5.05E-04	365
				15	0.26			300
Antifreeze	Liquid	8.60E-05	Both hands	15	0.26	0.00655		NA
Dish Soap	Liquid	2.04E-04 ⁴		Both hands	20	0.29		0.00655
			10		0.21	300		
Dishwasher Detergent	Liquid/ Gel	9.70E-06	10% of hands	1	0.038	0.00655		365
				300				
Laundry Detergent	Liquid	1.40E-05 ⁴	Both hands	20	0.29	0.00655		365
				10	0.21			300
Paint and Floor Lacquer	Liquid	3.00E-05	Face, hands, arms	810	0.34	0.00981		NA
Textile Dye	Aqueous	4.70E-06 ⁴	Both hands	20	0.29	0.00655	NA	
SPF	Foam	5.00E-04	Face, hands, arms	Attic 360	0.34	0.01	NA	
				Basement 360				
				Garage 180				

Consumer Product Scenario	Form	Max ¹ Weight Fraction	Exposed Surface Area	Duration of Use ² (min)	Absorption Fraction ³	Film Thickness (cm)	Permeability Coefficient (Kp, cm/hr)	Frequency of Use (days/year)
NA = not applicable								
¹ The use of “Max” (<i>i.e.</i> , maximum) here does not indicate use of a theoretical maximum or upper limit but refers to the highest identified weight fraction for a given product type based on the available data. See the Supplemental File [<i>Consumer Exposure Assessment Modeling Input Parameters</i>].								
² Durations of use were adjusted for dermal exposure for two scenarios: dishwashing detergent and laundry detergent. The model default durations listed in Table 2-39 above are based on machine run times and would not be appropriate for dermal contact duration.								
³ Absorption fractions are estimated using duration of exposures; therefore, distinct absorption fractions are estimated and applied for high-end vs. central tendency durations. This term is only used in estimation of dose using the fraction absorbed model.								
⁴ Dilution fractions were applied to three scenarios: dish soap (0.7%), laundry detergent (1.6%), and textile dye (10%). See the Supplemental File [<i>Consumer Exposure Assessment Modeling Input Parameters</i>] for details.								

2.4.3.4 Consumer Exposure Results

Estimated inhalation and dermal exposures are presented below for all consumer conditions of use. Scenarios that involve frequent (*i.e.*, daily) exposure intervals present acute and chronic exposure estimates for consumer users and acute exposure estimates for users and bystanders. Scenarios that involve intermittent or infrequent exposure intervals present acute exposure estimates only for users and bystanders.

2.4.3.4.1 Surface Cleaner

Acute and chronic inhalation and dermal exposures to 1,4-dioxane present as a byproduct in surface cleaner were evaluated. Concentrations of 1,4-dioxane in surface cleaners range from 0.36 to 9 ppm (up to 0.0009%). CEM 2.1 default inputs for all-purpose liquid cleaner were used as the basis for duration of use and mass of product used. The room of use (Zone 1) is a bathroom and the dermal surface area reflects the inside of one hand. Note that the bathroom is selected as the room of use as a measure of conservatism since it has a smaller room volume than other interior rooms. The weight fractions and other inputs are not specific to bathroom cleaner but are intended to reflect general surface cleaner. It This scenario assumes dermal contact during wiping/cleaning activities and may involve inhibited evaporation from the skin surface.

Inhalation exposure estimates are presented below. See the Supplemental File [*Consumer Exposure Modeling Results and Risk Estimates*] for exposure results and associated risk estimates.

Table 2-41 Estimated Inhalation Exposure: Surface Cleaner

Scenario Description	Duration of Use (min)	Weight Fraction	Mass Used (g)	Product User or Bystander	8-hr Max TWA (mg/m ³)	LADC (mg/m ³)
Acute						
High-Intensity User	High End (30)	Max (9.0E-06)	High End (300)	User	5.0E-03	---
				Bystander	9.5E-04	---
Chronic						

Scenario Description	Duration of Use (min)	Weight Fraction	Mass Used (g)	Product User or Bystander	8-hr Max TWA (mg/m ³)	LADC (mg/m ³)
High-Intensity User	High End (30)	Max ¹ (9.0E-06)	High End (300)	User	---	1.0E-03
Moderate-Intensity User	Central Tendency (15)	Max (9.0E-06)	Central Tendency (200)	User	---	5.6E-04

¹Although, generally, mean weight fractions were utilized in all chronic modeling (high-intensity and moderate-intensity user scenarios), a mean could not be estimates for this scenario based on source information.

Dermal exposure estimates are presented below and are based on the permeability model within CEM 2.1. See the Supplemental File [*Consumer Exposure Modeling Results and Risk Estimates*] for exposure results and associated risk estimates, including those based on the fraction absorbed model within CEM 2.1.

Table 2-42 Estimated Dermal Exposure: Surface Cleaner

Scenario Description	Duration of Use (min)	Weight Fraction (%)	Receptor	ADR (mg/kg/day)	LADD (mg/kg/day)
Acute					
High-Intensity User	High End (30)	Max (9.0E-06)	Adult (≥21 years)	7.7E-06	---
			Children (16-20 years)	7.2E-06	---
			Children (11-15 years)	7.9E-06	---
Chronic					
High-Intensity User	High End (30)	Max ¹ (9.0E-06)	Adult (≥21 years)	---	5.6E-06
Moderate-Intensity User	Central Tendency (15)	Max (9.0E-06)	Adult (≥21 years)	---	2.3E-06

¹Although, generally, mean weight fractions were utilized in all chronic modeling (high-intensity and moderate-intensity user scenarios), a mean could not be estimates for this scenario based on source information.

2.4.3.4.2 Antifreeze

Acute inhalation and dermal exposures to 1,4-dioxane present as a byproduct in antifreeze were evaluated. Concentrations of 1,4-Dioxane in antifreeze range from 0.01 to 86 ppm (up to 0.0086%). CEM 2.1 default inputs for anti-freeze liquid were used as the basis for duration of use and mass of product used. The room of use (Zone 1) is a garage and the dermal surface area reflects the inside of one hand. This scenario assumes dermal contact during pouring activities and is not expected to involve inhibited evaporation from the skin surface.

Inhalation exposure estimates are presented below. See the Supplemental File [*Consumer Exposure Modeling Results and Risk Estimates*] for exposure results and associated risk estimates.

Table 2-43 Estimated Inhalation Exposure: Antifreeze

Scenario Description	Duration of Use (min)	Weight Fraction	Mass Used (g)	Product User or Bystander	8-hr Max TWA (mg/m ³)
Acute					
High-Intensity User	High End (15)	Max (8.6E-05)	High End (150)	User	1.6E-02
				Bystander	4.0E-03

Dermal exposure estimates are presented below and are based on the fraction absorbed model within CEM 2.1. See the Supplemental File [*Consumer Exposure Modeling Results and Risk Estimates*] for exposure results and associated risk estimates, including those based on the permeability model within CEM 2.1.

Table 2-44 Estimated Dermal Exposure: Antifreeze

Scenario Description	Duration of Use (min)	Weight Fraction (%)	Receptor	ADR (mg/kg/day)
Acute				
High-Intensity User	High End (15)	Max (150)	Adult (≥21 years)	5.12E-04
			Children (16-20 years)	4.80E-04
			Children (11-15 years)	5.24E-04

2.4.3.4.3 Dish Soap

Acute and chronic inhalation and dermal exposures to 1,4-dioxane present as a byproduct in dish soap were evaluated. Concentrations of 1,4-dioxane in dish soap range from 0.7 to 204 ppm (up to 0.02%). CEM 2.1 default inputs for hand dishwashing soap/liquid serves as the basis for duration of use and an [American Cleaning Institute exposure and risk screening methods document](#) serves as the basis for mass of product used during hand dishwashing. The room of use (Zone 1) is a kitchen and the dermal surface area reflects both hands. A 0.7% dilution factor is applied. This scenario assumes immersive dermal contact in the 0.7% dish soap solution during washing activities and may involve inhibited evaporation from the skin surface.

Inhalation exposure estimates are presented below. See the Supplemental File [*Consumer Exposure Modeling Results and Risk Estimates*] for exposure results and associated risk estimates.

Table 2-45 Estimated Inhalation Exposure: Dish Soap

Scenario Description	Duration of Use (min)	Weight Fraction	Mass Used (g)	Product User or Bystander	8-hr Max TWA (mg/m ³)	LADC (mg/m ³)
Acute						

Scenario Description	Duration of Use (min)	Weight Fraction	Mass Used (g)	Product User or Bystander	8-hr Max TWA (mg/m ³)	LADC (mg/m ³)
High-Intensity User	High End (20)	Max (2.04E-04)	High End (84)	User	3.0E-02	---
				Bystander	5.4E-03	---
Chronic						
High-Intensity User	High End (20)	Central Tendency (2.40E-05)	High End (84)	User	---	7.1E-04
Moderate-Intensity User	Central Tendency (10)	Central Tendency (2.40E-05)	Central Tendency (48)	User	---	3.3E-04

Dermal exposure estimates are presented below and are based on the permeability model within CEM 2.1. See the Supplemental File [*Consumer Exposure Modeling Results and Risk Estimates*] for exposure results and associated risk estimates, including those based on the fraction absorbed model within CEM 2.1.

Table 2-46 Estimated Dermal Exposure: Dish Soap

Scenario Description	Duration of Use (min)	Weight Fraction (%)	Receptor	ADR (mg/kg/day)	LADD (mg/kg/day)
Acute					
High-Intensity User	High End (20)	Max (2.04E-04)	Adult (≥21 years)	3.1E-06	---
			Children (16-20 years)	2.9E-06	---
			Children (11-15 years)	3.1E-06	---
Chronic					
High-Intensity User	High End (20)	Central Tendency (2.40E-05)	Adult (≥21 years)	---	2.6E-07
Moderate-Intensity User	Central Tendency (10)	Central Tendency (2.40E-05)	Adult (≥21 years)	---	1.1E-07

2.4.3.4.4 Dishwashing Detergent

Acute and chronic inhalation and dermal exposures to 1,4-dioxane present as a byproduct in dishwashing detergent were evaluated. Concentrations of 1,4-dioxane in dishwashing detergent range from 0.86 to 9.7 ppm (up to 0.001%). CEM 2.1 default inputs for on machine dishwashing detergent (liquid/gel) were used as the basis for duration of use and mass of product used. The room of use (Zone 1) is a kitchen and the dermal surface area reflects 10% of hands. This scenario assumes brief dermal contact during loading activities and is not expected to involve inhibited evaporation from the skin surface.

Inhalation exposure estimates are presented below. See the Supplemental File [*Consumer Exposure Modeling Results and Risk Estimates*] for exposure results and associated risk estimates.

Table 2-47 Estimated Inhalation Exposure: Dishwasher Detergent

Scenario Description	Duration of Use (min)	Weight Fraction	Mass Used (g)	Product User or Bystander	8-hr Max TWA (mg/m ³)	LADC (mg/m ³)
Acute						
High-Intensity User	High End (50)	Max (9.7E-06)	High End (40)	User	6.9E-04	---
				Bystander	1.2E-04	---
Chronic						
High-Intensity User	High End (50)	Central Tendency (5E-06)	High End (40)	User	---	7.1E-05
Moderate-Intensity User	Central Tendency (45)	Central Tendency (5E-06)	Central Tendency (20)	User	---	2.9E-05

Dermal exposure estimates are presented below and are based on the fraction absorbed model within CEM 2.1. See the Supplemental File [*Consumer Exposure Modeling Results and Risk Estimates*] for exposure results and associated risk estimates, including those based on the permeability model within CEM 2.1.

Table 2-48 Estimated Dermal Exposure: Dishwasher Detergent

Scenario Description	Duration of Use ¹ (min)	Weight Fraction (%)	Receptor	ADR (mg/kg/day)	LADD (mg/kg/day)
Acute					
High-Intensity User	(1)	Max (9.7E-06)	Adult (≥21 years)	3.2E-06	---
			Children (16-20 years)	3.0E-06	---
			Children (11-15 years)	3.3E-06	---
Chronic					
High-Intensity User ²	(1)	Central Tendency (5E-06)	Adult (≥21 years)	---	1.2E-06
Moderate-Intensity User ²	(1)	Central Tendency (5E-06)	Adult (≥21 years)	---	9.9E-07

¹ The exposure duration applied for dermal exposures to dishwashing detergent were adjusted to 1 minute, as the scenario default exposure duration is based on the run time of a dishwasher, not on expected dermal contact time.

² For this scenario, the distinct chronic dermal estimates are a result of a difference in frequency of use (365 days/yr for high-intensity users and 300 days/yr for moderate-intensity users).

2.4.3.4.5 Laundry Detergent

Acute and chronic inhalation and dermal exposures to 1,4-dioxane present as a byproduct in laundry detergent were evaluated. Concentrations of 1,4-dioxane in laundry detergent range from 0.05 to 14 ppm (up to 0.0014%). CEM 2.1 default inputs for laundry detergent (liquid) were used as the basis for duration of use and mass of product used. The room of use (Zone 1) is a utility room and the dermal surface area reflects both hands. A 1.6% dilution factor is applied. This scenario assumes immersive dermal contact in the 1.6% laundry detergent solution during hand washing activities and may involve inhibited evaporation from the skin surface.

Inhalation exposure estimates are presented below. See the Supplemental File [*Consumer Exposure Modeling Results and Risk Estimates*] for exposure results and associated risk estimates.

Table 2-49 Estimated Inhalation Exposure: Laundry Detergent

Scenario Description	Duration of Use (min)	Weight Fraction	Mass Used (g)	Product User or Bystander	8-hr Max TWA (mg/m ³)	LADC (mg/m ³)
Acute						
High-Intensity User	High End (50)	Max (1.4E-05)	High End (20)	User	1.5E-03	---
				Bystander	2.7E-04	---
Chronic						
High-Intensity User	High End (50)	Central Tendency (6E-06)	High End (20)	User	---	1.3E-04
Moderate-Intensity User	Central Tendency (45)	Central Tendency (6E-06)	Central Tendency (10)	User	---	7.1E-05

Dermal exposure estimates are presented below and are based on the permeability model within CEM 2.1. See the Supplemental File [*Consumer Exposure Modeling Results and Risk Estimates*] for exposure results and associated risk estimates, including those based on the fraction absorbed model within CEM 2.1.

Table 2-50 Estimated Dermal Exposure: Laundry Detergent

Scenario Description	Duration of Use ¹ (min)	Weight Fraction (%)	Receptor	ADR (mg/kg/day)	LADD (mg/kg/day)
Acute					
High-Intensity User	High End (20)	Max (1.4E-05)	Adult (≥21 years)	4.8E-07	---
			Children (16-20 years)	4.5E-07	---
			Children (11-15 years)	4.9E-07	---
Chronic					
High-Intensity User	High End (20)	Central Tendency (6E-06)	Adult (≥21 years)	---	1.5E-07
Moderate-Intensity User	Central Tendency (10)	Central Tendency (6E-06)	Adult (≥21 years)	---	6.2E-08
¹ The exposure duration applied for dermal exposures to laundry detergent were adjusted to equal the default exposures times for dish soap, as this dermal exposure scenario is intended to approximate dermal contact from hand washing of clothing, whereas the default exposure durations for the laundry detergent scenario are based on run times of the washing machine.					

2.4.3.4.6 Paints and Floor Lacquer

Acute inhalation and dermal exposures to 1,4-dioxane present as a byproduct in paints or floor lacquer were evaluated. Concentrations of 1,4-dioxane in paints and floor lacquer range from 0.02 to 30 ppm (up to 0.003%). Westat Survey data on latex paint were used as the basis for duration of use and mass of product used. The room of use (Zone 1) is a bedroom and the dermal surface area reflects the face, hands, and arms. This scenario assumes dermal contact during painting activities and is not expected to involve inhibited evaporation from the skin surface.

Inhalation exposure estimates are presented below. See the Supplemental File [*Consumer Exposure Modeling Results and Risk Estimates*] for exposure results and associated risk estimates.

Table 2-51 Estimated Inhalation Exposure: Paints and Floor Lacquer

Scenario Description	Duration of Use (min)	Weight Fraction	Mass Used (g)	Product User or Bystander	8-hr Max TWA (mg/m ³)
Acute					
High-Intensity User	95 th Percentile (810)	Max (3E-05)	95 th Percentile (26025)	User	2.0E-02
				Bystander	7.5E-03

Dermal exposure estimates are presented below and are based on the fraction absorbed model within CEM 2.1. See the Supplemental File [*Consumer Exposure Modeling Results and Risk Estimates*] for exposure results and associated risk estimates, including those based on the permeability model within CEM 2.1.

Table 2-52 Estimated Dermal Exposure: Paints and Floor Lacquer

Scenario Description	Duration of Use (min)	Weight Fraction (%)	Receptor	ADR (mg/kg/day)
Acute				
High-Intensity User	95 th Percentile (810)	Max (3E-05)	Adult (≥21 years)	1.96E-03
			Children (16-20 years)	1.85E-03
			Children (11-15 years)	2.03E-03

2.4.3.4.7 Textile Dye

Acute inhalation and dermal exposures to 1,4-dioxane present as a byproduct in textile dye were evaluated. An identified concentration of 1,4-dioxane in textile dye is 4.7 ppm (up to 0.00047%). CEM 2.1 default inputs for textile and fabric dyes were used as the basis for duration of use and mass of product used. The room of use (Zone 1) is a utility room and the dermal surface area reflects both hands. A 10% dilution factor is applied. This scenario assumes immersive dermal contact in the 10% dye solution during dyeing activities and may involve inhibited evaporation from the skin surface.

Inhalation exposure estimates are presented below. See the Supplemental File [*Consumer Exposure Modeling Results and Risk Estimates*] for exposure results and associated risk estimates.

Table 2-53 Estimated Inhalation Exposure: Textile Dye

Scenario Description	Duration of Use (min)	Weight Fraction	Mass Used (g)	Product User or Bystander	8-hr Max TWA (mg/m ³)
Acute					
High-Intensity User	High End (20)	Max (4.7E-06)	High End (100)	User	8.5E-04
				Bystander	1.5E-04

Dermal exposure estimates are presented below and are based on the permeability model within CEM 2.1. See the Supplemental File [*Consumer Exposure Modeling Results and Risk Estimates*] for exposure results and associated risk estimates, including those based on the fraction absorbed model within CEM 2.1.

Table 2-54 Estimated Dermal Exposure: Textile Dye

Scenario Description	Duration of Use (min)	Weight Fraction ¹ (%)	Receptor	ADR (mg/kg/day)
Acute				
High-Intensity User	High End (20)	Max (4.7E-06)	Adult (≥21 years)	6.4E-07
			Children (16-20 years)	6.0E-07
			Children (11-15 years)	6.5E-07

2.4.3.4.8 Spray Polyurethane Foam

Acute inhalation and dermal exposures to 1,4-dioxane present as a byproduct in SPF were evaluated. Concentrations of 1,4-dioxane in SPF range from <0.5 to 500 ppm (up to 0.05% in mixed SPF) and the selected weight fraction aligns with that used in the occupational exposure assessment. Three rooms of use (Zone 1) were assumed: the basement, the attic, and the garage. The dermal surface area reflects the face, hands, and arms. Duration of use is based on loading rate and application surface area, but it aligns well with the durations assumed in the occupational exposure assessment (see Appendix G for more details). This scenario assumes dermal contact during application activities and are not expected to involve inhibited evaporation from the skin surface.

While application of SPF insulation products may primarily be occupational, a “do it yourself” or DIY installation of SPF is possible. There are consumer products available that may expose consumers (users and bystanders) to 1,4-dioxane.

Inhalation exposure estimates are presented below. See the Supplemental File [*Consumer Exposure Modeling Results and Risk Estimates*] for exposure results and associated risk estimates.

Table 2-55 Estimated Inhalation Exposure: SPF

Scenario Description	Duration of Use (min)	Weight Fraction	Mass Used (g)	Product User or Bystander	8-hr Max TWA (mg/m ³)
Acute					
Basement ¹	(360) ²	Max (5.0E-04)	4.5 ³	User	8.9E-01
				Bystander	7.4E-01
Attic ¹	(360) ²	Max (5.0E-04)	4.5 ³	User	1.9E-01
				Bystander	7.1E-02
Garage ¹	(180) ²	Max (5.0E-04)	2.5 ³	User	1.6E-01
				Bystander	1.2E-01

¹ SPF scenarios are not described in the same manner as the other product scenarios, as they are based on home application areas: basement, attic, and garage, each with distinct air exchange rates and interzonal ventilation rates.

Scenario Description	Duration of Use (min)	Weight Fraction	Mass Used (g)	Product User or Bystander	8-hr Max TWA (mg/m ³)
² Durations of use are not described as “high-end” in these scenarios because they are not based on a distribution; however, they are based on loading rates and application surface areas and align with occupational exposure scenario durations (excluding time for set-up and without considering multiple jobs per day). ³ Mass of use was not an input in MCCEM as it was in the CEM model. These masses instead reflect the total mass of chemical released in each exposure setting. These were estimated using loading ratios, application surface areas, emission rate per square inch, and decay rate per hour. Please refer to the Supplemental File [<i>Consumer Exposure Assessment Modeling Input Parameters</i>] for more details.					

Dermal exposure estimates are presented below and are based on the fraction absorbed model within CEM 2.1. See the Supplemental File [*Consumer Exposure Modeling Results and Risk Estimates*] for exposure results and associated risk estimates, including those based on the permeability model within CEM 2.1.

Table 2-56 Estimated Dermal Exposure: SPF

Scenario Description	Duration of Use (min)	Weight Fraction (%)	Receptor	ADR (mg/kg/day)
Acute				
Basement, Attic, Garage ¹	(360, 360, 180) ²	Max (5.0E-04)	Adult (≥21 years)	1.0E-03
			Children (16-20 years)	9.7E-04
			Children (11-15 years)	1.0E-03
¹ SPF scenarios are not described in the same manner as the other product scenarios, as they are based on home application areas: basement, attic, and garage, each with distinct air exchange rates and interzonal ventilation rates. For dermal exposures, there is no difference across these scenarios, as the maximum fraction absorbed is estimated and applied for either duration (360 or 180 minutes). ² Durations of use are not described as “high-end” in these scenarios because they are not based on a distribution; however, they are based on loading rates and application surface areas and align with occupational exposure scenario durations (excluding time for set-up and without considering multiple jobs per day).				

3 HAZARDS (Effects)

3.1 Environmental Hazards

3.1.1 Approach and Methodology

As part of problem formulation, EPA reviewed and characterized the environmental hazards associated with 1,4-dioxane. EPA identified the following sources of environmental hazard data for 1,4-dioxane: *Health Canada* ([Health Canada, 2010](#); [ECJRC, 2002](#); [OECD, 1999](#); [NICNAS, 1998](#)), *European Union risk assessment report* ([ECJRC, 2002](#)), *SIDS initial assessment profile for 1,4 Dioxane* ([OECD, 1999](#)), and *National Industrial Chemicals Notification and Assessment Scheme* ([Health Canada, 2010](#); [ECJRC, 2002](#); [OECD, 1999](#); [NICNAS, 1998](#)). These sources concluded that the hazard of 1,4-dioxane to aquatic organisms is low. Also, 1,4-dioxane's potential hazard to terrestrial organism is low due to the chemical's potential to migrate to groundwater from soil environments. These conclusions pertaining to 1,4-dioxane's low hazard effects to the environment resulted in determining that the chemical was a low priority for ecotoxicity. Although the assessment documents mentioned above provide detailed information regarding the environmental hazard of 1,4-dioxane to aquatic and terrestrial organisms, they do not account for additional and more recent information published on the chemical. EPA conducted a systematic review on 1,4-dioxane as described in the *Application of Systematic Review in TSCA Risk Evaluations* ([U.S. EPA, 2018b](#)) and *Strategy for Assessing Data Quality in TSCA Risk Evaluations* ([U.S. EPA, 2018e](#)).

EPA completed the review of environmental hazard data/information sources during risk evaluation using the data quality review evaluation metrics and the rating criteria described in the *Application of Systematic Review in TSCA Risk Evaluations* ([U.S. EPA, 2018b](#)). Studies were assigned an overall quality level of high, medium, or low. The data quality evaluation results are outlined in *Supplemental File: Data Quality Evaluation of Environmental Hazard Studies* ([U.S. EPA, 2019d](#)). With the data available, EPA only used studies with an overall quality level of high or medium for quantitative analysis during data integration. Studies assigned an overall quality level of low were used qualitatively to characterize the environmental hazards of 1,4-dioxane. Any study assigned an overall quality level of unacceptable was not used for data integration.

Toxicity to Aquatic Organisms

EPA identified nine high quality studies that contained aquatic toxicity data (*i.e.*, fish, aquatic invertebrates, algae). Aquatic toxicity studies considered in this assessment are summarized in Table 3-1..

This assessment evaluated studies that followed standard test guidelines (*e.g.*, Office of Chemical Safety and Pollution Prevention (OCSP)), Organisation for Economic Co-operation and Development [OECD]). Also, non-standard toxicity tests that followed procedures were evaluated that were determined to be scientifically sound according to the *Application of Systematic Review in TSCA Risk Evaluations* document ([U.S. EPA, 2018b](#)).

Table 3-1. Acceptable acute aquatic toxicity studies that were evaluated for of 1,4-Dioxane

Test Organism	Duration	Endpoint	Hazard Value (mg/L) ¹	Effect Type	Reference Evaluation Ranking
Acute ²	Fish	96-hour LC ₅₀	13,000	Mortality	Dow Chemical (1989a) High
		96-hour LOEC	10,000		
		96-hour LC ₅₀	10,000 6,700	Mortality	Dawson et al. (1977) High
		96-hour LC ₅₀	1,236 9,872		
		96-hour LC ₅₀	9,850 10,800	Mortality	Geiger et al. (1990) High
	Invertebrates	24-hour EC ₅₀	8,450	Behavior, Equilibrium	Bringmann and Kuehn (1982) High
		24-hour LC ₅₀	4,700	Immobilization	Bringmann and Kuhn (1977) High
		48-hour EC ₅₀	4,269	Mortality	Brooke (1987) High
Chronic ²	Fish	32-day MATC	>145	Growth/Weight	Dow Chemical (1989a) High
				Hatchability	
	Survival				
Development					
	28-day LOEC	565	Survival	Johnson et al. (1993) High	
Algae ³	Short-term	8-day LOEC	575	Population, growth rate	Bringman and Kuhn (1977) High
		8-day EC ₅₀	575	Population	Bringmann and Kuhn (1978) High
		8-day EC ₅₀	575	Population	
		8-day LOEC	5,600	Population, Growth Rate	
		8-day	5,600	Population	
		10-day	5,600	Biomass	

¹Values in the table are presented in the number of significant figures reported by the study authors.
²Acute and chronic hazard data are reported for fish and invertebrates
³Because algae can cycle through several generations in hours to days, the data for algae was assessed together regardless of duration (*i.e.*, 48-hrs to 96-hrs).

Toxicity to Fish

Four high quality studies were evaluated to characterize the acute toxicity of 1,4-dioxane exposure to fish. The acute 96-hour LC₅₀ values for fish range from 1,236 mg/L for fathead minnow (*Pimephales promelas*) to 6,700 mg/L for inland silversides (*Menidia beryllina*).

Two high quality studies were evaluated to characterize the chronic toxicity of 1,4-dioxane exposure to fish. In a chronic study, medaka (*Oryzias latipes*) were exposed to measured concentrations of 1,4-dioxane ranging from 50 mg/L to 6,933 mg/L for 28 days under flow-

through conditions. There were effects on growth and survival ([Johnson et al., 1993](#)). A low observed effect concentration (LOEC) of 565 mg/L was reported. In another study, fathead minnows (*P. promelas*) were exposed to 1,4-dioxane for 32 days to mean measured concentrations of 3, 27.6, 40.3, 65.3, 99.7 and 145 mg/L to observe the effects on embryonic development (*i.e.*, hatching, larval development, and larval survival) under flow-through conditions. No effects were observed based on larval survival so a maximum acceptable toxicant concentration (MATC) of 145 mg/L was calculated ([Dow Chemical, 1989a](#)).

Invertebrates

Three high quality studies that were evaluated to characterize the toxicity of 1,4-dioxane to aquatic invertebrates. Brooke ([1987](#)) reported a 48-hour EC₅₀ of 4,269 mg/L to *Daphnia magna* and a 96-hour LC₅₀ of 2,274 mg/L to amphipods (*Gammarus pseudolimnaeus*). The amphipod study is also a receptor for the benthic environment. Also, a 24-hour EC₅₀ of 4,700 mg/L was reported by Bringmann and Kuhn ([1977](#)).

Toxicity to Algae Species

To assess the toxicity of 1,4-dioxane to algae, two acceptable high studies were evaluated. Bringmann and Kunn ([1977](#), [1978](#)) studied the effects of 1,4-dioxane exposure on population growth rate in *Microcystis aeruginosa* and *Scenedesmus quadricauda*. In *M. aeruginosa*, cell inhibition occurred after 8-days of exposure and *S. quadricauda* at nominal concentrations under static conditions. The EC₅₀ of 575 mg/L and 5,600 mg/L were reported for *M. aeruginosa* and *S. quadricauda*, respectively.

Algae data in this assessment for 1,4-dioxane were assessed as acute and chronic endpoints regardless of duration and not separated into acute and chronic, because durations normally considered acute for other species (*e.g.*, 48, 72 hours) can encompass several generations of algae.

3.1.2 Weight of Scientific Evidence

The evaluation for environmental hazard data for 1,4-dioxane using the data quality review evaluation metrics and the rating criteria is described in the *Application of Systematic Review in TSCA Risk Evaluations* ([U.S. EPA, 2018b](#)). During data integration stage of the systematic review process, EPA analyzed, synthesized, and integrated information regarding 1,4-dioxane's toxicity. This involved evaluating evidence for quality and relevance, using a Weight of the Scientific Evidence (WoE) approach ([U.S. EPA, 2018b](#)).

During data evaluation of the relevant 1,4-dioxane studies, a rating of high, medium, or low for quality based on the TSCA criteria described in the *Application of Systematic Review in TSCA Risk Evaluations* was applied ([U.S. EPA, 2018b](#)). Only data/information rated as high, medium, or low for quality was used for the environmental risk assessment. While integrating environmental hazard data for 1,4-dioxane, EPA gave more weight and consideration to relevant data/information rated high or medium for quality. Any information rated as unacceptable was not used to characterize the hazard of 1,4-dioxane. The factors for determining if environmental data/information were relevant, were based on whether the source had biological, physical/chemical, and environmental relevance ([U.S. EPA, 1998](#)):

- **Biological relevance** – correspondence among the taxa, life stages, and processes measured or observed and the assessment endpoint.
- **Physical/chemical relevance** – correspondence between the chemical or physical agent tested and the chemical or physical agent constituting the stressor of concern.
- **Environmental relevance** – correspondence between test conditions and conditions in the region of concern ([U.S. EPA, 1998](#)).

EPA used this weight-of-evidence approach to assess hazard data and develop COCs. Given the available data, EPA only used studies assigned an overall quality level of high or medium to derive COCs for each taxonomic group. To calculate COCs, EPA derived geometric means for each trophic level that had comparable toxicity values (*e.g.*, multiple EC₅₀s measuring the same or comparable effects from various species within a trophic level). EPA did not use non-definitive toxicity values (*e.g.*, EC₅₀ > 48 mg/L) to derive geometric means because these concentrations of 1,4-dioxane were not high enough to establish an effect on the test organism.

To assess aquatic toxicity from acute exposures, data for three taxonomic groups were available: fish, aquatic invertebrates and algae. For each taxonomic group, data were available for these species as shown in Table 3-1. For acute or short-term exposure, the most biologically relevant species are *Microcystis aeruginosa* ([Bringman and Kuhn, 1977](#)) and *Daphnia magna* ([Brooke, 1987](#)).

The effects of 1,4-dioxane via the sediment pathway were not quantitatively assessed because 1,4-dioxane is expected to remain in aqueous phase and not adsorb to sediment due to its water solubility (>800 g/L) and low partitioning to organic matter (Log K_{oc} = 0.4). As stated in Sections 2.1 and 5.4.2 Appendix E, 1,4-dioxane concentrations in sediment pore water are expected to be similar to the concentrations in the overlying water and any detection of the chemical in sediments is likely from pore water and not the sorption potential to the sediment solids.

To assess aquatic toxicity from chronic exposures, data for three fish studies were evaluated. The most sensitive species were a 28-day LOEC of 565 mg/L measuring growth and survival in *P. promelas* ([Dow Chemical, 1989a](#)).

To assess the toxicity of 1,4-dioxane to algae, data for two species were available from high quality studies. The most sensitive endpoint reported for algae (*Microcystis aeruginosa*) was a 8-day EC₅₀ of 575 mg/L from Bringman and Kuhn ([1977](#)).

Concentrations of Concern (COC)

The concentrations of concern (COCs) for aquatic species were calculated based on the environmental hazard data for 1,4-dioxane, using the weight of evidence approach described above and using EPA methods ([Suter, 2016](#); [U.S. EPA, 2013c, 2012d](#)). For 1,4-dioxane, EPA derived an acute COC, a chronic COC, and an algal COC (see Table 3-2.).

After weighing the scientific evidence and selecting the appropriate toxicity values from the integrated data to calculate an acute and chronic COC, an assessment factor (AF) was applied according to EPA methods ([Suter, 2016](#); [U.S. EPA, 2013c, 2012d](#)). The application of UFs provides a lower bound effect level that would likely encompass more sensitive species not

specifically represented by the available experimental data. Assessment factors also account for differences in inter- and intra-species variability, as well as laboratory-to-field variability. These AFs are dependent on the availability of datasets that can be used to characterize relative sensitivities across multiple species within a given taxa or species group. However, they are often standardized in TSCA risk evaluations because of the limited data available for most industrial chemicals. For fish and aquatic invertebrates (*e.g.*, daphnia), the acute COC values are divided by an AF of 5. For chronic COCs, an AF of 10 is used ([U.S. EPA, 2013c](#), [2012d](#)).

Table 3-2. Concentrations of Concern (COCs) for Aquatic Toxicity

Environmental Toxicity	Effects	Hazard Value	Assessment Factor	Concentration of Concern (COC)	Reference	Score
<i>Algae (Short-term)</i>						
<i>Microcystis aeruginosa</i> 8-day EC ₅₀	Growth Rate	575 mg/L	10	57,500 µg/L	Bringman and Kuhn (1977)	High
<i>Chronic toxicity</i>						
<i>Pimephales promelas</i> 32-d LOEC	Grow and Survival	145 mg/L	10	14,500 µg/L	Dow Chemical (1989a)	High

The concentrations of concern (COCs) for aquatic species were calculated based on the environmental hazard for 1,4-dioxane using the weight of evidence approach described above and EPA methods ([Suter, 2016](#); [U.S. EPA, 2013c](#), [2012d](#)). For 1,4-dioxane algae was the most biological and environmental relevant species for short-term exposure to the chemical. As stated in the previous section, algae endpoint was assessed separately and was not evaluated for an acute or chronic COCs because durations normally considered acute for other species (*e.g.*, 48, 72 hours) can encompass several generations of algae.

The short-term toxicity to algae concentrations of concern (COC) was derived from an 8-day algae study where the EC₅₀ is 575 mg/L ([Geiger et al., 1990](#)). This value was then divided by the assessment factor (AF) of 10 for algae.

The algal COC = (575 mg/L) / AF of 10 = 57.5 mg/L x 1000 = 57,500 µg/L or ppb.

- The algal COC is 57,500 ppb.

For the chronic COC, the lowest chronic toxicity value is from a chronic 32-day MATC fathead minnow study of > 145 mg/L ([Brooke, 1987](#)). This value was divided by an assessment factor of 10 then multiplied by 1,000 to convert from mg/L to µg/L or ppb.

The lowest value for 32-day fish MATC = 145 mg/L / 10 = 14.5 x 1000 = 14,500 µg/L or ppb. Therefore, the chronic COC for 1,4-dioxane is 14,500 ppb based on the lowest chronic toxicity value.

3.2 Human Health Hazards

3.2.1 Approach and Methodology

EPA used the approach described in Figure 3-1 to evaluate, extract and integrate 1,4-dioxane's human health hazard and dose-response information. This approach is based on the *Application*

of Systematic Review in TSCA Risk Evaluations (U.S. EPA, 2018b) and the Framework for Human Health Risk Assessment to Inform Decision Making (U.S. EPA, 2014d).

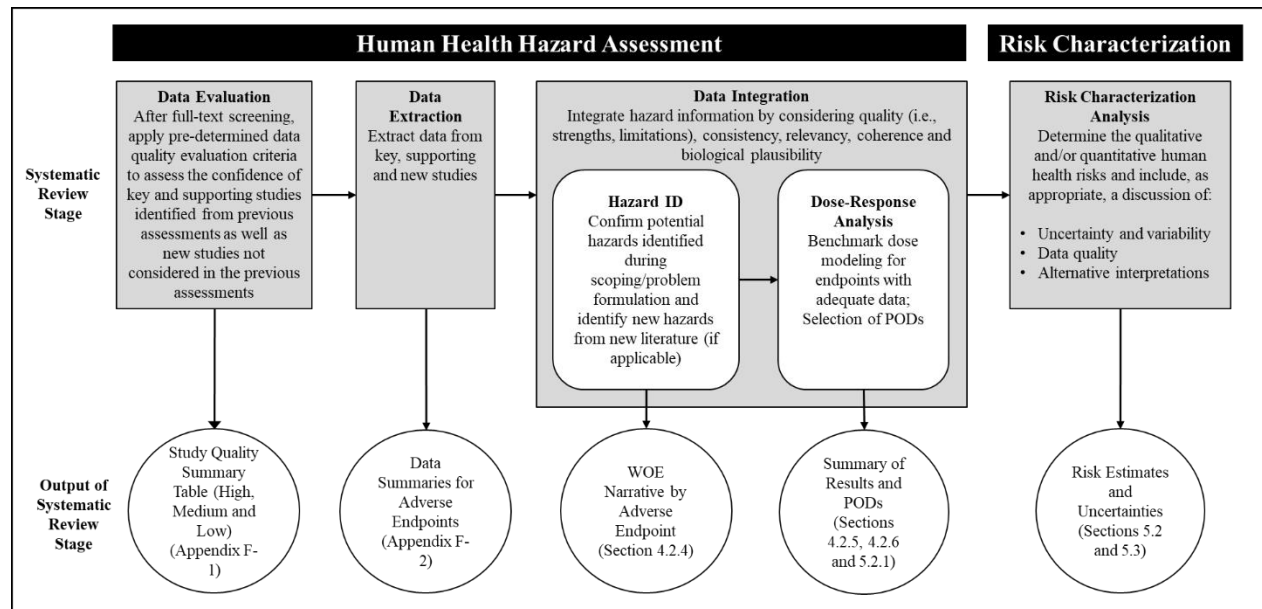


Figure 3-1. EPA Approach to Human Health Hazard Identification and Dose-Response for 1,4-Dioxane

Specifically, EPA reviewed key and supporting information from previous hazard assessments [EPA IRIS Assessments (U.S. EPA, 2013d, 2010), an ATSDR Toxicological Profile (ATSDR, 2012), a Canadian Screening Assessment (Health Canada, 2010), a European Union (EU) Risk Assessment Report ECJRC (2002), and an Interim AEGL (U.S. EPA, 2005b)]. EPA also screened and evaluated new studies that were published since these reviews, as identified in the literature search conducted for 1,4-dioxane (*1,4-Dioxane (CASRN 123-91-1) Bibliography: Supplemental File for the TSCA Scope Document, EPA-HQ-OPPT-2016-0723*).

The new literature was screened against inclusion criteria in the PECO statement and the relevant studies (*e.g.*, potentially useful for dose-response) were further evaluated using the data quality criteria for human, animal, and *in vitro* studies described in the *Application of Systematic Review in TSCA Risk Evaluations* (U.S. EPA, 2018b). EPA skipped the screening step of the key and supporting studies and entered them directly into the data evaluation step based on their relevance to the risk evaluation. Hazard studies by all routes of exposure were included since inhalation exposures are directly relevant to workers and oral exposures can be used in route-to-route extrapolation for dermal risk to workers.

EPA considered studies of low, medium, or high confidence for hazard identification and dose-response analysis. Information that was rated unacceptable was not included in the risk evaluation. Appendix I presents the information on human health hazard endpoints (acute, non-cancer, and cancer) for all acceptable studies (with low, medium, or high scores).

EPA has not developed data quality criteria for all types of hazard information. This is the case for toxicokinetics and many types of mechanistic data which EPA typically uses for qualitative

support when synthesizing evidence. As appropriate, EPA summarized and qualitatively evaluated the quality of these data to determine the extent to which they could contribute to hazard characterization.

Following the data quality evaluation, EPA extracted the toxicological information from each relevant study (Figure 3-1. EPA Approach to Human Health Hazard Identification and Dose-Response for 1,4-Dioxane). In the last step, the strengths and limitations of the data are evaluated for each endpoint and a weight-of-the-scientific evidence narrative is developed. Also, data for each selected hazard endpoint is modeled to determine the dose-response relationship (Appendix K). Finally, the results are summarized, and the uncertainties are presented.

Adverse health effects associated with inhalation exposure to 1,4-dioxane were identified by considering the quality and weight-of-the-scientific evidence to identify key endpoints. The potential mode of action (MOA) for cancer was evaluated according to the framework for MOA analysis described in the EPA [Guidelines for Carcinogen Risk Assessment \(U.S. EPA, 2005a\)](#). Information for each adverse hazard endpoint (acute and chronic non-cancer and cancer) was evaluated and integrated with information on toxicokinetics and MOA in a weight-of-the-scientific evidence narrative (Section 3.2.3). Information on MOA was evaluated in Section 3.2.4. The evidence for genotoxicity is summarized in Appendix I.1.5.

Data for the dose-response assessment were selected from the key studies and dose-response modeling was performed, when the data were amenable to modeling, for adverse hazard endpoints from those studies (Section 3.2.6). The dose-response assessment included analyses of the non-cancer and cancer endpoints for inhalation and oral exposures identified in the hazard identification. Limited toxicological data are available by the dermal route, so the dose-response data from oral exposures were used to extrapolate to dermal exposures according to the European Chemical Agency's *Guidance on information requirements and chemical safety assessment, Chapter R.8: Characterisation of dose [concentration]-response for human health* ([ECHA, 2008](#)).

3.2.2 Toxicokinetics

EPA accepted conclusions about the validity of toxicokinetic data and physiologically-based pharmacokinetic (PBPK) models based on previous peer reviews. In the 2013 EPA IRIS assessment of 1,4-dioxane ([U.S. EPA, 2013d](#)), the quality of the toxicokinetic data (published through 2013) and PBPK models were evaluated according to established standard operating procedures (SOPs) and a quality assurance project plan. SOPs for identification, organization, and evaluation of absorption, distribution, metabolism, and elimination (ADME) and toxicokinetic studies and models have since been updated and consolidated into *An Umbrella Quality Assurance Project Plan (QAPP) for PBPK Models* ([U.S. EPA, 2018f](#)). In addition, the IRIS assessment followed procedures contained in *Approaches for the Application of Physiologically Based Pharmacokinetic (PBPK) Models and Supporting Data in Risk Assessment* ([U.S. EPA, 2006a](#)).

In addition to the toxicokinetic studies summarized in the IRIS assessment, two additional toxicokinetic studies identified in the literature search ([Göen et al., 2016](#); [Take et al., 2012](#)) were considered in the weight-of-the-scientific evidence evaluation.

Absorption

Following inhalation exposure, 1,4-dioxane enters systemic circulation. In a study with four adult male volunteers exposed to a concentration of 50 ppm, uptake of 1,4-dioxane into plasma was rapid and approached steady-state conditions by 6 hours ([Young et al., 1977](#)). In a slightly larger study (6 individuals/group), volunteers were exposed to 20 ppm 1,4-dioxane for 8 hours. Mean blood concentrations were 0.98 mg/L after 4 hours and 1.1 mg/L after 8 hours, indicating that blood concentrations were approaching steady state within four hours. Volunteers in the same study who exercised for 10 minutes during each hour of the exposure had higher mean blood concentrations, reaching 1.48 mg/L after 4 hours and 1.47 mg/L after 8 hours ([Göen et al., 2016](#); [1977](#); [Young et al., 1976](#)). Systemic uptake of 1,4-dioxane following inhalation exposure has also been demonstrated in animal studies. In rats inhaling 50 ppm 1,4-dioxane for 6 hours, plasma concentrations averaged 7.3 µg/mL ([Young et al., 1978a, b](#)). In male rats exposed to 250 ppm, 1,4-dioxane reached steady-state blood concentrations within three hours ([Take et al., 2012](#)).

No human data are available to evaluate oral absorption of 1,4-dioxane. In male rats administered [¹⁴C]-1,4-dioxane via oral gavage at single doses of 10, 100, or 1,000 mg/kg or as 17 consecutive doses of 10 or 1,000 mg/kg/day, 75-98% of the administered radioactivity (depending on dose) was recovered in the urine while only 1-2% of administered radioactivity was recovered in feces, indicating that 1,4-dioxane is highly absorbed by the gastrointestinal tracts ([Young et al., 1978a, b](#)). Another study in male rats showed that, following a single oral gavage dose of 65 mg/kg-bw, maximum blood concentrations peaked 60 minutes after exposure. 1,4-Dioxane was still detected in blood at 480 minutes but not at 720 minutes following exposure ([Take et al., 2012](#)).

Dermal absorption studies using human skin (*in vitro*) and nonhuman primates (*in vivo*) measured reduced absorption compared to other routes of exposure, due in part to evaporation of 1,4-dioxane. [Bronaugh \(1982\)](#) measured *in vitro* penetration of 1,4-dioxane through excised human skin under occluded and unoccluded conditions. Absorption was recorded 205 minutes after application of radiolabeled 1,4-dioxane dissolved in lotion. Dermal penetration of 1,4-dioxane in lotion was 3.2% of the applied dose for the occluded condition and 0.3% for the unoccluded situation. In this study, rapid evaporation was observed, decreasing the amount available for dermal absorption. [Marzulli et al. \(1981\)](#) exposed rhesus monkeys to radiolabeled 1,4-dioxane (in methanol or skin lotion vehicle) for 24 hours under unoccluded conditions on the forearm. Approximately 2-3% of the original radiolabel was cumulatively recovered in urine over a 5-day period, but it is not clear how the study accounted for metabolism. In this risk evaluation, a tiered approach was used to characterize dermal absorption in the dermal exposure assessment (see Section 2.4.1.1.13).

Distribution

There are no data available on the distribution of 1,4-dioxane in human tissues. Based on limited data in animal studies, 1,4-dioxane is expected to evenly distribute to major organs.

[Take et al. \(2012\)](#) observed distribution to multiple systemic tissues (lung, liver, brain, kidney, and abdominal fat) in rats following administration via inhalation, oral, or combined inhalation and oral exposures. 1,4-Dioxane concentrations in these tissues reached steady state after 180 minutes of inhalation exposure. 1,4-Dioxane in these tissues remained detectable 120 minutes

after exposure ended but was non-detectable after 360 minutes. Following a single oral gavage exposure, 1,4-dioxane reached peak concentrations in all of these tissues 60 minutes after exposure and was no longer detectable in tissue 720 minutes after exposure. Intraperitoneal (i.p.) injection studies in rats found roughly even distribution of radiolabeled 1,4-dioxane in the tissues observed (whole blood, brain, liver, kidney, spleen, lung, colon, testes and skeletal muscle) with no evidence of appreciable accumulation of 1,4-dioxane or HEAA in tissues ([Mikheev et al., 1990](#); [Woo et al., 1977b](#); [Mikheev et al., 1990](#); [Woo et al., 1977b](#)).

It is not known whether 1,4-dioxane or metabolites can cross the placenta or enter breast milk. 1,4-Dioxane is quickly eliminated and is hydrophilic, properties that suggest that it may be less likely to be detected in breast milk following exposure. However, PBPK modeling based on experimentally derived partition coefficients for 1,4-dioxane suggest a high degree (18%) of lactational transfer of 1,4-dioxane ([Fisher et al., 1997](#)). There are currently no measurements of 1,4-dioxane in milk following human or animal exposures available for comparison to this model prediction.

Metabolism

1,4-Dioxane is metabolized in humans and rats by oxidation (Figure 4-2) ([Göen et al., 2016](#); [Braun and Young, 1977](#); [Woo et al., 1977c](#)). The primary metabolite of 1,4-dioxane in systemic circulation appears to be HEAA. HEAA may tautomerize to the potentially reactive lactone 1,4-dioxane-2-one, but the equilibrium is heavily weighted towards metabolism to HEAA under physiological conditions ([Woo et al., 1977c](#); [Young et al., 1977](#)). The majority of 1,4-dioxane that enters systemic circulation is metabolized. HEAA content detected in urine exceeded concentrations of 1,4-dioxane by a ratio of 118:1 in workers exposed to a TWA of 1.6 ppm for 7.5 hours ([Young et al., 1976](#)) and by a ratio of 3,100:1 in rats inhaling 50 ppm 1,4-dioxane for 6 hours ([Young et al., 1978a, b](#)). In adult male volunteers exposed to 50 ppm for 6 hours ([Young et al., 1977](#)), over 99% of inhaled 1,4-dioxane (assuming negligible exhaled excretion) appeared in the urine as HEAA. The linear elimination of 1,4-dioxane in both plasma and urine indicated that 1,4-dioxane metabolism was a nonsaturated, first-order process at this exposure level.

Induction of CYP450 increases the amount of HEAA in urine and suppression of CYP450 decreases the amount of HEAA in urine, demonstrating that 1,4-dioxane metabolism is in part mediated by CYP450 ([1978, 1977c](#)). Following oral exposure, 1,4-dioxane induces several CYP450 isomers in liver microsomes including CYP2B1/2, CYP2C11, CYP2E1, and CYP3A, but not CYP4A1 ([Nannelli et al., 2005](#)). EPA evaluated two new metabolism studies (data evaluation results in Appendix I) that measured *in vitro* hepatic microsomal CYP2E1 enzyme activity ([Patil et al., 2015](#); [Shah et al., 2015](#)). 1,4-Dioxane exhibited dose-dependent inhibition of the CYP2E1-mediated p-nitrophenol hydrolase activity ([Patil et al., 2015](#)) and inhibited the metabolism of water-soluble substrates of CYP450 in liver microsomes ([Shah et al., 2015](#)).

Local metabolism of 1,4-dioxane may result in tissue-specific metabolites that could contribute to tissue-specific toxicity. Following oral exposure in rats, 1,4-dioxane induced CYP2E1 expression and increase CYP2E1 mRNA in kidneys and nasal mucosa, indicating induction is mediated by transcriptional control. In contrast, 1,4-dioxane induced CYP2E1 without any change in mRNA in liver tissue and there was no CYP2E1 induction in lung tissue ([Nannelli et](#)

al., 2005). Differences in CYP2E1 induction mechanisms in liver, kidney, and nasal mucosa suggest that induction is controlled in a tissue-specific manner.

Metabolism of 1,4-dioxane generally appears to follow first-order kinetics, and there is some evidence for metabolic saturation following oral or intravenous (i.v.) exposure at high doses. Also, as i.v. doses increase, the percentage of urinary HEAA decreases, while the percentage of 1,4-dioxane in exhaled air increases (Young et al., 1978a). This effect was observed in rats after a single i.v. dose and occurred when blood levels were near 100 µg/mL (Young et al., 1978b; Kociba et al., 1975).

In contrast, no evidence of metabolic saturation has been reported following inhalation exposure. In a 13-week inhalation study, metabolic saturation was not observed at plasma concentrations up to 730 and 1,054 µg/mL in male and female rats, respectively (Kasai et al., 2008). Following 12 weeks of inhalation exposure to 400-3200 ppm 1,4-dioxane, plasma concentrations increased linearly with dose, consistent with first-order kinetics. The lack of metabolic saturation in the Kasai et al. (2008) study is likely attributed to 1) enhanced metabolism due to induction of P450 enzymes (including CYP2E1) by 13 weeks of repeated inhalation exposure to 1,4-dioxane, and/or 2) toxicokinetic differences between oral and inhalation exposures (first-pass metabolism following oral ingestion may enhance the saturation effect because the liver receives higher exposure).

Take et al. (2012) exposed rats to 1,4-dioxane by inhalation and oral gavage (single-route and simultaneous multi-route exposures) and observed a synergistic effect of combined exposures on systemic concentrations. During multi-route exposures (which resulted in high systemic concentrations of 1,4-dioxane), ingested 1,4-dioxane was not cleared as rapidly as it was under oral-only exposure. There was less of an impact of combined exposures on the clearance of inhaled 1,4-dioxane. This difference in clearance rates between inhalation and oral exposure routes further indicates a first-pass effect on the rate of metabolism of 1,4-dioxane from oral exposure.

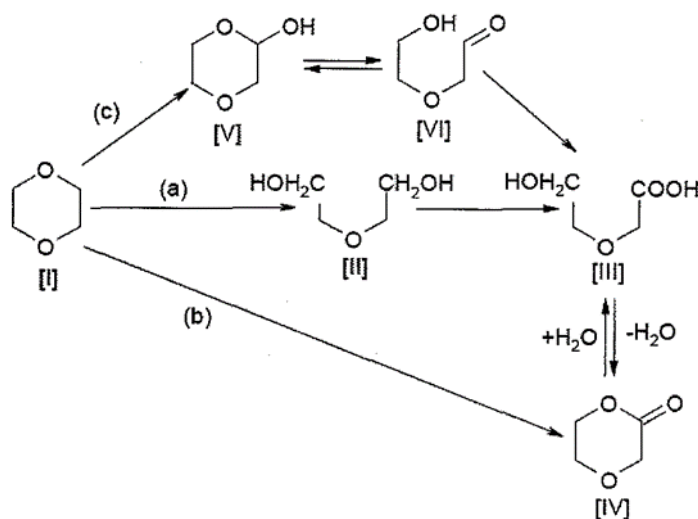


Figure 3-2. 1,4-Dioxane Metabolism Pathways

I= 1,4-dioxane; II = diethylene glycol; III = p-hydroxyethoxy acetic acid (HEAA); IV = 1,4-dioxane-2-one; V = 1,4-dioxane-2-ol; VI = hydroxyethoxy acetaldehyde

Elimination

Elimination of 1,4-dioxane in humans and rats is primarily via urine in the form of the metabolite HEAA ([Göen et al., 2016](#); [1978a](#); [Young et al., 1976](#)). The elimination half-life of 1,4-dioxane in plasma was approximately 1 hour in humans and rats and elimination of HEAA in urine was 2.7 hours ([Young et al., 1977](#)). These short half-lives of 1,4-dioxane and the metabolite HEAA indicate that repeated daily exposures would not be expected to result in the accumulation of 1,4-dioxane or HEAA in workers' bodies. First-order kinetics, in which the amount eliminated will be dependent on the maximum blood/plasma concentration and not on time may also explain the lack of accumulation.

Physiologically-Based Pharmacokinetic (PBPK) Models

EPA did not use PBPK models for the derivation of points of departure (PODs) for 1,4-dioxane or use a PBPK model for route-to-route or cross-species extrapolation in this risk evaluation. The 2010 and 2013 EPA IRIS assessments of 1,4-dioxane evaluated several empirical toxicokinetic models, PBPK models, and supporting data ([Sweeney et al., 2008](#); [Fisher et al., 1997](#); [Leung and Paustenbach, 1990](#); [Reitz et al., 1990](#); [1978a](#); [Young et al., 1977](#)) and concluded that none were adequate for use in dose-extrapolation between species.

Recent toxicokinetics studies include [Take et al. \(2012\)](#) and [Göen et al. \(2016\)](#). [Take et al. \(2012\)](#) provides time course toxicokinetic data in multiple tissues for rats exposed via inhalation, oral ingestion, and combined inhalation and oral ingestion. [Göen et al. \(2016\)](#) provides blood and urine data from human volunteers exposed via inhalation at a 1,4-dioxane concentration of 20 ppm for approximately 8 hours (with data spanning 24 hours). EPA reviewed the data in [Göen et al. \(2016\)](#) and concluded that observations in this more recent study are generally consistent with data from a previous study ([Young et al., 1977](#)). EPA concluded the inadequacies and calibration issues in the human PBPK model previously considered by EPA ([2013d](#)) would not be resolved by the additional data in [Göen et al. \(2016\)](#). Significant uncertainties remain regarding the appropriate internal dose metric that would be used. Specifically, there are uncertainties on whether the parent compound or metabolite (or some combination of both) are responsible for the observed effects of 1,4-dioxane, and uncertainty whether organ-specific or blood concentrations should be used.

3.2.3 Hazard Identification

For the human health hazard identification, EPA identified key and supporting studies from previous peer reviewed assessments and new studies published since 2009 (the year the most recent searches for oral studies were completed for the IRIS assessment) and evaluated them against the data quality criteria. This section summarizes the key, supporting and new studies, data on non-cancer hazards (Section 3.2.3.1), genetic toxicity and cancer hazards (Section 3.2.3.2) along with the results of the data quality evaluation (Appendix I). Potential modes of action for 1,4-dioxane toxicity related to the cancer endpoints were evaluated (Section 3.2.4). EPA reviewed the oral and inhalation studies to include in the weight-of-the-scientific evidence analysis, route-to-route extrapolation, and for the cancer classification.

3.2.3.1 Non-Cancer Hazards

EPA reviewed the reasonably available toxicity data on 1,4-dioxane by the inhalation, oral, and dermal routes of exposure from acute, short term, subchronic, and chronic studies. No dermal toxicity studies were identified for 1,4-dioxane. The identified hazard endpoints in the studies were evaluated for consistency and relevance to humans, according to the *Application of Systematic Review in TSCA Risk Evaluations* (U.S. EPA, 2018b). The results of the data quality evaluation for the non-cancer studies (key and supporting studies and new studies) are described here and included in the data extraction summary tables in Appendix I. Study quality of controlled human exposure studies were not quantitatively evaluated because EPA has not yet developed data quality criteria for this type of study. While EPA could not quantitatively evaluate their study quality, those studies are included in this discussion to provide a more complete picture of the available evidence for 1,4-dioxane toxicity.

Toxicity Following Acute and Short-Term Exposure

EPA evaluated studies describing the acute and short-term toxicity of 1,4-dioxane in humans and in experimental animals. Each of these studies is discussed below, followed by a summary table (Table 3-3.) of the studies that EPA concluded were the highest quality and suitable for carrying forward with evidence integration in Section 3.2.5.

Controlled human studies reported few perceivable signs or symptoms following acute exposures to 1,4-dioxane. When effects were observed, acute exposure primarily caused irritation to the eyes, nose, and throat depending on the exposure duration and concentration. For example, [Ernstgard et al. \(2006\)](#) reported that 12 volunteers (6 men and 6 women) exposed to 1,4-dioxane at 20 ppm (*i.e.*, 72 mg/m³) for two hours at rest produced no symptoms of irritation, headache, fatigue, or nausea, whereas [Young et al. \(1977\)](#) reported eye irritation in 4 healthy male volunteers exposed for 6 hours to 50 ppm (180 mg/m³). Further, [Yant et al. \(1930\)](#) and [Wirth and Klimmer \(1936\)](#) reported that exposures of greater than 1000 ppm (3603 mg/m³) for short durations (minutes) elicited irritation of mucous membranes in human volunteers. In contrast to the controlled human volunteer studies, [Johnstone \(1959\)](#) reported the fatality of one worker after 1 week of occupational exposures to 1,4-dioxane, which was used as a cleaning agent. The mean measured air concentration in the area was 470 ppm (1694 mg/m³) (range, 208-650 ppm, 749-2342 mg/m³). An autopsy on the worker revealed pathological effects in the liver, kidney, lung, and brain.

In experimental animals, acute and short-term exposures to 1,4-dioxane have been shown to cause comparable signs of toxicity as identified in acutely exposed humans, including eye and nasal irritation, clinical signs of central nervous system (CNS) depression (including staggered gait, narcosis, paralysis, coma, and death), liver and kidney degeneration and necrosis, and death (U.S. EPA, 2013a, 2005b).

The available acute toxicity studies in experimental animals include inhalation studies aimed at identifying adverse effects other than mortality (*i.e.*, [Mattie et al. \(2012\)](#); [Drew et al. \(1978\)](#)).

Drew et al. (1978) performed an acute 4-hour inhalation (whole body) exposure study in male Sprague-Dawley rats. Animals (15 animals serving as their own controls) were exposed to 1,4-dioxane vapors (>99% pure) at concentrations of 0, 3603 or 7207 mg/m³. The authors reported

an increase in the activities of several serum enzymes associated with liver function in all treated animals compared to controls.

Mattie et al. (2012) performed an acute 6-hour inhalation (whole body) exposure study in male/female F344/DuCrI rats. Animals (10/sex/group) were exposed to 1,4-dioxane vapors (>99% pure) at 0, 429, 1013, 2875, 7920 or and 21,630 mg/m³. Effects were limited to vacuolar changes in the nasal cavities (olfactory and respiratory epithelium) at two days post-exposure, but not in rats after a two-week recovery period.

The available short-term toxicity studies in experimental animals include two-week inhalation studies in adult rats (*i.e.*, [Mattie et al. \(2012\)](#); [Goldberg et al. \(1964\)](#)) and one oral (gavage) developmental toxicity study in female rats exposed on gestation days 9 to 15 (*i.e.*, [Giavini et al. \(1985\)](#)).

Mattie et al. (2012) performed a two-week inhalation (whole body) toxicity study in male/female F344/DuCrI rats. Animals (16/sex/group) were exposed to 1,4-dioxane vapors (>99% pure) at 0, 378, 5599, and 11,690 mg/m³ for 6 hours/day, 5 days/week, for two weeks. Animals were sacrificed on post-exposure day 1 or day 14. The authors reported lesions in the nasal cavity, kidney, and liver (including hepatic single cell necrosis) in the exposed animals on post-exposure day 1. Liver effects were still present in exposed animals on post-exposure day 14. The authors identified a LOAEC of 378 mg/m³, based on the liver effects.

In a separate two-week inhalation (whole body) toxicity study, Goldberg et al. (1964) exposed female Sprague-Dawley (CFE) rats (8/group) to 1,4-dioxane vapors (purity not stated) at concentrations of 0, 5405, 10,810, or 21,620 mg/m³ for 4 hours/day, 5 days/week, for two weeks. The authors identified a NOAEC of 5405 mg/m³, based on CNS effects (*i.e.*, decreased avoidance behavior) in the mid- and high-concentration exposure groups.

In a developmental toxicity study, Giavini et al. (1985) administered 1,4-dioxane (99% pure) by oral gavage to pregnant Sprague Dawley rats (18-20 per dose group) at dose levels of 0, 250, 500, or 1,000 mg/kg/d on gestation days 6-15. In the high-dose group, dams' food consumption decreased at early timepoints and increased at later timepoints while maternal weight gain slightly decreased. Fetal birth weight and ossification of the sternbrae significantly decreased at the highest dose. There was a of doubling in the rate of hemisternbrae in the 500 mg/kg/d dose group relative to the lower dose group, though this effect was not statistically significant. The authors identified a NOAEL of 500 mg/kg/d and a LOAEL of 1,000 mg/kg/d based on the reduced fetal weights and delayed ossification.

Of the available acute and short-term studies, EPA concluded that the studies performed in experimental animals represented the highest quality data from which to assess potential risks to workers. EPA considered the human exposure studies as supporting information, given the general consistency of effects seen in humans and experimental animals. However, there were limitations with the human studies that precluded their use for quantitative risk assessment, including for example, the absence of measures of systemic effects (*e.g.*, serum chemistry panels). Therefore, EPA selected the studies listed in Table 3-3. (described in more detail in Appendix I) with a data quality rating of medium or high for evidence integration and evaluation.

Table 3-3. Acceptable Studies Evaluated for Toxicity of 1,4-Dioxane Following Acute or Short-term Exposure^a

ACUTE			
Data Source	Study Description ^b	Hazards Evaluated; Effects reported; POD	Data Quality Rating
Drew et al. (1978)	4-hour inhalation (whole body) study in rats; 0, 3603 or 7207 mg/m ³	Clinical Chemistry; Increased serum liver enzymes; LOAEC = 3603 mg/m ³	Medium
Mattie et al. (2012)	6-hour inhalation (whole body) study in rats; 0, 429, 1013, 2875, 7920 and 21,630 mg/m ³	Body Weight, Irritation, Hepatic, Renal, Respiratory; Vacuolar change in olfactory and respiratory epithelium (2 rats at two days but not 2 weeks after exposure); NOAEC = 2875 mg/m ³	Medium
SHORT-TERM			
Data Source	Study Description	Hazards Evaluated; Effects reported; POD	Data Quality Rating
Mattie et al. (2012)	10-day inhalation (whole body) study in rats; 6 hours/day, 5 days/week for two weeks; 0, 378, 5599 and 11,690 mg/m ³	Irritation, Hepatic, Renal, Respiratory; Lesions in nasal cavity, liver, and kidney; hepatic single cell necrosis; LOAEC = 378 mg/m ³	High
Goldberg et al. (1964)	10-day inhalation (whole body) study in rats; 4 hours/day, 5 days/week for two weeks; 0, 5405, 10,810 or 21,620 mg/m ³	Body Weight, Neurological/ Behavior; Decreased avoidance response; NOAEC = 5405 mg/m ³	Medium
DEVELOPMENTAL			
Data Source	Study Description	Hazards Evaluated; Effects reported; POD	Data Quality Rating
Giavini et al. (1985)	Oral (gavage) developmental study in rats (gestation days 6 to 15); 0, 250, 500, or 1000 mg/kg-d	Prenatal Development; Delayed ossification of the sternebrae and reduced fetal body weight; NOAEL = 500 mg/kg-d	High
^a For further details, see the data extraction summary table in Appendix I.			
^b Concentrations in ppm were converted to mg/m ³ using the following equation: ppm*mw (88.1)/24.45. 24.45 is the gas constant at 760 mm Hg (101 kPa) atmospheric pressure and at 25 °C.			

Subchronic and Chronic Non-Cancer Hazards- Inhalation

EPA evaluated studies describing the subchronic and chronic inhalation toxicity of 1,4-dioxane in animal studies. The results of the data evaluation are given in Table 3-4. and in the data extraction summary table in Appendix I.

Table 3-4. Acceptable Studies Evaluated for Non-Cancer Subchronic or Chronic Toxicity of 1,4-Dioxane Following Inhalation Exposure

Data Source	Study Description	Hazard Evaluated	Data Quality Rating
Kasai et al. (2008)	13-week inhalation study in rats	Mortality, Systemic Hepatic, Renal, Respiratory, Hematology, Clinical Chemistry	High
Kasai et al. (2009)	2-year chronic toxicity/cancer inhalation bioassay in rats	Mortality, Systemic, Hepatic, Renal, Respiratory, Hematological and Immune, Clinical Chemistry/Biochemistry, Nutrition and Metabolic, Reproductive, Cancer	High

In Kasai et al. (2008), 6-week-old F344/DuCrj rats (10/sex/group) were exposed to vaporized 1,4-dioxane (>99% pure) at concentrations of 0, 100, 200, 400, 800, 1600, 3200, or 6400 ppm (0, 360, 721, 1441, 2883, 5765, 11,530 or 23,060 mg/m³, respectively) for 6 hours/day, 5 days/week, for 13 weeks in whole body inhalation chambers. All rats in the 6400 ppm (23,060 mg/m³) group died by the end of the first week of exposure; at lower doses, mortality rates were not affected. The study authors determined the most sensitive endpoint to be nuclear enlargement in the respiratory epithelium, which was noted in both sexes, and identified a LOAEC of 100 ppm (360 mg/m³). EPA considers the toxicological significance of this effect to be equivocal, as it is found in any cell responding to stress (*i.e.*, adaptive response), transcribing mRNA (*i.e.*, biomarker of exposure), or undergoing proliferation (*i.e.*, normal cell cycle) (U.S. EPA, 2013d). While the proliferation may be in response to a carcinogenic agent, the impact on the progression from initiated cell to tumor remains unclear. Therefore, EPA considers the NOAEC for this study to be 100 ppm (360 mg/m³) based on statistically significantly increased relative lung weights (7-13%) in females at 200 ppm (721 mg/m³) and higher (p < 0.01 or 0.05). Dose-related increases in vacuolization of the olfactory epithelium was observed at the same concentrations with statistically significant increased observed at 800 ppm (2883 mg/m³) and higher (p < 0.01). Atrophy of the olfactory epithelium was also seen, although the dose-response was less clear.

In a 2-year chronic study (Kasai et al., 2009), male 6-week-old F344/DuCrj rats were exposed to vaporized 1,4-dioxane (>99% pure) at concentrations of 0, 50, 250, or 1250 ppm (0, 180, 900, or 4500 mg/m³, respectively) for 6 hours/day, 5 days/week, for 104 weeks in whole body inhalation chambers. Increased mortality was seen in the 1250 ppm (4504 mg/m³) group. Noncancer effects were seen in the nasal cavity, liver, and kidneys. Based on chronic nasal toxicity, including atrophy, respiratory metaplasia, and nuclear enlargement in the olfactory epithelium, and nuclear enlargement in the respiratory epithelium, the study authors identified the LOAEC to be 50 ppm (180 mg/m³). The study authors did not identify a NOAEC. As described above, the EPA does not typically consider nuclear enlargement alone to be an adverse effect. Thus, EPA concluded that the LOAEC for this study is 50 ppm (180 mg/m³) based on respiratory metaplasia and atrophy of the olfactory epithelium, which were both statistically significantly increased from controls (p < 0.01). Effects on the liver (histopathologic changes, including preneoplastic changes, increased weight, and altered liver enzyme) and kidneys (including histopathologic lesions, changes in kidney weight, serum chemistry, and urinalysis indices) in this study were observed at concentrations higher than those associated with olfactory and respiratory effects (Kasai et al., 2009).

EPA review of non-cancer inhalation hazards indicates that sub-chronic or chronic inhalation exposure to 1,4-dioxane is associated with effects in the olfactory epithelium, liver, and kidneys ([Kasai et al., 2009](#)) and changes in body weight and relative lung weight ([Kasai et al., 2008](#)). The most sensitive endpoints—respiratory metaplasia and atrophy of the olfactory epithelium—occurred at 50 ppm (180 mg/m³) after chronic (2-year) inhalation exposure in rats ([Kasai et al., 2009](#)).

Subchronic and Chronic Non-Cancer Hazards - Dermal

No repeated-dose dermal toxicity studies were identified on 1,4-dioxane. The available data suggest that delivery of 1,4-dioxane *via* the inhalation and oral routes of exposure result in comparable toxic endpoints. EPA performed route-to-route extrapolation to derive dermal PODs based on data from oral and inhalation exposures studies. There are uncertainties associated with extrapolation from either of these routes. The available inhalation studies were performed by whole body exposure rather than nose only exposure, which may have led to additional dosing by the oral and dermal routes of exposure, due to deposition on fur and the grooming behavior of rodents. EPA does not have information about the extent of 1,4-dioxane exposure through the oral pathway during whole body exposure, but inhalation doses used as the basis for dermal POD derivation in route-to-route extrapolation may underestimate total exposures achieved in whole body inhalation studies. Unlike dermal exposures, chemicals go through first pass metabolism after oral exposure before entering systemic circulation. EPA does not know which of these routes is most representative of risks from dermal exposures. It should also be noted that EPA was unable to conclude with certainty that comparable toxic endpoints would be associated with the dermal route of exposure, considering the expected quantitative ADME differences and the absence of an adequate PBPK model. Notwithstanding these uncertainties, EPA considered route-to-route extrapolation appropriate, considering the comparable toxic endpoints identified in the available repeated-dose oral/inhalation toxicity studies and the uncertainty with the putative toxicant (*i.e.*, 1,4-dioxane or a metabolite(s)).

Subchronic and Chronic Non-Cancer Hazards - Oral

The toxicity of 1,4-dioxane following oral exposure was evaluated in several subchronic or chronic drinking water studies ([2009](#); [Kano et al., 2008](#); [JBRC, 1998](#); [NCI, 1978](#); [Kociba et al., 1974](#); [Argus et al., 1965](#)). These studies and results of the data quality evaluation are presented in Table 3-5. and in Appendix I.

Table 3-5. Acceptable Subchronic and Chronic Studies Evaluated for Non-Cancer Toxicity of 1,4-Dioxane Following Oral Exposure

Data Source	Study Description	Hazard Evaluated	Data Quality Rating
Kociba et al. (1974)	2-year drinking water study in rats	Mortality, Body Weight, Hepatic, Renal, Cancer	High
Kano et al. (2009) ; also reported as JBRC (1998)	2-year drinking water chronic toxicity/ cancer bioassay in rats and mice	Body Weight, Hepatic, Renal, Hematological, Respiratory, Cancer	High
NCI (1978)	110-week (rats) or 90-week (mouse) drinking water chronic toxicity/ cancer bioassay	Mortality, Gastrointestinal, Hepatic, Renal, Respiratory, Cancer	Low
Argus et al. (1965)	64.5-week drinking water cancer bioassay in rats	Hepatic, Renal, Hematological, Respiratory, Cancer	Medium
Argus et al. (1973)	13 month drinking water study in rats	Hepatic, Renal, Respiratory, Cancer	Low
Kano et al. (2008)	13-week drinking water study in rats	Body Weight, Hepatic, Renal, Respiratory, Nervous System, Hematological	Medium
Dow Chemical (1989c)	11-week drinking water repeat dose oral <i>in vivo</i> DNA repair in rats	Body Weight, Hepatic, Genotoxicity	Medium

¹ Male rat data were evaluated as unacceptable.

1,4-Dioxane (purity not reported) was administered to 6-8-week-old Sherman rats (60/sex/dose) for up to 716 days via drinking water at concentrations of 0, 0.01, 0.1, or 1% ([Kociba et al., 1974](#)). The authors calculated the mean daily doses for males and females to be 0, 9.6, 94, or 1015 mg/kg-d and 0, 19, 148, or 1599 mg/kg-d, respectively. Mortality was increased in the high-dose groups. Noncancer effects occurred in the liver and kidneys. The most sensitive endpoints, regeneration of the liver (as indicated by hepatocellular hyperplastic nodule formation) and kidney (specifically, the renal tubular epithelium), were reported in male rats. The authors identified a LOAEL of 94 mg/kg-d and a NOAEL of 9.6 mg/kg-d.

Male and female rats (35/sex/dose) and mice (50/sex/dose) were administered 1,4-dioxane (>99.95% pure) for 110 or 90 weeks, respectively, via drinking water at concentrations of 0, 0.5, or 1% ([NCI, 1978](#)). Investigators calculated the average daily intakes of 1,4-dioxane to be as follows: male rats received 0, 240, or 530 mg/kg-d; female rats received 0, 350, or 640 mg/kg-d; male mice received 0, 720, or 830 mg/kg-d (decreased dose spacing due to decreased water consumption in high-dose mice); and female mice received 0, 360, or 860 mg/kg-d. Mortality was increased among treated rats. Noncancer effects were observed in the stomach (males only), liver (females only), and kidneys (both sexes). Based on gastric ulcers and renal cortical tubular degeneration in male rats, the authors determined the LOAEL in this study is 240 mg/kg-d; a NOAEL was not established ([NCI, 1978](#)). Increased mortality also occurred in mice. Noncancer effects on the respiratory system (pneumonia and rhinitis) were noted in both sexes, resulting in a LOAEL of 380 mg/kg-d. A NOAEL was not established in this study ([NCI, 1978](#)).

Results from a two-year drinking water study conducted on F344/DuCrj rats and Crj:BDF1 mice (50/sex/dose) by the Japan Bioassay Research Center ([JBRC, 1998](#)) have also been published as

Yamazaki et al. (1994) and Kano et al. (2009). 1,4-Dioxane (>99% pure) was administered at concentrations of 0, 200, 1000, or 5000 ppm; these concentrations were reported by Kano et al. (2009) to be the following approximate doses: male rats received 0, 11, 55, or 274 mg/kg-d; female rats received 0, 18, 83, or 429 mg/kg-d; male mice received 0, 49, 191, or 677 mg/kg-d; and female mice received 0, 66, 278, or 964 mg/kg-d.

In rats, slower growth rates and decreased terminal body weight were noted in high-dose groups of both sexes, as were changes in hematology and clinical chemistry and increased relative liver weight. Noncancer effects were observed in the nasal cavity, liver, and kidneys. Based on the liver effects (mixed cell foci and increased relative liver weight) in males, the LOAEL in this study is 55 mg/kg-d; the NOAEL is 11 mg/kg-d (Kano et al., 2009).

In mice, mortality was increased in females at the highest dose. Growth rates, terminal body weights, and water consumption were decreased in both sexes. Changes in hematology and clinical chemistry occurred in both sexes, as did increased lung weights. Respiratory, kidney, and liver effects also were observed. The LOAEL for female mice in this study is 278 mg/kg-d, based on inflammation in the nasal cavity; the NOAEL is 66 mg/kg-d. The LOAEL for male mice in this study is 191 based on changes in serum liver enzymes; the NOAEL is 49 mg/kg-d (Kano et al., 2009).

Argus et al. (1965) administered 1,4-dioxane (purity not reported) to 26 adult male Wistar rats for 64.5 weeks via drinking water at a concentration of 1%, which was calculated to be equivalent to 640 mg/kg-d. Noncancer effects were noted in the liver, kidney, and lungs. The LOAEL is 640 mg/kg-d based on glomerulonephritis and histological changes (enlarged hyperchromic nuclei and large cells with reduced cytoplasmic basophilia) observed in the liver at the only dose tested.

A follow-up study (Argus et al., 1973) exposed male Sprague Dawley rats (28-32/group) to 1,4-dioxane (purity not reported) for up to 13 months via drinking water at concentrations of 0, 0.75, 1, 1.4, or 1.8%, which are calculated to be equivalent to 0, 430, 574, 803, or 1032 mg/kg-d. Noncancer effects on the liver, kidney and lung were observed. The LOAEL is 430 mg/kg-d, based on histopathological lesions in the liver and kidney at the lowest dose tested. A NOAEL was not identified in this study.

Kano et al. (2008) administered 1,4-dioxane (>99% pure) to 6-week-old F344/DuCrj rats and Crj:BDF1 mice (10/sex/group) for 13 weeks via drinking water at concentrations of 0, 640, 1600, 4000, 10000, or 25000 ppm. The investigators calculated the approximate daily intake of 1,4-dioxane to be as follows: male rats received doses of 0, 52, 126, 274, 657, or 1554 mg/kg-d; female rats received 0, 83, 185, 427, 756, or 1614 mg/kg-d; male mice received 0, 86, 231, 585, 882, or 1570 mg/kg-day, and female mice received 0, 170, 387, 898, 1620, or 2669 mg/kg-day. Significant decreases in food and water consumption were noted among high-dose rats of both sexes, with final body weights reduced in the two highest dose levels. Respiratory, olfactory, brain, liver, and kidney effects were noted in rats. Nuclear enlargement of the respiratory epithelium of the nasal cavity (reported as at least 4 times the size in diameter as normal nuclei) and hepatocyte swelling were the most sensitive effects reported in male rats. As with the inhalation studies, the EPA does not consider nuclear enlargement to be an adverse effect; thus,

based on liver histopathology findings, the LOAEL is 126 mg/kg-day and the NOAEL is 52 mg/kg-day.

Decreased body weights and water consumption were also noted in mice. Several clinical chemistry parameters were changed and respiratory, olfactory, lung, and liver effects were seen. The most sensitive effects in mice, nuclear enlargement and degeneration of bronchial epithelium, occurred in females at 387 mg/kg-day, making the NOAEL 170 mg/kg-day ([Kano et al., 2008](#)).

Male SD rats (4-6/group) were administered 1,4-dioxane (>99% pure) in drinking water at doses of 0, 10, or 1000 mg/kg-d for 11 weeks, 7 days/week ([Dow Chemical, 1989c](#)). Positive (*i.e.*, dimethylnitrosamine) and vehicle controls were run concurrently. Repeated dosing at 1000 mg/kg-day 1,4-dioxane resulted in increased liver to body weight ratio and increased (1.5 fold) hepatic DNA synthesis with minimal hepatocellular swelling.

The EPA review of non-cancer oral hazards indicate that the key endpoints for 1,4-dioxane occur in the nasal cavity, lungs, liver, kidneys, and brain. The most sensitive effects were in the liver (degeneration and necrosis of hepatocytes) and kidneys (degeneration and necrosis of renal tubular cells) and occurred at 94 mg/kg-d; the NOAEL for liver and kidney effects is 9.6 mg/kg-d ([Kociba et al., 1974](#)).

3.2.3.2 Genetic Toxicity and Cancer Hazards

Genetic Toxicity

The genotoxicity of 1,4-dioxane has been tested in over 40 *in vitro* and *in vivo* studies. Briefly, 1,4-dioxane has been tested for genotoxic potential using various *in vitro* systems including prokaryotic organisms (*S. typhimurium* strains and *E. coli* strains), non-mammalian eukaryotic organisms, and mammalian cells, and *in vivo* systems using several strains of mice and rats. EPA previously evaluated these data in the IRIS assessment of 1,4-dioxane and concluded that 1,4-dioxane is either nongenotoxic or weakly genotoxic based on a weight-of-the-evidence analysis of the *in vitro* and *in vivo* genotoxicity studies ([U.S. EPA, 2013d](#)). That conclusion was based on the observations that 1,4-dioxane was not genotoxic in the large majority of *in vitro* systems tested, and that positive genotoxic responses were generally observed in the presence of cytotoxicity. It was not genotoxic in half of the available *in vivo* mammalian assays, although several studies have shown positive effects at or above doses of 1000 mg/kg/d.

In this risk evaluation, EPA considered the conclusions of the 2013 IRIS assessment and evaluated the data quality for the studies used to support those conclusions (Appendix I.1.5). EPA also identified and evaluated two key studies that were published after 2013 and had an acceptable data quality rating, shown in Table 3-6. These studies include two *in vivo* micronucleus assays that assessed the genotoxic potential of 1,4-dioxane in bone marrow and in liver ([Itoh and Hattori, 2019](#)) and two *in vivo* mutagenicity assays ([Itoh and Hattori, 2019](#); [Gi et al., 2018](#)). Each of these studies is summarized below, followed by EPA's interpretation of how these studies add to the weight-of-the-scientific evidence evaluation from the IRIS assessment on the potential for 1,4-dioxane to cause genotoxicity and/or mutagenicity.

Table 3-6. Acceptable New Studies Evaluated for Genetic Toxicity of 1,4-Dioxane

Data Source	Study Description	Hazards Evaluated	Findings	Data Quality Rating
Itoh and Hattori (2019)	<i>In vivo</i> micronuclei in rat bone marrow and liver	Micronuclei cell damage	Negative in bone marrow Positive in liver	High
	<i>In vivo</i> mutagenicity in rats	Gene mutation with <i>Pig-a</i> assay	Negative	
Gi et al. (2018)	<i>In vivo</i> mutagenicity in transgenic rats	Gene mutation GST-P-positive foci induction and cell proliferation	Positive	High

Itoh and Hattori (2019) investigated the ability of 1,4-dioxane (purity not stated) to induce micronuclei in the bone marrow of male F344 rats administered a single dose of 1,4-dioxane by gavage (water vehicle; 10 mL/kg) at dose levels of 1000, 2000, or 3000 mg/kg.

Cyclophosphamide served as the positive control. At 24 or 48 hours post dosing, bone marrow was harvested and the incidence of micronucleated immature erythrocytes (MNIE) was counted in a total of 2000 immature erythrocytes (IE) from each animal. At 24 hours, a statistically significant increase in the incidence of MNIE was observed in the 2000 mg/kg dose group. The authors concluded that this change was not toxicologically relevant because the value was within the laboratory's historical control range and no dose-dependency was observed. At 48 hours, a statistically significant decrease in the percentage of IE was observed in the 3000 mg/kg dose group. The positive control showed the expected statistically significant increase in MNIE at 24 hours. Based on these results, the authors concluded that 1,4-dioxane was not genotoxic in the bone marrow of rats.

The above findings are consistent with some of the mixed results from the bone marrow micronucleus studies summarized in the IRIS assessment. For example, Tinwell and Ashby (1994) performed mouse bone marrow micronucleus assays using male CBA mice and male C57BL6 mice. No increases in micronuclei were detected in male CBA mice 24 hours after treatment with a single dose of 1800 mg/kg 1,4-dioxane by oral gavage, and a non-statistically significant increase in micronuclei (*i.e.*, 1.6-fold) was reported in male C57BL6 mice treated with a single oral gavage dose of 3600 mg/kg. The authors concluded that 1,4-dioxane was not clastogenic under their test conditions. Comparable negative findings were reported by Mirkova (1994). The author reported no increases in bone marrow micronuclei in male BALB/c mice 24 hours after treatment with a single dose of 5,000 mg/kg by oral gavage. In contrast, Mirkova (1994) also reported a dose-dependent and statistically significant increase in the incidence of bone marrow micronuclei in male and female C57BL6 mice 24 and 48 hours after dosing by oral gavage with 900, 1800, or 3600 mg/kg. No micronuclei were detected in bone marrow of animals receiving a dose of 450 mg/kg. Additionally, Roy et al. (2005) reported dose-dependent and statistically significant increases in bone marrow micronuclei in male CD-1 mice administered 1,4-dioxane for five days at dose levels of 1500, 2500, or 3500 mg/kg-d. Based on

the results of Itoh and Hattori (2019) and the results of other investigations, noted above and summarized in the IRIS assessment, EPA concluded that the available bone marrow micronucleus assays suggest that 1,4-dioxane is genotoxic *in vivo* at high doses. The discrepant findings across studies may be due to methodological differences in the studies and/or differences in the sensitivity between specific strains of rats and mice.

In separate studies, Itoh and Hattori (2019) performed liver micronucleus assays to explore the potential mode of action by which 1,4-dioxane induced liver adenomas and carcinomas in chronically exposed rodents. The authors used three different study designs, including the juvenile rat (JR) method, the dosing before partial hepatectomy (pre-PH) method, and the dosing after PH (post-PH) method. In each of these studies, animals were administered either one or two doses of 1,4-dioxane by gavage (water vehicle; 10 mL/kg) at dose levels of 1000, 2000, or 3000 mg/kg. Diethylnitrosamine served as the positive control for clastogenicity in the JR and pre-PH studies, whereas carbendazim served as the positive control for aneugenicity in the post-PH study. In the JR study, animals were dosed on days 1 and 2, and livers were harvested on day 6. In the pre-PH study, animals were dosed on day 1, PH was performed on day 2, and livers were harvested on day 6. In the post-PH study, PH was performed on day -1, animals were dosed on day 1, and livers were harvested on day 4. For each of the studies, the authors evaluated liver-to-body weight ratios (*i.e.*, relative liver weight), micronucleated hepatocytes (MNH) among 2000 hepatocytes (excluding metaphase and nuclear fragment cells), and classified hepatocytes as mononucleated, binucleated, or multinucleated (*i.e.*, 3 or more nuclei). In the JR study, dose-dependent and statistically significant increases in MNH were observed in all treated animals. No changes were reported in relative liver weight or hepatocyte classifications. In the pre- and post-PH studies, dose-dependent, statistically significant increases in MNH were observed in all treated animals. In the pre-PH study, no changes in relative liver weights were reported, although binucleated hepatocytes were increased, albeit not statistically, in the high dose group. In the post-PH study, statistically significant increases in relative liver weights were reported in the low- and mid-dose groups; however, no changes in hepatocyte classification were observed. Based on these results, the authors concluded that 1,4-dioxane is clastogenic in the liver.

The MNH findings reported by Itoh and Hattori (2019) are consistent with the liver micronucleus assay results summarized in the IRIS assessment. For example, Morita and Hayashi (1998) reported dose-dependent and statistically significant increases in MNH in pre-PH male CD-1 mice administered 1,4-dioxane by gavage at dose levels of 2000 and 3000 mg/kg. Unlike Itoh and Hattori (2019), Morita and Hayashi (1998) did not identify MNH in mice that received a dose of 1000 mg/kg. Additionally, Roy et al. (2005) reported dose-dependent and statistically significant increases in MNH in male CD-1 mice administered 1,4-dioxane for five days at dose levels of 2500 or 3500 mg/kg-d. The authors did not identify MNH in mice administered 1500 mg/kg-d. Therefore, EPA concluded that the findings reported by Itoh and Hattori (2019) indicate that 1,4-dioxane is genotoxic *in vivo* in high dose experiments.

Itoh and Hattori (2019) also evaluated the potential of 1,4-dioxane (purity not stated) to induce gene mutations in the *in vivo* *Pig-a* assay. Male F344 rats were dosed by gavage (saline vehicle; 10 mL/kg-bw) on day 1 with 1000, 2000, or 3000 mg/kg. Prior to dosing (*i.e.*, day -1), peripheral

blood was sampled, as pre-treatment control values. Animals were then dosed on day 1 and peripheral blood was sampled on post-treatment days 15 and 20.

7,12-Dimethylbenz[a]anthracene (DMBA) served as the positive control. Erythrocytes were screened by flow cytometry analysis for CD59 negative cells, a marker of mutation in the *Pig-a* gene. No statistically significant differences were found at any dose level of 1,4-dioxane or sampling time compared to controls. DMBA-treated animals exhibited the expected statistically significant increase in CD59 negative cells on post-treatment days 15 and 20.

In a separate *in vivo* gene mutation assay, Gi et al. (2018) administered various doses of 1,4-dioxane (purity > 99.9%) to *gpt* delta transgenic F344 rats in drinking water for 16 weeks. The daily intake values were 0, 18.7, 92.3, and 440.2 mg/kg-d in one experiment, and 0, 0.02, 0.2, 1.9 mg/kg-d in a second experiment. A positive control was not included in these experiments. Body weights and liver-to-body weight ratios were statistically significantly decreased or increased, respectively, in animals from the high-dose group (*i.e.*, 440.2 mg/kg-d) compared to controls. The *gpt* mutation frequency in packaged phages from hepatic DNA and GST-P-positive foci per unit area of liver were increased in a dose-dependent manner and achieved statistical significance in the high-dose group compared to controls. The spectra of mutations in the high-dose group included statistically significant increases in A:T to G:C transitions and A:T to T:A transversions in the high-dose group. In the mid-dose group (*i.e.*, 92.3 mg/kg-d), the *gpt* mutation frequency was not statistically significantly different than the control values, although a statistically significant increase in A:T- to -T:A transversion frequency was reported. No additional statistically significant changes in mutation frequency were identified in the low dose group for transitions (*i.e.*, G:C to A:T), transversions (*i.e.*, A:T to C:G, G:C to C:G), deletions (*i.e.*, single or > double base pairs), or insertions (*i.e.*, single base pairs). Among several cell proliferation, cell cycle regulation, and DNA damage repair gene expression changes studied in the livers of *gpt* delta transgenic rats, a significant increase in PCNA was observed in the high-dose group. The authors interpreted these findings as support that 1,4-dioxane is a genotoxic carcinogen that induces hepatocarcinogenesis through a mutagenic mode of action.

Based on the above studies, the negative results reported by Itoh and Hattori (2019) are consistent with the negative results from the *in vitro* gene mutation studies summarized in the IRIS assessment. However, it is unclear whether the doses used by Itoh and Hattori (2019), albeit significantly high (up to 3,000 mg/kg), provided sufficient delivery to the bone marrow to induce mutations in the *Pig-a* gene. In contrast, Gi et al., (2018) reported positive *in vivo* mutagenicity findings in transgenic rats administered 1,4-dioxane by drinking water at the highest intake dose of 440 mg/kg/d. Gi et al., reported no genotoxic or mutagenic effect in transgenic animals in the lowest dose group (18.7 mg/kg/day).

Based on the weight of scientific evidence, EPA concluded that there is some evidence for genotoxicity *in vivo* at high doses, but there is insufficient evidence to conclude that 1,4-dioxane is mutagenic or induces cancer through a mutagenic mode of action.

Carcinogenicity via Inhalation Exposure

A human study of breast cancer incidence in participants in the California Teacher Study (active and retired female teachers and administrators) from 1995-2011, (n=112,378 women) examined

the association between breast cancer and exposure to ambient air concentrations of 1,4-dioxane ([Garcia et al., 2015](#)) (Table 3-7.). Exposure was determined using the National-Scale Air Toxics Assessment Modeled air concentrations. No significant association was found between breast cancer incidence and modeled annual average ambient air concentrations of 1,4-dioxane based on participant’s residential address. Though these data provide some insight on low-level exposures to 1,4-dioxane, they are not particularly informative with regard to any association between occupational exposures and the potential for developing breast cancer. Two occupational studies ([U.S. EPA, 2013d](#); [Buffler et al., 1978](#); [Thiess et al., 1976](#)) were inconclusive about cancer risk from 1,4-dioxane but they were limited by small sample sizes.

In the key inhalation cancer study for this risk evaluation ([Kasai et al., 2009](#)), groups of male F344 rats (50/group) were exposed to 0, 50, 250 and 1250 ppm (0, 180, 900 and 4500 mg/m³) of 1,4-dioxane for 6 hours/day, 5 days/week, for 2 years. The incidences of the following tumors were increased: hepatomas; nasal squamous cell carcinomas; renal cell carcinomas; peritoneal mesotheliomas; mammary gland fibroadenomas; Zymbal gland adenomas; and subcutis fibromas. In the key inhalation cancer study for this risk evaluation ([Kasai et al., 2009](#)), groups of male F344 rats (50/group) were exposed to 0, 50, 250 and 1250 ppm (0, 180, 900 and 4500 mg/m³) of 1,4-dioxane for 6 hours/day, 5 days/week, for 2 years. The incidences of the following tumors were increased: hepatomas; nasal squamous cell carcinomas; renal cell carcinomas; peritoneal mesotheliomas; mammary gland fibroadenomas; Zymbal gland adenomas; and subcutis fibromas.

Table 3-7. Studies Evaluated for Cancer Following Inhalation Exposure to 1,4-Dioxane

Data Source	Study Description	Hazards Evaluated	Data Quality Rating
Garcia et al. (2015)	Cohort study of hazardous air pollutants and breast cancer risk in California teachers	Breast cancer incidence	High
Kasai et al. (2009)	2-year inhalation bioassay- male rats	Cancer- liver, nasal, renal, peritoneal, mammary gland, Zymbal gland, and skin	High

Carcinogenicity via Dermal Exposure

No dermal carcinogenicity studies were identified for 1,4-dioxane. Therefore, as stated above under Section 3.2.3.1, EPA applied a route-to-route extrapolation from the oral and inhalation carcinogenicity studies to derive dermal PODs.

Carcinogenicity via Oral Exposure

EPA evaluated the available carcinogenicity studies on 1,4-dioxane by the oral route of exposure, including Kociba et al. (1974), JBRC (1998), Kano (2009), and NCI (1978). These studies (Table 3-8.) provide data regarding the carcinogenic effects of 1,4-dioxane by the oral route of exposure and are summarized in Section 3.2.3.1. EPA used these studies for deriving dermal PODs as discussed under Section 3.2.6.

Table 3-8. Studies Evaluated for Cancer Following Oral Exposure to 1,4-Dioxane

Data Source	Study Description	Hazards	Data Quality Rating
Kociba et al. (1974)	2-year drinking water study- Sherman rats (60/sex/group)	Cancer- liver, respiratory	High
JBRC (1998) , Kano et al. (2009)	2-year drinking water study- F344/DuCrj rats and Crj:BDF1 mice (50/sex/group)	Cancer- liver, nasal, peritoneum, mammary gland, skin	High
NCI (1978)	2-year drinking water study- Osborne-Mendel rats (35/sex/group) and B6C3F1 mice (50/sex/group)	Cancer- liver, nasal, testis/epididymis	Low

Kociba et al. (1974) administered 1,4-dioxane to 6-8-week old Sherman rats (60/sex/group) via drinking water for two years. The incidences of hepatocellular carcinomas and squamous cell carcinoma of the nasal turbinates were increased among the high-dose group (1%; equivalent to an average dose (male and female) of 1,307 mg/kg/d). No increase in tumor formation was seen in the mid-dose group. Zero tumors occurred in the low-dose group.

As noted previously, Kano et al. (2009) is one of several publications based on a 2-year drinking water study performed by the Japan Bioassay Research Center. Groups of F344/DuCrj rats and Crj:BDF1 mice (50/sex/group) were exposed to 1,4-dioxane (>99% pure) at levels of 0, 200, 1000, or 5000 ppm and 0, 500, 2000, or 8000 ppm, respectively. Increased incidences of hepatocellular adenomas and carcinomas and tumors (squamous cell carcinomas) of the nasal cavity occurred in high-dose male and female rats. Peritoneal mesotheliomas in males also were increased at the highest dose, and males showed increasing trends in mammary gland fibroadenoma and subcutis fibroma, a fibroma or mass underneath the cutis layer of the skin. Females showed an increased incidence of mammary gland adenoma or fibroadenoma.

3.2.4 Potential Modes of Action for 1,4-Dioxane Toxicity

EPA evaluated the evidence supporting plausible modes of action (MOA) of 1,4-dioxane carcinogenicity for specific tumor locations using the modified Hill criteria for MOA analysis described in EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a). EPA considered available evidence from animal cancer bioassays, genotoxicity studies, specific MOAs proposed in the literature, and the analysis previously presented in the IRIS Toxicological Review of 1,4 Dioxane (U.S. EPA, 2013d).

EPA specifically considered MOAs for liver and nasal tissue carcinogenicity of 1,4-dioxane. There is insufficient chemical-specific information about kidney, peritoneal, mammary gland, zymbal gland or subcutis tumors to support MOA analysis for these tumor types.

Potential MOAs for 1,4-dioxane liver carcinogenicity

Liver tumors are a principal tumor site of 1,4-dioxane, and the liver is the site for which the most information exists. The MOA for 1,4-dioxane induction of liver tumors was previously

considered inconclusive ([U.S. EPA, 2013d](#)). In this risk evaluation, EPA considered evidence for several of the potential MOAs for 1,4-dioxane liver carcinogenicity (see Appendix J), including:

Metabolic saturation, cytotoxicity and proliferative regeneration. In this hypothesized MOA, metabolic saturation leads to the accumulation of the parent compound 1,4-dioxane, which causes liver tumors through cytotoxicity and subsequent regenerative proliferation. Dourson et al. ([2017](#); [2014](#)) (proposed specific key events and compiled evidence from animal bioassays ([McConnell, 2013](#); [Kociba et al., 1974](#))). EPA evaluated the current evidence for this proposed MOA for 1,4-dioxane carcinogenicity in depth (Appendix J) using the framework for MOA analysis described in the EPA [Guidelines for Carcinogen Risk Assessment](#) ([U.S. EPA, 2005a](#)).

Based on evidence that cytotoxicity is not a necessary key event, the lack of consistent dose-response concordance between key events in the MOA and carcinogenicity, data gaps in support of specific key events, and the plausibility of alternate MOAs that would also be consistent with experimental observations, EPA determined that existing evidence is not sufficient to support the MOA for liver tumors proposed by Dourson et al. ([2017](#); [2014](#)).

Cell proliferation in the absence of cytotoxicity. It is possible that 1,4-dioxane or a metabolite leads to cell proliferation in the absence of cytotoxicity. This potential MOA has not been articulated in the peer-reviewed literature and there is insufficient information to determine the specific key events through which 1,4-dioxane may lead to proliferation.

Mutagenicity and other forms of genotoxicity. As described in Section 4.2.3.2, EPA concluded that there is some evidence for genotoxicity *in vivo* at high doses, but insufficient evidence to determine whether 1,4-dioxane is mutagenic or induces cancer through a mutagenic MOA.

CAR/PXR-mediated effects. The nuclear receptors CAR and PXR have been proposed as mediators of 1,4-dioxane induced liver toxicity and carcinogenicity. Mechanistic evidence from other chemicals indicates that CAR agonists may lead to proliferation and liver tumors in the absence of cell death ([Elcombe et al., 2014](#)). While this is a plausible MOA for 1,4-dioxane carcinogenicity, the key events in the MOA linking 1,4-dioxane to CAR-mediated carcinogenicity have not been clearly articulated in the literature and 1,4-dioxane has not been identified as a CAR agonist. One 16-week drinking water exposure study in transgenic rats evaluated a panel of CYP enzymes that are induced by nuclear receptors CAR, PXR, PPAR α , or AhR and found no changes in mRNA expression of these CYPs in rat livers following 1,4-dioxane exposure ([Gi et al., 2018](#)). No studies have evaluated this mechanism in the presence of tumor formation.

EPA considered evidence for these potential MOAs (see Appendix J) and concluded that there is insufficient evidence to determine the MOA of 1,4-dioxane liver carcinogenicity.

Potential MOAs for 1,4-dioxane carcinogenicity in nasal tissue

EPA also considered evidence for specific MOAs of 1,4-dioxane carcinogenicity in nasal tissue. Tumors in the nasal cavity have been observed in rats and mice following drinking water ([Kano et al., 2009](#)) exposure and in rats following inhalation exposure ([Kasai et al., 2009](#)). Kasai et al. (2009) and Kano et al. (2009) consider several potential key events that may contribute to carcinogenicity in nasal tissue, including:

- biotransformation of 1,4-dioxane to toxic metabolites in nasal tissue, which is rich in metabolic enzymes
- cell injury followed by regenerative hyperplasia
- long-term stimulation of the nasal epithelia with high concentrations of 1,4-dioxane and/or its metabolites
- indirect interactions with DNA, such as genomic instability associated with alterations in cell cycling.

There is insufficient mechanistic information to fully evaluate the extent to which any these key events may contribute to nasal tumors, but evidence from the 2-year bioassays provide some clues that are relevant for MOA. The wide distribution of tumors reported throughout the nasal cavity and the consistency of nasal tumor incidence across oral and inhalation exposures ([Kasai et al., 2009](#); Kano et al, [2009](#)) suggests that nasal tumors may be the result of systemic delivery rather than portal of entry delivery. In addition, several of the nasal tumor types observed in these studies are rare. A two-year study on the effects of 1,4-dioxane exposure via drinking water, reported increased incidence of several rare nasal tumors that had never been observed in the laboratory's historical control data, including esthesioneuroepithelioma, rhabdomyosarcoma and sarcoma (not otherwise specified) in rats and esthesioneuroepithelioma and adenocarcinoma in mice ([Kano et al., 2009](#)). Rare tumor types such as these are unlikely to be explained by a generic cytotoxic response that is more common.

EPA concluded that there is insufficient evidence to determine the MOA of 1,4-dioxane carcinogenicity in nasal tissue.

Overall MOA conclusions

There is currently insufficient information to determine the MOA of 1,4-dioxane carcinogenicity for any tumor location. 1,4-Dioxane carcinogenicity may be mediated by different MOAs for different tumor sites and the role of metabolites in the carcinogenicity of 1,4-dioxane in different tissue types is unknown. In the absence of other information about MOA, EPA often takes the health-protective approach of assuming a linear no-threshold risk model consistent with a mutagenic MOA. To characterize the sensitivity of 1,4-dioxane cancer models to assumptions about MOA, EPA developed dose-response for both linear and threshold cancer models for liver tumors (see Appendix K). Cancer risk calculations in Section 5.2 and subsequent risk determinations are based on a linear no-threshold model in the absence of sufficient evidence for any of the hypothesized MOAs.

3.2.5 Weight of Scientific Evidence

The weight-of-the-scientific evidence evaluation provides a narrative concluding with the recommended approach to dose-response assessment. The information on human health hazard

was integrated using a weight-of-the-scientific evidence strategy where the strengths, limitations and relevance of the data were analyzed and summarized across studies within each hazard endpoint in narrative form. The best available human health hazard science was selected for dose-response modeling based on integrating the results of the data quality evaluation, MOA information and weight-of-the-scientific evidence. Liver, kidney, and nasal toxicity were the primary noncancer health effects associated with exposure to 1,4-dioxane. The weight-of-the-scientific evidence is presented for acute toxicity (2 studies), chronic toxicity (7 studies), and carcinogenicity (4 studies).

Acute and Short-term Toxicity

EPA evaluated studies on the acute and short-term effects from exposures to 1,4-dioxane in humans and experimental animals. The available human studies indicated that 1,4-dioxane exposures at 72 mg/m³ for two hours was well tolerated in human volunteers, with no signs or symptoms of adverse effects, whereas exposures at 180.2 mg/m³ for six hours caused eye irritation in human volunteers ([Ernstgard et al., 2006](#); [Young et al., 1977](#)). Johnstone ([1959](#)) reported the fatality of one worker after one week of exposures to high concentrations of 1,4-dioxane (*i.e.*, 1700 mg/m³). An autopsy on the worker showed pathological effects in the liver, kidney, and brain.

Each of the human studies provide supporting information for comparable effects seen in experimental animals; however, they were not carried forward for concentration-response analyses because of inherent limitations with each. For example, the controlled human exposure studies were based on single concentration exposures and only assessed visible signs of impairment and participant reported symptoms. No evaluations were performed for signs of potential systemic effects (*e.g.*, serum chemistry panels).

As shown in Table 3-3., acute and short-term exposures to 1,4-dioxane in experimental animals have been shown to cause irritation of the mucous membranes and adverse effects on the liver and kidney ([Mattie et al., 2012](#)). Of the available studies on experimental animals, EPA selected the high quality short-term exposure study conducted by Mattie et al. ([2012](#)) instead of the medium quality short-term study conducted by Goldberg et al. ([1964](#)) as the basis for dose-response analysis for several reasons. Mattie et al. ([2012](#)) exposed male/female rats to 1,4-dioxane at concentrations of 0, 378, 5599, or 11,690 mg/m³ for 6 hours/day, 5 days/week for two weeks and assessed effects on the nasal cavity, liver, and kidney. In contrast, Goldberg et al. ([1964](#)) exposed female rats to 1,4-dioxane at concentrations of 0, 5405, 10,810, or 21,620 mg/m³ for 4 hours/day, 5 days/week, for two weeks and only assessed effects on neurological function. EPA concluded that the exposure duration used by Mattie et al. ([2012](#)) was more comparable to short-term worker exposures (*i.e.*, 8 hours/day, 5 days/week). Further, the range of exposure concentrations used by Mattie et al. ([2012](#)) encompassed the concentrations used in the acute, single exposure rat studies, where liver effects (*i.e.*, 4-hour LOAEC = 3603 mg/m³) or respiratory effects (*i.e.*, NOAEC 2875 mg/m³) were reported ([Mattie et al., 2012](#); [Drew et al., 1978](#)). In contrast, the lowest concentration (*i.e.*, 5405 mg/m³) used by Goldberg et al. ([1964](#)) exceeded both of these concentrations, and as noted above, the authors only assessed effects on neurological function. Therefore, EPA selected the short-term effect levels from Mattie et al. ([2012](#)) as the basis for dose-response assessment and quantification of potential risks to workers from acute/short-term exposures to 1,4-dioxane, as discussed in Section 3.2.6.

Chronic Toxicity

Key chronic non-cancer effects observed following inhalation and oral exposures to 1,4-dioxane include centrilobular necrosis in the liver, degeneration of the olfactory epithelium, and degeneration of the kidney ([2009](#); [Kasai et al., 2009](#); [Kano et al., 2008](#); [NCI, 1978](#); [Kociba et al., 1974](#); [1973](#); [Argus et al., 1965](#)).

Non-cancer liver effects reported in the oral or inhalation exposure studies included degeneration and necrosis, hepatocyte swelling, cells with hyperchromic nuclei, spongiosis hepatis, hyperplasia, and clear and mixed cell foci of the liver ([Kano et al., 2008](#); [NCI, 1978](#); [Kociba et al., 1974](#); [Argus et al., 1973](#); [1965](#)).

Lesions in the olfactory epithelium and respiratory epithelium were reported in both inhalation and drinking water exposure studies ([Kasai et al., 2009](#)). The uniform distribution of nasal lesions throughout the olfactory and respiratory epithelium (rather than distribution consistent with airflow), the consistency of effects in oral and inhalation studies, and the fact that 1,4-dioxane is absorbed into systemic circulation following inhalation exposure indicates that these nasal lesions may be primarily the result of systemic delivery rather than portal of entry effects.

Kidney toxicity was noted following inhalation and oral exposures ([Kasai et al., 2009](#); [NCI, 1978](#); [Kociba et al., 1974](#); [1973](#); [Argus et al., 1965](#)), and kidney damage at high doses is characterized by degeneration of the cortical tubule cells, necrosis with hemorrhage, and glomerulonephritis ([NCI, 1978](#); [Kociba et al., 1974](#); [Argus et al., 1965](#)). The lowest dose reported to produce kidney damage is 94 mg/kg-day ([Kociba et al., 1974](#)). Cortical tubule degeneration was seen at higher doses in the NCI ([1978](#)) bioassay (240 mg/kg-d, male rats), and glomerulonephritis was reported for rats given doses of ≥ 430 mg/kg-d ([Argus et al., 1973](#); [1965](#)).

EPA considered two high quality studies that evaluated the noncancer effects of inhalation exposure to 1,4-dioxane, including one 13-week exposure study in male and female rats ([Kasai et al., 2008](#)) and one 2-year exposure study in male rats ([Kasai et al., 2009](#)). Both studies reported effects in the olfactory epithelium and respiratory epithelium at the lowest doses tested. EPA performed dose-response assessment using information from in the 2-year exposure study ([Kasai et al., 2009](#)) because it evaluated effects at lower doses and the conditions of the study are most representative of long-term occupational exposures.

EPA evaluated seven studies that address the noncancer effects of 1,4-dioxane following oral exposure, including two high quality two-year drinking water exposure studies ([Kano et al., 2009](#); [Kociba et al., 1974](#)) one medium quality 13-week drinking water study ([Kano et al., 2008](#)), one medium quality 63-week drinking water study in rat ([Argus et al., 1965](#)), one medium quality developmental toxicity study ([Giavini et al., 1985](#)), and two low quality drinking water studies in mice ([NCI, 1978](#)) and rats ([Argus et al., 1973](#); [1965](#)). The NCI study was rated as low quality because of differences in the study timing for control and treated animals and fluctuations in treatment levels due to variation in water intake. The Argus study was rated as low quality due to insufficient data reporting and a lack of information on test substance purity, animal husbandry conditions, health outcomes in control groups, or statistical methods.

Giavini et al. ([1985](#)) provide some evidence of developmental toxicity at the highest dose tested in the presence of slight maternal toxicity. There are data limitations for reproductive and

developmental endpoints, including a lack of multigenerational reproduction studies or neurodevelopmental studies.

The most sensitive endpoints identified among the oral exposure studies were liver and kidney toxicity reported in Kociba et al. (1974) and Kano et al. (2009). EPA performed dose-response assessment on the three two-year drinking water exposure studies (Kano et al., 2009; NCI, 1978; Kociba et al., 1974) as well as the 13-week drinking water study (Kano et al., 2008) because these are studies that identified the most sensitive chronic effects of oral exposure.

Cancer Classification

EPA re-evaluated the reasonably available evidence according to the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a) that was previously summarized in the IRIS assessment (U.S. EPA, 2013d). Evidence from the human studies did not support or refute an association between occupational or general population exposure and increased risk of cancer, and by itself does not establish a clear causal relationship. 1,4-Dioxane exposure in animal studies leads to tumors in multiple tissues at multiple sites (Table 3-8.) other than the initial points of contact (oral and inhalation) in males and females. There are data gaps for the potential carcinogenic effects of 1,4-dioxane from inhalation and dermal exposure in humans and from dermal exposure in animals.

Human occupational studies examining the association between 1,4-dioxane exposure and increased cancer risk are inconclusive because they are limited by small cohort size and a small number of reported cancer cases (Buffler et al., 1978; Thiess et al., 1976). A large, high quality cohort study (Garcia et al., 2015) found no association between exposure to ambient levels of 1,4-dioxane in air and breast cancer rates. This study looked only at breast cancer rates following ambient levels of exposure and as such cannot be used to extrapolate to all cancers or to evaluate risks from higher levels of exposure relevant to occupational settings.

Studies in multiple animal species show that chronic exposure to 1,4-dioxane induces tumors in multiple tissues by both oral and inhalation exposure (Table 3-7. and Table 3-8.). In accordance with the Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005a), EPA concluded that 1,4-dioxane is “likely to be carcinogenic to humans” based on animal evidence of carcinogenicity at multiple sites, in multiple species, and multiple routes of exposure. This is consistent with the conclusions in EPA’s IRIS assessment (U.S. EPA, 2013d) and conclusions of other agencies. The NTP classifies 1,4-dioxane as “reasonably anticipated to be a human carcinogen” (NTP, 2016), IARC classifies 1,4-dioxane as “possibly carcinogenic to humans (IARC, 1999), and NIOSH classifies it as a “potential occupational carcinogen” (NIOSH, 2004).

This hazard was carried forward for dose-response analysis. In the dose-response assessment, EPA modeled cancer risk using data from four two-year cancer bioassays (Kano et al., 2009; Kasai et al., 2009; NCI, 1978; Kociba et al., 1974).

3.2.6 Dose-Response Assessment

3.2.6.1 Potentially Susceptible Subpopulations

Certain human subpopulations may be more susceptible to exposure to 1,4-dioxane than others. Some individuals may be more biologically susceptible to the effects of 1,4-dioxane due to lifestage, genetic variability or pre-existing health conditions that increase variability in human response to chemical exposures. Variations in CYP enzyme expression may contribute to susceptibility because multiple CYP enzymes are involved in metabolism of 1,4-dioxane, including CYP2E1. There are large variations in CYP2E1 expression and functionality in humans ([Lipscomb et al., 2003](#)) and similar variation in other CYPs involved in 1,4-dioxane metabolism are possible.

Pre-existing conditions affecting the liver may also impair metabolism in some individuals. For example, fatty liver disease has been associated with reduced CYP function. Other pre-existing conditions affecting the kidneys, upper respiratory system, and other organs targeted by 1,4-dioxane could make some individuals more susceptible. Although data are limited, the available evidence from gestational exposures to 1,4-dioxane provides some evidence of the potential for developmental toxicity. The offspring of pregnant women may therefore be at greater risk from exposure. The variability in human susceptibility to 1,4-dioxane, including variability in CYPs, is reflected in the selection of the uncertainty factor for human variability included in the benchmark margin of exposure (MOE).

3.2.6.2 Points of Departure for Human Health Hazard Endpoints

The dose-response assessment included analysis of all non-cancer and cancer endpoints, followed by an overall synthesis that includes a characterization of the risk estimates across endpoints, the strength of the mode of action information of each endpoint, and the anticipated relevance of each endpoint to humans, including potentially exposed or susceptible populations and lifestages. EPA evaluated the data from studies described in Section 3.2 to characterize the dose-response relationships of 1,4-dioxane for oral and inhalation exposures. EPA first determined whether each hazard endpoint in the key studies had adequate information to perform dose-response analysis. This was informed by the IRIS assessment ([U.S. EPA, 2013d](#)), which evaluated dose-response data within the studies identified in Section 3.2. EPA defines a POD as the dose-response point that marks the beginning of a low-dose extrapolation. This point can be the lower bound on the dose for an estimated incidence, or a change in response level from a dose-response model (*i.e.*, BMD), a NOAEL or a LOAEL for an observed incidence or change in the level of response.

3.2.6.2.1 Acute/Short-term POD for Inhalation Exposures

EPA identified Mattie et al. ([2012](#)) as the highest quality study and most relevant for use in deriving an acute inhalation point of departure (POD). Mattie et al. ([2012](#)) reported a LOAEC of 104.8 ppm (378 mg/m³) for liver effects in male/female rats exposed to 1,4-dioxane for 6-hour/day for 5 days/week for 2 weeks. This is the most sensitive endpoint reported in the available acute and short-term toxicity studies. EPA assumed that the selection of this endpoint for dose-response analysis and risk characterization would be protective of potential acute/short-term effects to the nasal cavity, lungs, and brain.

EPA evaluated the endpoints in Mattie et al. (2012) to determine whether the data were amenable to BMD modeling. Single cell necrosis of the liver in female rats, the most sensitive liver toxicity endpoint in the study, was not amenable to BMD modeling because the response rate is high (87.5%) at the lowest exposure concentration, and all non-control concentrations have nearly the same response level. The data do not provide dose-response information near the benchmark response rate (BMR) of 10%. Consistent with EPA's Benchmark Dose Technical Guidance (U.S. EPA, 2012b) section 2.1.5, the data provide little useful information about the dose-response relationship at lower doses. EPA therefore used a LOAEC approach to identify a point of departure based on short-term effects of 1,4-dioxane on liver toxicity.

EPA applied a duration adjustment to the LOAEC to normalize the concentration from the exposure conditions used by Mattie et al. (2012) to that of workers (*i.e.*, 8 hours/day, 5 days/week). The duration adjusted POD (POD_{ADJ}) was calculated as follows:

$$\text{POD}_{\text{ADJ}} = \text{POD} \times \frac{6 \text{ hours}}{8 \text{ hours}}$$

Where,

POD_{ADJ} = the duration adjusted LOAEC_{ADJ}

POD = the LOAEC

Following EPA's *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (U.S. EPA, 1994b), EPA converted the POD_{ADJ} value of 78.7 ppm (283.5 mg/m³) to a human equivalent concentration (POD_{HEC}) using the regional gas dose ratio (RGDR) approach for extrapulmonary effects by calculating a dosimetric adjustment factor (DAF), which is based on the ratio between the animal and human blood:air partition coefficients, as shown below:

$$\text{DAF} = \frac{(\text{Hb/g})_A}{(\text{Hb/g})_H}$$

where:

(Hb/g)_A = the animal blood:air partition coefficient, and

(Hb/g)_H = the human blood:air partition coefficient

Sweeney et al. (2008) measured the blood:air partition coefficients for 1,4-dioxane in rats (*i.e.*, (Hb/g)_A = 1861) and humans (*i.e.*, (Hb/g)_A = 1666). The resulting DAF equates to 1.117; however, when the DAF is greater than 1, EPA applies a default value of 1 (U.S. EPA, 1994b) (see Table 3-9.).

The resulting acute inhalation POD_{HEC} is 78.7 ppm (283.5 mg/m³) and was considered protective of liver effects from short-term worker exposures.

EPA applied a composite uncertainty factor (UF) of 300 for the acute inhalation benchmark MOE for short-term/acute effects, based on the following considerations:

- An interspecies uncertainty/variability factor of 3 (UF_A) was applied for animal-to-human extrapolation to account for toxicodynamic differences between species. This uncertainty factor is comprised of two separate areas of uncertainty to account for differences in the toxicokinetics and toxicodynamics of animals and humans. In this assessment, the toxicokinetic uncertainty was accounted for by the calculation of an HEC and application of a DAF as outlined in the RfC methodology ([U.S. EPA, 1994b](#)). As the toxicokinetic differences are thus accounted for, only the toxicodynamic uncertainties remain, and an UF_A of 3 is retained to account for this uncertainty.
- A default intraspecies uncertainty/variability factor (UF_H) of 10 was applied to account for variation in sensitivity within human populations due to limited information on the impact of gender, age, health status, or genetic makeup.
- A LOAEC-to-NOAEC uncertainty factor (UF_L) of 10 was applied because the POD from the principle study was a LOAEC.

The acute inhalation benchmark MOE of 300 was used to interpret the MOE risk estimates for each short-term/acute use scenario.

3.2.6.2.2 Acute/Short-term POD for Dermal Exposures Extrapolated from Inhalation Studies

In the absence of data from dermal exposure studies, EPA generated an acute dermal POD for 1,4-dioxane by extrapolating from the acute inhalation POD derived from the Mattie et al. ([2012](#)) study. The acute inhalation POD was used to derive an absorbed human equivalent dose (HED). Route-to-route extrapolation is considered appropriate. While there is no specific EPA guidance on extrapolating from one route to another, EPA considered guidance from other countries. Three criteria from [IGHRC \(2006\)](#) are considered here: 1) there are not adequate toxicity data available by the dermal route, 2) the effects are systemic and 3) while there are first pass effects in oral studies this extrapolation uses an inhalation study where there are not first pass effects (see Section 4.2.2). The fraction of dioxane absorbed through skin in human exposures is accounted for in the exposure estimates in Section 2.4. EPA therefore developed dermal PODs in terms of absorbed dermal HEDs (rather than applied dermal HEDs which would account for dermal absorption).

The acute inhalation POD_{HEC} of 78.7 ppm (283.5 mg/m³) for liver effects from short-term occupational exposures was converted to an absorbed dermal HED using the following equation:

dermal HED (mg/kg-d) = absorbed inhalation dose ÷ body weight

where the absorbed inhalation dose = POD_{HEC} (mg/m³) × inhalation volume × 100% (inhalation absorption) and body weight is 80 kg. Inhalation volume is 10 m³ (*i.e.*, 1.25 m³/hour over an 8 hour shift) based on REACH guidance on information requirements and chemical safety assessment ([ECHA, 2010](#)). The inhalation absorption estimates were based on experimental data by the inhalation route (*i.e.*, Young *et al.*, [1977](#); [1976](#)) where 1,4-dioxane is readily absorbed in humans), however the available studies did not measure the parameters needed for a quantitative

estimate of the fraction absorbed. Given this qualitative estimate and the absence of quantitative inhalation absorption data, 100% inhalation absorption is assumed.

The resulting acute absorbed dermal HED is 35.4 mg/kg/day and is considered protective of liver effects and other systemic effects from short-term exposures.

EPA applied the same composite uncertainty factor (UF) of 300 for the acute dermal benchmark MOE for short-term/acute effects as the inhalation POD based on the following considerations:

- An interspecies uncertainty/variability factor of 3 (UF_A) was applied for animal-to-human extrapolation to account for toxicodynamic differences between species. This uncertainty factor is comprised of two separate areas of uncertainty to account for differences in the toxicokinetics and toxicodynamics of animals and humans. In this assessment, the toxicokinetic uncertainty in the inhalation study was accounted for by the calculation of an HEC and application of a DAF as outlined in the RfC methodology ([U.S. EPA, 1994b](#)). As the toxicokinetic differences are thus accounted for, only the toxicodynamic uncertainties remain, and an UFA of 3 is retained to account for this uncertainty.
- A default intraspecies uncertainty/variability factor (UF_H) of 10 was applied to account for variation in sensitivity within human populations due to limited information on the impact of gender, age, health status, or genetic makeup.
- A LOAEC-to-NOAEC uncertainty factor (UF_L) of 10 was applied because the POD from the principle study was a LOAEC.

The acute inhalation benchmark MOE of 300 was used to interpret the MOE risk estimates for each short-term/acute use scenario.

3.2.6.2.3 Acute/Short-term POD for Oral Exposures Extrapolated from Inhalation Studies

In the absence of data from oral exposure studies, EPA generated an acute oral POD for 1,4-dioxane by extrapolating from the acute inhalation POD derived from the Mattie et al. (2012) study. The acute inhalation POD was used to derive an oral human equivalent dose (HED) using an approach consistent with the approach used to derive the acute dermal POD.

The acute inhalation POD_{HEC} of 78.7 ppm (283.5 mg/m³) for liver effects from short-term occupational exposures was converted to an oral HED using the following equation:

$$\text{oral HED (mg/kg-d)} = \text{absorbed inhalation dose} \div \text{body weight}$$

where the absorbed inhalation dose = POD_{HEC} (mg/m³) × inhalation volume × 100% (inhalation absorption) and body weight is 80 kg. Inhalation volume is 10 m³ (*i.e.*, 1.25 m³/hour over an 8 hour shift). 100% inhalation absorption is assumed.

The resulting acute oral HED is 35.4 mg/kg/day and is considered protective of liver effects and other systemic effects from short-term exposures.

EPA applied the same composite uncertainty factor (UF) of 300 for the acute oral benchmark MOE for short-term/acute effects as the inhalation POD based on the following considerations:

- An interspecies uncertainty/variability factor of 3 (UF_A) was applied for animal-to-human extrapolation to account for toxicodynamic differences between species. This uncertainty factor is comprised of two separate areas of uncertainty to account for differences in the toxicokinetics and toxicodynamics of animals and humans. In this assessment, the toxicokinetic uncertainty in the inhalation study was accounted for by the calculation of an HEC and application of a DAF as outlined in the RfC methodology ([U.S. EPA, 1994b](#)). As the toxicokinetic differences are thus accounted for, only the toxicodynamic uncertainties remain, and an UFA of 3 is retained to account for this uncertainty.
- A default intraspecies uncertainty/variability factor (UF_H) of 10 was applied to account for variation in sensitivity within human populations due to limited information on the impact of gender, age, health status, or genetic makeup.
- A LOAEC-to-NOAEC uncertainty factor (UF_L) of 10 was applied because the POD from the principle study was a LOAEC.

The acute inhalation benchmark MOE of 300 was used to interpret the MOE risk estimates for each short-term/acute use scenario.

3.2.6.2.4 Chronic Non-Cancer POD for Inhalation Exposures

EPA performed dose-response analyses on the noncancer endpoints reported by Kasai et al., (2009), which included effects in the respiratory tract (*i.e.*, squamous cell metaplasia of the nasal respiratory epithelium, squamous cell hyperplasia of the nasal respiratory epithelium, respiratory metaplasia of the nasal olfactory epithelium, atrophy of the nasal olfactory epithelium, hydropic change in the lamina propria and sclerosis in the lamina propria of the nasal cavity) and the liver (*i.e.*, centrilobular necrosis of the liver). EPA selected this two-year inhalation toxicity study because it is most relevant for deriving inhalation points of departure (PODs) for long-term human exposures.

EPA evaluated the noncancer endpoints to determine whether the data were amenable to BMD modeling. For the data sets that were amenable to BMD modeling, EPA followed the benchmark dose modeling software (BMDS) guidance ([U.S. EPA, 2012b](#)) and used BMDS version 2.704. A benchmark response (BMR) of 10% extra risk was used for all endpoints to estimate the BMCL₁₀ (the lower 95% bound on the concentration estimated to produce a 10% increased incidence over background) (see Table 3-9.). For the data sets that were not amenable to BMD modeling, the NOAECs and LOAECs were used as the inhalation PODs (see Table 3-9.). Additional information on the BMD methods and criteria used for assessing adequacy of model fit can be found in Appendix K (Benchmark Dose Analysis).

Duration adjustments were applied to the PODs (*i.e.*, BMCL_{10S}, NOAECs, or LOAECs) to normalize the concentrations from the exposure conditions used by ([Kasai et al., 2009](#)) (*i.e.*, 6 hours/day, 5 days/week) to that of workers (*i.e.*, 8 hours/day, 5 days/week) (see Table 3-9.). The adjusted PODs (*i.e.*, POD_{ADJS}) were calculated as follows:

$$\text{POD}_{\text{ADJ}} = \text{POD} \times \frac{6 \text{ hours}}{8 \text{ hours}}$$

Where,

POD_{ADJ} = the duration adjusted BMCL_{ADJ}, NOAEC_{ADJ}, or LOAEC_{ADJ}

POD = the BMCL₁₀, NOAEC, or LOAEC

Following EPA's *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* ([U.S. EPA, 1994b](#)), EPA converted the POD_{ADJ} to a human equivalent concentration (POD_{HEC}). The HEC was calculated by the application of a dosimetric adjustment factor (DAF), a ratio of animal and human physiologic parameters which is dependent on the nature of the contaminant (particle or gas) and the target site (*e.g.*, systemic or portal of entry). 1,4-Dioxane is miscible with water and has a high blood:air partition coefficient. Typically, highly water-soluble and directly reactive chemicals (*i.e.*, Category 1 gases) partition predominantly into the upper respiratory tract, induce portal-of-entry effects, and do not accumulate significantly in the blood. 1,4-Dioxane induces effects in the respiratory tract, liver, and kidneys, and it has been measured in the blood after inhalation exposure ([Kasai et al., 2008](#)). The observations of systemic effects and measured blood levels resulting from 1,4-dioxane exposure indicate that this compound is absorbed into the bloodstream and distributed throughout the body. Thus, 1,4-dioxane might be best described as a water-soluble and non-directly reactive gas. Gases such as these are readily taken up into respiratory tract tissues and can also diffuse into the blood ([Medinsky and Bond, 2001](#)). Observations from rat inhalation studies suggest that nasal effects are primarily due to systemic delivery. Kasai et al. (2009) reported uniformly distributed lesions in the olfactory epithelium and respiratory epithelium lacking an anterior-posterior gradient. Typically, for highly soluble and reactive gases, injury follows the main inspiratory airstreams and the majority of chemical is removed in the airways. Therefore, sites of injury typically correlate with airflow patterns where chemical delivery rates are highest. Lesions induced by inhaled irritants also typically show an anterior-posterior gradient. The uniform distribution of nasal lesions following 1,4-dioxane exposure suggests that lesions may result primarily from systemic delivery. For the purposes of dosimetric extrapolation, EPA therefore treated 1,4-dioxane as a systemic acting gas.

EPA used the RGDR approach for systemic effects by calculating a DAF based on the ratio between the animal and human blood:air partition coefficients, as shown below:

$$DAF = \frac{(Hb/g)_A}{(Hb/g)_H}$$

where:

(Hb/g)_A = the animal blood:air partition coefficient, and

(Hb/g)_H = the human blood:air partition coefficient

As noted previously, the measured blood:air partition coefficients in rats (*i.e.*, (Hb/g)_A = 1861) and humans (*i.e.*, (Hb/g)_H = 1666) results in a DAF of 1.117. Therefore, EPA applied a default value of 1 ([U.S. EPA, 1994b](#)) (see Table 3-9.).

Of the available POD_{HEC} values, EPA selected the POD_{HEC} of 12.8 mg/m^3 for effects on the olfactory epithelium (*i.e.*, metaplasia and atrophy). These effects were the most pronounced and sensitive endpoints in the two-year inhalation study reported by Kasai et al. (2009). EPA considered these respiratory effects relevant for worker exposures. Given that other systemic effects occurred at higher concentration levels, basing the chronic POD_{HEC} on respiratory effects should be protective against other systemic effects in workers.

EPA applied a composite UF of 30 for the chronic inhalation benchmark MOE, based on the following considerations:

- An interspecies uncertainty factor (UF_A) of 3 to account for species differences in animal to human extrapolation. An interspecies uncertainty/variability factor of 3 (UF_A) was applied for animal-to-human extrapolation to account for toxicodynamic differences between species. This uncertainty factor is comprised of two separate areas of uncertainty to account for differences in the toxicokinetics and toxicodynamics of animals and humans. In this assessment, the toxicokinetic uncertainty was accounted for by the calculation of an HEC and application of a dosimetric adjustment factor as outlined in the RfC methodology (U.S. EPA, 1994b). As the toxicokinetic differences are thus accounted for, only the toxicodynamic uncertainties remain, and an UF_A of 3 is retained to account for this uncertainty.
- A default intraspecies uncertainty/variability factor (UF_H) of 10 was applied to account for variation in sensitivity within human populations due to limited information on the impact of gender, age, health status, or genetic makeup.
- A Subchronic-to-Chronic uncertainty factor (UF_S) was not applied because the key study used a chronic exposure protocol.

The chronic inhalation benchmark MOE of 30 was used to interpret the MOE risk estimates for each chronic use scenario.

Table 3-9. Model selection and duration-adjusted HEC estimates for BMCLs (from best fitting BMDS models) or NOAECs/LOAECs from the 2-year inhalation study by Kasai et al. (2009) in Male F344/DuCrj rats^a.

Endpoint	BMR	Model ^b	BMC ₁₀ (ppm) ^c	BMCL ₁₀ or NOAEC/LOAEC (ppm) ^c	BMCL _{ADJ} or NOAEC _{ADJ} /LOAEC _{ADJ} (worker ppm) ^d	BMCL _{HEC} or NOAEC _{HEC} /LOAEC _{HEC} (worker mg/m ³) ^e	Benchmark MOE
<i>Respiratory Effects</i>							
Squamous cell metaplasia; respiratory epithelium	10%	Log Probit	218	160	120	432.4	30
Squamous cell hyperplasia; respiratory epithelium	10%	Quantal Linear	679	429	323	1163.9	30
Respiratory metaplasia; olfactory epithelium	10%	BMDL ^h	6.47	4.74	3.56	12.8	30
Atrophy; olfactory epithelium ^f	--	LOAEC	--	50	37.5	135.1	300
Hydropic change; lamina propria	10%	Log Logistic	68.5	46.8	35.1	126.5	30
Sclerosis; lamina propria ^g	--	NOAEC	--	50	37.5	135.1	30
<i>Liver Effects</i>							
Centrilobular necrosis; Liver	10%	Log Probit	232	44.0	33.0	119	30
<p>Bold and shaded cells indicate the PODs selected for use in risk characterization</p> <p>^a Data quality evaluations for all endpoints are high (see Appendix I).</p> <p>^b Best fitting models were determined using current BMDS guidance (U.S. EPA, 2012b).</p> <p>^c BMC₁₀ = Concentration at specified extra risk (benchmark dose); BMCL₁₀ = 95% lower bound on concentration at specified extra risk.</p> <p>^d POD_{ADJ} (ppm) = BMCL or LOAEC or NOAEC × 6 hours ÷ 8 hours. *POD_{ADJ} (ppm) values were converted to mg/m³ values based on the following: POD_{ADJ} (ppm) × molecular weight of 1,4-dioxane (88.1 g/mole) ÷ 24.45 (gas constant at 760 mm Hg and at 25 °C).</p> <p>^e POD_{HEC} (mg/m³) = BMCL_{ADJ} × DAF (<i>i.e.</i>, (Hb/g)A ÷ (Hb/g)H)</p> <p>^f Atrophy of the olfactory epithelium was not amenable to BMD modeling because the response rate is high (80%) at the lowest exposure concentration, and all non-control concentrations have nearly the same response level. The data do not provide dose-response information near the benchmark response rate (BMR) of 10%. Consistent with EPA's Benchmark Dose Technical Guidance (U.S. EPA, 2012b) section 2.1.5, the data provide little useful information about the dose-response relationship at lower doses.</p>							

^g Only one BMDS model (dichotomous Hill) could provide a statistically adequate fit to these data, however this model fit implied a high degree of curvature immediately below the observed LOAEL, a pattern that the experimental data could not support or refute. Due to the uncertainty in model shape, a BMDL value is not proposed for this endpoint.

^h Of the adequately fitting models (p-value > 0.1), “the AIC values for gamma, multistage, quantal-linear, and Weibull models are equivalent and the lowest and, in this case, essentially represent the same model” and, because they all result in the same BMDL value of 4.7 ppm

ⁱ BMD modeling for respiratory metaplasia of the olfactory epithelium is in Appendix K.4

3.2.6.2.5 Chronic Cancer Unit Risk for Inhalation Exposures *i.e.*, Inhalation Unit Risk (IUR)

EPA performed dose-response analyses on the cancer endpoints reported by Kasai et al. (2009). 1,4-Dioxane was associated with a statistically significant increase in the incidences and/or statistically significant dose-response trends for tumors in the respiratory tract and auditory canal (*i.e.*, nasal cavity squamous cell carcinomas and Zymbal gland (auditory sebaceous gland) adenomas) and other systemic tumors (*i.e.*, hepatocellular adenomas and carcinomas, renal cell carcinomas, peritoneal mesotheliomas, and mammary gland fibroadenomas, and subcutis fibromas). All tumors were considered of independent origin and included in the multi-tumor analysis. The incidences of adenomas and carcinomas were combined according to EPA’s *Guidelines for Carcinogen Risk Assessment* which advises that etiologically similar tumor types, *i.e.*, benign and malignant tumors of the same cell type, can be combined due to the possibility that benign tumors could progress to the malignant form (U.S. EPA, 2005a; McConnell et al., 1986).

BMD modeling was used to fit the dose-response data and calculate the inhalation PODs. The multistage cancer models available in the BMDS (version 2.704) were fit to the incidence data for each tumor type observed in rats exposed to 1,4-dioxane via inhalation (Kasai et al., 2009) to determine the degree (*e.g.*, 1st, 2nd, or 3rd) of the multistage model that best fit the data. In accordance with the EPA *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a), a benchmark response (BMR) of 10% was used to estimate the BMCL₁₀ (the lower 95% bound on the concentration estimated to produce a 10% increase in tumor incidence over background). The results of the model that best characterized the cancer incidences were selected (see Table 3-10.). Suitable multistage model fits were obtained for all tumor types included in the inhalation unit risk analysis. Additional information on the BMD methods and criteria used for assessing adequacy of model fit can be found in Appendix K (Benchmark Dose Analysis).

As discussed for the noncancer dose-response analyses, the BMCL₁₀ values were converted to duration adjusted values (*i.e.*, BMCL_{ADJS}) and dosimetrically adjusted to BMCL_{HECS}, using the same methods applied to the noncancer endpoints (as discussed above under “*Chronic Inhalation – Non-Cancer*”) (see Table 3-10.).

U.S. EPA (2013d) applied a linear low-dose approach to derive inhalation unit risk values. This approach is used when the mode of action (MOA) is unknown or unclear. The inhalation unit risk (IUR) for humans is defined as the slope of the line drawn from the inhalation POD (BMCL_{HEC}) through the origin. To calculate the IUR, the benchmark response rate (0.1) was divided by the BMCL_{HEC} values (see Table 3-10.).

Given the multiplicity of tumor sites, basing the overall IUR on one tumor site may underestimate risk. Consistent with recommendations of the NRC (1994) and EPA’s *Guidelines*

[for Carcinogen Risk Assessment \(U.S. EPA, 2005a\)](#), EPA estimated the total risk and upper bound risk for multiple tumor sites. The MS-Combo model (which is implemented using BMDS) was utilized to calculate the concentration associated with a specified composite risk (the risk of developing any combination of tumors at any site), under the assumption that tumors in different tissues arise independently. MS-Combo is a peer-reviewed ([Versar, 2011](#)) module within BMDS that employs a combined probability function to calculate composite risk using the best-fitting BMDS multistage model parameters determined for each individual tumor. MS-Combo was applied to the best-fitting models for each tumor type from the ([Kasai et al., 2009](#)) study.

To test the sensitivity of the model to inclusion of liver tumor data, MS-Combo was run twice: first to evaluate combined cancer risk for all tumor sites and then to evaluate risk for all tumor sites excluding liver tumors (see Table 3-10.). This approach allows EPA to characterize the impact alternate nonlinear MOAs for liver carcinogenicity could have on overall cancer risk of 1,4-dioxane.

Note that the $BMCL_{ADJ}$, was calculated assuming a worker exposure scenario of 40 hours per week *i.e.*, 8 hours per day for 5 days per week. Therefore, the $BMCL_{HEC}$ and IUR estimates are appropriate for comparison with exposure scenarios of comparable duration. The IUR estimate is not the same as the EPA IRIS assessment where the IUR is estimated for a continuous exposure (*i.e.*, 24 hours per day for 7 days per week).

Table 3-10. Dose-response modeling summary results for male rat tumors associated with inhalation exposure to 1,4-dioxane for two years

Tumor Type ^a	Multistage Model Degree ^b	BMC ₁₀ (ppm) ^c	BMCL ₁₀ (ppm) ^c	BMCL _{ADJ} (worker ppm) ^d	BMCL _{HEC} (worker mg/m ³) ^{e-g}	IUR Estimate ^f (µg/m ³) ⁻¹
Nasal cavity squamous cell carcinoma	1	1107	630	473	1704	5.87E-08
Zymbal gland adenoma	1	1975	958	719	2591	3.86E-08
Hepatocellular adenoma or carcinoma	1	253	182	137	492	2.03E-07
Renal cell carcinoma	1	1975	958	719	2589	3.86E-08
Peritoneal mesothelioma	1	82.2	64.4	48	174	5.75E-07
Mammary gland fibroadenoma	1	1635	703	527	1900	5.26E-08
Subcutis fibroma	1	142	81.9	61.4	221	4.52E-07
MS-Combo for all tumor types (including liver) ^h		38.9	31.3	23.5	84.6	1.18E-06
MS-Combo for all tumor types (omitting liver) ⁱ		46.0	35.9	26.9	97.0	1.03E-06

Bold and shaded cells indicate the IURs selected for use in risk characterization

^aTumor incidence data from Kasai et al. (2009). Data quality evaluations for all endpoints are high (see Appendix I).

^bBest-fitting multistage model degree following current BMDS guidance (U.S. EPA, 2014b, 2012b). Model selections for renal cell carcinoma and Zymbal gland adenoma differ from the (U.S. EPA, 2013d) IRIS assessment.

^cBMC₁₀ = Concentration at specified extra risk (benchmark dose); BMCL₁₀ = 95% lower bound on concentration at specified extra risk.

^dBMCL_{ADJ} (ppm) = BMCL₁₀ × 6 hours ÷ 8 hours.

^eBMCL_{ADJ} (ppm) values were converted to mg/m³ values based on the following: BMCL_{ADJ} (ppm) × molecular weight of 1,4-dioxane (88.1 g/mole) ÷ gas constant at 760 mm Hg and at 25 °C).

^fThe inhalation unit risk ($\mu\text{g}/\text{m}^3$)⁻¹ was derived from the BMCL_{HEC} , the 95% lower bound on the concentration associated with a 10% extra cancer risk. Specifically, by dividing the BMR (0.10) by the BMCL_{HEC} . Thus, representing an upper bound, continuous lifetime exposure estimate of cancer potency.

^g $\text{BMCL}_{\text{HEC}} (\text{mg}/\text{m}^3) = \text{BMCL}_{\text{ADJ}} \times \text{DAF}$ (*i.e.*, $(\text{Hb}/\text{g})\text{A} \div (\text{Hb}/\text{g})\text{H}$)

^hMS-combo model for all tumor types including liver is in Appendix K.16

ⁱMS-Combo model for all tumor types excluding liver is in Appendix K.17

3.2.6.2.6 Chronic Non-Cancer POD for Dermal Exposures Extrapolated from Chronic Inhalation Studies

The Kasai et al., (2009) study was used in deriving inhalation PODs for long-term human exposures. EPA extrapolated from an inhalation to dermal exposure to derive an absorbed human equivalent dose (HED). Systemic effects (including centrilobular necrosis of the liver and respiratory lesions believed to result primarily from systemic delivery) were used for route-to-route extrapolation. As described above (Section 4.2.6.2.3), EPA treated 1,4-dioxane as a systemic acting gas because experimental observations reported in Kasai et al., (2009) indicate that respiratory lesions result primarily from systemic delivery rather than portal of entry exposures. These respiratory endpoints are therefore relevant to systemic delivery from dermal exposures.

The chronic inhalation BMCL_{HEC} of $12.8 \text{ mg}/\text{m}^3$ for respiratory metaplasia (see Table 3-9.) from chronic inhalation exposures was converted to an absorbed dermal HED using the following equation:

dermal HED ($\text{mg}/\text{kg}\text{-d}$) = inhalation BMDL_{HEC} (mg/m^3) \times inhalation volume \times 100% (inhalation absorption) \div body weight

where the inhalation volume is for an 8-hour exposure \times $1.25 \text{ m}^3/\text{hour}$ and the body weight is 80 kg. The absorption estimates were based on experimental data by the inhalation route (*i.e.*, Young et al., (1977; 1976) where 1,4-dioxane is readily absorbed in humans. However, the available studies did not measure the parameters needed for a quantitative estimate of the fraction absorbed. Given this qualitative estimate and the absence of quantitative inhalation absorption data, 100% inhalation absorption is assumed.

The resulting chronic dermal HED of $1.6 \text{ mg}/\text{kg}/\text{day}$ was considered protective of systemic respiratory, liver and kidney effects from chronic worker exposures.

EPA applied the same composite uncertainty factor (UF) of 30 for the chronic dermal benchmark MOE as the chronic inhalation systemic because the dermal POD was extrapolated from the systemic effects in the inhalation study, based on the following considerations:

- An interspecies uncertainty/variability factor of 3 (UF_A) was applied for animal-to-human extrapolation to account for toxicodynamic differences between species. This uncertainty factor is comprised of two separate areas of uncertainty to account for differences in the toxicokinetics and toxicodynamics of animals and humans. In this assessment, the toxicokinetic uncertainty in the inhalation study was accounted for by the calculation of an HEC and application of a DAF as outlined in the RfC methodology ([U.S. EPA](#),

[1994b](#)). As the toxicokinetic differences are thus accounted for, only the toxicodynamic uncertainties remain, and an UFA of 3 is retained to account for this uncertainty.

- A default intraspecies uncertainty/variability factor (UF_H) of 10 was applied to account for variation in sensitivity within human populations due to limited information on the impact of gender, age, health status, or genetic makeup; and
- A LOAEC-to-NOAEC uncertainty factor (UF_L) was not needed, *i.e.*, a value of 1 was applied because a BMDL was derived and used.
- A Subchronic-to-Chronic uncertainty factor (UF_S) was not applied because the key study used a chronic exposure protocol.

The chronic inhalation benchmark MOE of 30 was used to interpret the MOE risk estimates for each chronic use scenario.

3.2.6.2.7 Chronic Non-Cancer POD for Dermal Exposures Extrapolated from Chronic Oral Studies

EPA generated oral human equivalent doses (HEDs) based on dose-response analysis of liver, kidney, and respiratory effects reported in several chronic oral studies. These were then translated to absorbed dermal HEDs via route-to-route extrapolation.

The non-cancer endpoints for dose response analysis from the studies by Kano et al. ([2009](#); [2008](#)), [Kociba et al. \(1974\)](#), and [NCI \(1978\)](#) were increased liver enzymes, nasal inflammation and other nasal effects (atrophy of nasal olfactory epithelium, nuclear enlargement of nasal respiratory epithelium, nasal adhesion), hepatocellular mixed foci, hepatocyte swelling, degeneration and necrosis of renal tubular cells and hepatocytes, and cortical tubule degeneration. NOAELs and LOAELs were obtained from Appendix I for those data that were not amenable to benchmark dose modeling (see Appendix K for guidance and criteria used for assessing adequacy of model fit). The highest dose in [Kano et al. \(2009\)](#) was removed from all analyses because of concerns regarding decreased water intake rate at the highest dose. Because all LOAELs and NOAELs were in the low-dose region, the exclusion of this data point only impacted BMD analyses. BMDS modeling was performed on the available data using BMDS version 2.704 and following current BMDS guidance ([U.S. EPA, 2012b](#)). Following EPA's *Recommended Use of Body Weight^{3/4} as the Default Method in Derivation of the Oral Reference Dose* ([U.S. EPA, 2011b](#)), human equivalent doses were calculated by multiplying rodent doses by (BW_A/BW_H)^{0.25} (where BW_A is the bioassay-specific rodent body weight, and BW_H is the default human body weight of 80 kg). The EPA IRIS assessment ([U.S. EPA, 2011b](#)) did not apply BW^{3/4} scaling to noncancer oral data since the guidance was finalized after the oral portion of the 1,4-dioxane ([U.S. EPA, 2013d](#)) IRIS assessment was posted (2013 was the completion year for the inhalation update).

As shown in Table 3-11., the oral HEDs were converted to absorbed dermal HEDs using the following equation:

$$\text{Absorbed dermal HED (mg/kg-d)} = \text{oral HED (mg/kg-d)} \times 100\% \text{ (oral absorption)}$$

The absorption estimates were based on experimental data by the oral (*i.e.*, Young *et al.*, [1978a, b](#)) route of exposure. Young *et al.* ([1978a, b](#)) estimated the oral absorption of 1,4-dioxane in rats to be nearly complete. Given this qualitative estimate and the absence of quantitative oral absorption data in experimental animals or humans, 100% oral absorption was assumed. Because oral absorption was assumed to be 100%, the extrapolated absorbed dermal HEDs are equal to the oral HEDs calculated for each endpoint.

EPA applied a composite UF of 30 for the chronic dermal benchmark MOE, based on the following considerations:

- An interspecies uncertainty/variability factor of 3 (UFA) was applied for animal-to-human extrapolation to account for pharmacodynamic differences between species. This uncertainty factor is comprised of two separate areas of uncertainty to account for differences in the toxicokinetics and toxicodynamics of animals and humans. In this assessment, the toxicokinetic uncertainty was accounted for by the calculation of an HED and application of BW^{3/4} scaling ([U.S. EPA, 2011b](#)). As the toxicokinetic differences are thus accounted for, only the toxicodynamic uncertainties remain, and an UFA of 3 is retained to account for this uncertainty.
- A default intraspecies uncertainty/variability factor (UF_H) of 10 was applied to account for variation in sensitivity within human populations due to limited information on the impact of gender, age, health status, or genetic makeup.
- A Subchronic-to-Chronic uncertainty factor (UF_S) was not applied because the key study used a chronic exposure protocol.

The chronic dermal benchmark MOE of 30 was used to interpret the MOE risk estimates for each use scenario.

Overall POD Selection for Chronic Non-Cancer Dermal Exposures

EPA evaluated dermal HEDs extrapolated both from oral (Table 3-11.) and inhalation (Section 3.2.6.2.6) studies and selected an absorbed dermal HED of 1.6 mg/kg-day based on respiratory metaplasia of the olfactory epithelium reported in male rats in by Kasai *et al.*, ([2009](#)) following inhalation exposure. This was the most sensitive systemic endpoint identified. Based on the uniform distribution of lesions relative to airflow, respiratory metaplasia was considered to be primarily a result of systemic delivery as opposed to a portal of entry effect and therefore relevant to systemic effects from dermal exposures. It is possible that portal of entry effects contribute to the respiratory toxicity in this study, however, the selected POD is supported by very similar PODs (less than a two-fold difference) derived from dose-response data on hepatocellular toxicity following drinking water exposure. Two independent studies ([Kociba *et al.*, 1974](#); [Kano *et al.*, 2009](#)) arrived at essentially identical PODs for hepatocellular toxicity in male rats following oral drinking water exposure, with both rounding to 2.6 mg/kg/day. The selected absorbed dermal HED of 1.6 mg/kg/day was considered protective of all systemic effects (*i.e.*, kidney, liver and respiratory effects) from chronic dermal worker exposures.

Table 3-11. Dose-response modeling summary results for oral non-cancer liver, kidney, and nasal effects and route-to-route extrapolated applied dermal HEDs

Study (data quality)	Gender/strain/species	Endpoint	BMR	Model	BMD (mg/kg-d)	BMDL or NOAEL (mg/kg-d)	BW _A (g) ^a	Oral HED ^b (mg/kg-d)	Absorbed Dermal HED ^c (mg/kg-d)
Kano et al. (2009); JBRC (1998) (high)	Male F344/DuCrj rats	Increases in serum liver enzymes (GOT, GPT, LDH, and ALP)	--	NOAEL ^d	--	55	432	14.9	14.9
		Atrophy of nasal olfactory epithelium; nasal adhesion and inflammation	--	NOAEL	--	55		14.9	14.9
		Hepatocellular mixed cell foci ^f	10%	Log Logistic ^e	16.7	9.57		2.6	2.6
			--	NOAEL	--	11	3.0	3.0	
	Female Crj:BDF1 mice	Nasal inflammation	--	NOAEL	--	66	35.9	9.6	9.6
	Male Crj:BDF1 mice	Increases in serum liver enzymes (GOT, GPT, LDH, and ALP)	--	NOAEL	--	49	47.9	7.7	7.7
Kano et al. (2008) (medium)	Male F344/DuCrj rats	Nuclear enlargement of nasal respiratory epithelium	--	NOAEL	--	52	335	13.2	13.2
		Hepatocyte swelling	--	NOAEL	--	52	335	13.2	13.2
Kociba et al. (1974) (high)	Male Sherman rats	Degeneration and necrosis of renal tubular cells and hepatocytes ^f	--	NOAEL	--	9.6	405	2.6	2.6
NCI (1978) (low)	Female OM rats	Cortical tubule degeneration	10%	Weibull	596	452	310	113	113

^a Body weights are study-specific time weighted averages. For Kano et al. (2009) and NCI (1978), these were obtained from Table 5-9 of the (U.S. EPA, 2013d) IRIS assessment. For Kano et al. (2008), the published body weight at the LOAEL or NOAEL for the species/sex was used. For Kociba et al. (1974), the time weighted average BW of male rats was approximated by digitizing data from the published growth curve (low-dose and control animals).
^b POD=dose x (BW_A/BW_H)^{0.25}. BW_A = study-specific values (see above). BW_H=80 kg. The oral assessment of (U.S. EPA, 2013d), which preceded the inhalation update portion of the assessment and the BW^{3/4} scaling guidance (U.S. EPA, 2011b) did not perform this conversion.
^c Applied dermal HED (mg/kg-d) = oral HED (mg/kg-d) × 100% (oral absorption)
^d NOAELs listed in this table were obtained from Appendix I. These endpoints were not amenable to benchmark dose modeling.
^e Highest dose omitted.
^f BMD modeling for hepatocellular mixed cell foci is in Appendix K.18; degeneration and necrosis of renal tubular cells and hepatocytes is based on a NOAEL

3.2.6.2.8 Chronic Cancer Unit Risk for Dermal Exposures *i.e.*, Cancer Slope Factor (CSF) extrapolated from Chronic Inhalation Studies

EPA used route-to-route extrapolation to generate dermal CSFs for all systemic tumors based on the IURs derived from a 2-year inhalation cancer bioassay in male rats (Kasai et al., 2009). As described above in Section 3.2.6.2.3), EPA treated 1,4-dioxane as a systemic acting gas because experimental observations reported in Kasai et al. (2009) indicate that respiratory toxicity results primarily from systemic delivery rather than portal of entry exposures. Respiratory tumors were therefore considered relevant to systemic delivery from dermal exposures and are included in this analysis.

The BMCLs that were used to calculate inhalation IURs were converted from inhalation air concentrations to doses based on inhalation volume and body weights for male rats (Kasai et al., 2009). Following *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a), human equivalent doses were calculated for each tumor type by multiplying rodent doses by $(BW_A/BW_H)^{0.25}$ (where BW_A is the bioassay-specific rodent body weight, and BW_H is the default human body weight of 80 kg). The human equivalent doses were adjusted to absorbed dermal exposures (*i.e.*, internal doses) by multiplying by the percent of inhalation absorption. The absorbed dermal human equivalent dose was used as the point of departure (POD). To calculate a cancer slope factor (CSF), the benchmark response rate (0.1) was divided by the POD. A CSF is a plausible upper bound lifetime cancer risk from chronic ingestion of a chemical per unit of mass consumed per unit body weight, per day (mg/kg day).

The $BMCL_{HECS}$ (see Table 3-11.) were converted to absorbed dermal HEDs using the following equations:

animal BMDL (mg/kg-d) = inhalation BMCL (mg/m³) × animal inhalation volume ÷ animal body weight × 3.60 mg/m³ per ppm

BMDL_{HED} (mg/kg-d) = animal BMDL (mg/kg-d) × animal body weight × (human body weight ÷ animal body weight)^{3/4} ÷ human body weight

dermal BMDL_{HED} (mg/kg-d) = human equivalent BMDL × inhalation absorption

dermal CSF (mg/kg-d)⁻¹ = BMR / dermal BMDL_{HED} (mg/kg-d)

where the animal inhalation volume is for the exposure duration of the animal study (6 hours / 24 hours) × 0.36 m³/day for rats, the animal body weight for rats is 0.380 kg, the human body weight is 80 kg.

The inhalation absorption estimates were based on experimental data by the inhalation route (*i.e.*, Young et al., 1977; 1976) where 1,4-dioxane is readily absorbed in humans, however the available studies did not measure the parameters needed for a quantitative estimate of the fraction absorbed. Given this qualitative estimate and the absence of quantitative inhalation absorption data, 100% inhalation absorption is assumed. Because of this, the BMDL_{HEDS} are equal to the dermal BMDL_{HEDS}. To convert the dermal BMDL_{HED} to a dermal CSF, EPA used a BMR of 10%.

The resulting cancer slope factors for dermal exposures are shown below in Table 3-12. and the slope factors for the combined systemic tumors 1.4E-2 per mg/kg/day (including liver) and 1.2E-2 per mg/kg/day (omitting liver) are considered protective of all tumor types for chronic worker exposures.

Table 3-12. Cancer slope factor for dermal exposures extrapolated from studies for male rat tumors associated with inhalation exposure to 1,4-dioxane for two years

<i>Systemic Effects</i>					
Tumor Type ^a	BMCL ₁₀ (ppm) ^b	Animal BMDL ^c (mg/kg/day)	BMDL _{HED} ^d (worker mg/kg/day)	Dermal BMDL _{HED} ^d (worker mg/kg/day)	Dermal CSF Estimate ^e (mg/kg/day) ⁻¹
Nasal cavity squamous cell carcinoma	630	537	141	141	7.1E-04
Zymbal gland adenoma	958	817	214	214	4.7E-04
Hepatocellular adenoma or carcinoma	182	155	41	41	2.4E-03
Renal cell carcinoma	958	817	214	214	4.7E-04
Peritoneal mesothelioma	64.4	55	14	14	7.1E-03
Mammary gland fibroadenoma	703	599	157	157	6.4E-04
Subcutis fibroma	81.9	70	18	18	5.6E-03
MS-Combo systemic (including liver) ^f	31.3	27	7	7	1.4E-02
MS-Combo systemic (omitting liver) ^f	35.9	31	8	8	1.2E-02

Bold and shaded cells indicate the PODs selected for potential use in risk characterization

^aTumor incidence data from Kasai et al. (2009). Data quality evaluations for all endpoints are high (see Appendix I).

^bBMCL₁₀ = 95% lower bound on concentration at specified extra risk as shown in Table 3-9..

^canimal BMDL (mg/kg/day) calculated with equations above

^dBMDL_{HED} (mg/kg/day) calculated with equations above using allometric BW^{3/4} scaling

^eThe CSF (mg/kg/day)⁻¹ was derived from the BMCL_{HED}, the 95% lower bound on the concentration associated with a 10% extra cancer risk. Specifically, by dividing the BMR (0.10) by the BMDL_{HED}. Thus, representing an upper bound, continuous lifetime exposure estimate of cancer potency.

^f MS-Combo models for all tumors including and excluding liver are in Appendix K.16 and Appendix K.17

3.2.6.2.9 Chronic Cancer Unit Risk for Dermal Exposures *i.e.*, Cancer Slope Factor (CSF) extrapolated from Chronic Oral Studies

EPA generated oral CSFs based on data from cancer bioassays in rats and mice. Oral CSFs were then converted to dermal CSFs by route-to-route extrapolation. Based on data from chronic 2-year drinking water studies in F344 rats and Crj:BDF1 mice (Kano et al., 2009), Sherman rats (Kociba et al., 1974), OM rats and B6C3F₁ mice (NCI, 1978), 1,4 dioxane produced a statistically significant increase in incidence and/or a statistically significant dose-response trend for the following tumor types: nasal squamous cell carcinomas, peritoneal mesotheliomas, hepatomas, and subcutis fibromas. All tumors were considered of independent origin and included in the multi-tumor analysis. The incidence of adenomas and carcinomas were combined according to EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a) which advises that etiologically similar tumor types, *i.e.*, benign and malignant tumors of the same cell type, can be combined due to the possibility that benign tumors could progress to the malignant form (U.S. EPA, 2005a; McConnell et al., 1986).

BMD modeling was used to fit the dose-response data and calculate the POD. The multistage cancer models available in the BMDS (version 2.704) were fit to the incidence data for each tumor type observed to determine the degree (*e.g.*, 1st, 2nd, or 3rd) of the multistage model that

best fit the data. In accordance with the EPA *Guidelines for Carcinogen Risk Assessment* ([U.S. EPA, 2005a](#)), a benchmark response (BMR) of 10% was used to estimate the BMDL10 (the lower 95% bound on the dose estimated to produce a 10% increase in tumor incidence over background) and the results of the model that best characterized the cancer incidences were selected. Liver tumors in female mice reported in ([Kano et al., 2009](#)) were not initially amenable to multistage models due to the steep slope and apparent plateau of the response. EPA therefore used individual animal data obtained from study authors to model the time-to-tumor effect in this dataset using the Multistage Weibull Model and applying an Extra Risk of 50% as the BMR to avoid excess extrapolation. Ultimately suitable multistage model fits were obtained for all tumor types included in the analysis. Additional information on BMD methods and model selection, and guidance and criteria used for assessing adequacy of model fit, can be found in Appendix K (Benchmark Dose Analysis).

Following *Guidelines for Carcinogen Risk Assessment* ([U.S. EPA, 2005a](#)), human equivalent doses were calculated for each tumor type by multiplying rodent doses by $(BW_A/BW_H)^{0.25}$ (where BW_A is the bioassay-specific rodent body weight, and BW_H is the default human body weight of 80 kg). The human equivalent dose was used as the point of departure (POD). To calculate a cancer slope factor (CSF), the benchmark response rate (0.1) was divided by the POD. A CSF is a plausible upper bound lifetime cancer risk from chronic ingestion of a chemical per unit of mass consumed per unit body weight, per day (mg/kg day).

Given the multiplicity of tumor sites, basing the overall CSF on one tumor site may underestimate risk. Consistent with recommendations of the NRC ([1994](#)) and EPA's *Guidelines for Carcinogen Risk Assessment* ([U.S. EPA, 2005a](#)), the total risk and upper bound risk for multiple tumor sites was estimated in a manner similar to that for inhalation (see above). Briefly, MS-Combo model (which is implemented using BMDS) was utilized to calculate the dose associated with a specified composite risk (the risk of developing any combination of tumors at any site), under the assumption that tumors in different tissues arise independently. For studies that observed liver tumors, MS-Combo was applied twice to evaluate uncertainties related to model choice and mechanisms: one MS-Combo model run included all tumors, while an additional model run excluded liver tumors.

The dose-response modeling results for cancer hazards from oral exposure in rats (Table 3-13.) indicate that the CSF from MS-Combo including or excluding the liver tumors is within a factor of 2. Female rats appear to be about two times less sensitive than males. In mice, only liver tumors were reported and modeling is therefore focused on liver tumors. Female mice appear to be more sensitive to liver tumors than male mice.

As shown in Table 3-13., the oral CSFs were converted to absorbed dermal CSFs using the following equation:

$$\text{Dermal CSF (mg/kg-d)}^{-1} = \text{oral CSF (mg/kg-d)}^{-1} \div 100\% \text{ (oral absorption)}$$

The absorption estimate was based on experimental data by the oral (*i.e.*, Young *et al.*, [1978a, b](#)) route of exposure as previously discussed. Because inhalation absorption is assumed to be 100%, the dermal CSFs are equal to the oral CSFs.

Overall Cancer Slope Factor Selection for Chronic Cancer Risk from Dermal Exposures

EPA evaluated dermal CSF extrapolated from inhalation (Section 4.2.6.2.7) and oral (Section 4.2.6.2.8) exposure studies and selected a dermal CSF of $1.2\text{E-}1$ ($\text{mg}/\text{kg}\text{-d}$)⁻¹ based on liver tumors in female mice exposed via drinking water ([Kano et al., 2009](#)). Female mice appear to be the most sensitive group tested in drinking water studies, but they were not tested in inhalation exposure studies. Cancer slopes derived from combined systemic tumors in male and female rats exposed via drinking water are approximately an order of magnitude less sensitive, with a CSF of $1.0\text{E-}2$ in female rats and $2.1\text{E-}2$ in male rats.

Dermal cancer risks extrapolated from inhalation (Section 3.2.6.2.8) and oral studies (Section 3.2.6.2.9) calculated in male rats are generally consistent (less than a two fold difference). For example, the CSFs calculated for combined systemic tumors (including the liver) in male rats are $1.4\text{E-}2$ ($\text{mg}/\text{kg}/\text{day}$)⁻¹ in the inhalation study and $2.1\text{E-}2$ ($\text{mg}/\text{kg}/\text{day}$)⁻¹ in the drinking water study. CSFs calculated for combined systemic tumors omitting liver in male rats were $1.2\text{E-}2$ ($\text{mg}/\text{kg}/\text{day}$)⁻¹ in the inhalation study and $1.3\text{E-}2$ ($\text{mg}/\text{kg}/\text{day}$)⁻¹ in the drinking water study. These are shown in the summaries in Table 3-12. and Table 3-13.. Overall, the selected dermal CSF based on liver tumors in female mice is expected to be protective of other systemic tumors types.

Table 3-13. Dose-response modeling summary results for oral CSFs and route-to-route extrapolated dermal CSFs.

Study (data quality) ^a	Gender/strain/species	Endpoint	BMR	MS ^o	BMD (mg/kg-d)	BMDL (mg/kg-d)	BW _A (g)	POD ^b (mg/kg-d)	Oral CSF (mg/kg-d) ⁻¹	Dermal CSF ^c (mg/kg-d) ⁻¹
Kano et al. (2009) (high)	Male F344/DuCrj rats	Nasal squamous cell carcinoma	10%	2	365	242	432	65.6	1.5E-03	1.5E-03
		Peritoneal mesothelioma	10%	2	77.7	35.4		9.60	1.0E-02	1.0E-02
		Hepatocellular adenoma or carcinoma	10%	2	61.7	28.3		7.67	1.3E-02	1.3E-02
		Subcutis fibroma	10%	1	154	85.0		23.0	4.3E-03	4.3E-03
		MS-Combo (excluding liver)	10%	N/A	55.2	28.1		7.62	1.3E-02	1.3E-02
		MS-Combo (including liver)	10%	N/A	35.1	17.8		4.83	2.1E-02	2.1E-02
	Female F344/DuCrj rats	Nasal squamous cell carcinoma	10%	1	376	214	267	51.4	1.9E-03	1.9E-03
		Mammary gland adenoma	10%	1	177	99.1		23.8	4.2E-03	4.2E-03
		Hepatocellular adenoma or carcinoma	10%	2	79.8	58.1		14.0	7.1E-03	7.1E-03
		MS-Combo (excluding liver)	10%	N/A	120	76.5		18.4	5.4E-03	5.4E-03
		MS-Combo (including liver)	10%	N/A	57.6	41.6		10.0	1.0E-02	1.0E-02
	Female Crj:BDF1 mice	Hepatocellular adenoma or carcinoma ^d	50%	1	35.5	27.0	35.9	3.93	1.2 E-01	1.2 E-01
Male Crj:BDF1 mice	Hepatocellular adenoma or carcinoma	10%	1	71.0	44.0	47.9	6.88	1.5E-02	1.5E-02	

Study (data quality) ^a	Gender/strain/species	Endpoint	BMR	MS ^o	BMD (mg/kg-d)	BMDL (mg/kg-d)	BW _A (g)	POD ^b (mg/kg-d)	Oral CSF (mg/kg-d) ⁻¹	Dermal CSF ^c (mg/kg-d) ⁻¹
Kociba et al. (1974) (high)	Sherman rats (M+F)	Nasal squamous cell carcinomas	10%	2	1981	1314	325	332	3.0E-04	3.0E-04
		Hepatocellular carcinoma	10%	1	940	584		147	6.8E-04	6.8E-04
NCI (1978) (low)	Female OM rats	Nasal squamous cell carcinoma	10%	1	176	122	310	30.4	3.3E-03	3.3E-03
		Hepatocellular adenoma	10%	1	132	94.1		23.5	4.3E-03	4.3E-03
	Male B6C3F ₁ mice	Hepatocellular adenoma or carcinoma	10%	1	164	117	32	16.5	6.1E-03	6.1E-03
	Female B6C3F ₁ mice	Hepatocellular adenoma or carcinoma	10%	1	49.1	38.8	30	5.40	1.9E-02	1.9E-02

Bold and shaded cells indicate the PODs selected for potential use in risk characterization

^a Applies to all of the endpoints listed in this table for each study. See Appendix I.

^b $POD = \text{dose} \times (BW_A/BW_H)^{0.25}$. $BW_H = 80$ kg. BW_A values are study-specific (obtained from Table 5-9 of the 1,4-Dioxane IRIS assessment)

^c $\text{Dermal CSF (mg/kg-d)}^{-1} = \text{Oral CSF (mg/kg-d)}^{-1} \div 100\%$ (oral absorption).

^d Model for hepatocellular adenoma or carcinoma in female mice is in Appendix K.28; Liver tumors in female mice were not initially amenable to multistage models due to the steep slope and apparent plateau of the response. EPA therefore used individual animal data obtained from study authors to model the time-to-tumor effect in this dataset using the Multistage Weibull Model and applying an Extra Risk of 50% as the BMR to avoid excess extrapolation.

3.2.7 Summary of Human Health Hazards

The results of the hazard identification and dose-response are summarized in Table 3-14..

Table 3-14. Summary of Hazard Identification and Dose-Response Values

Exposure Route	Endpoint Type	Hazard POD/HEC/Slope Factor ^a	Value	Units	Benchmark MOE ^b	Basis for Selection	Key Study
Inhalation	Short-term	Acute inhalation POD _{HEC}	283.5	mg/m ³	300 (UF _L = 10; UF _A = 3; UF _H = 10)	Systemic liver effect; Study duration relevant to worker short-term exposures	Mattie et al. (2012)
Dermal	Short-term	Acute dermal POD _{HED} extrapolated from an inhalation study	35.4	mg/kg/day	300 (UF _L = 10; UF _A = 3; UF _H = 10)		
Oral	Short-term	Acute oral POD _{HED} extrapolated from an inhalation study	35.4	mg/kg/day	300 (UF _L = 10; UF _A = 3; UF _H = 10)		
Inhalation	Non-Cancer	Human Equivalent Concentration (HEC)	12.8	mg/m ³	30 (UF _A = 3; UF _H = 10)	POD relevant for olfactory epithelium effects (<i>i.e.</i> , metaplasia and atrophy)	Kasai et al. (2009)
	Cancer	Inhalation Unit Risk (IUR)	1.18E-06	(µg/m ³) ⁻¹	N/A	Result of combined cancer modeling for male rats (including liver)	Kasai et al. (2009)
			1.03E-06	(µg/m ³) ⁻¹	N/A	Result of combined cancer modeling for male rats (excluding liver)	Kasai et al. (2009)
Dermal	Non-Cancer	Human Equivalent Dose (HED) extrapolated from an inhalation study	1.6	mg/kg/day	30 (UF _A = 3; UF _H = 10)	POD for systemic effects in the nasal cavity (respiratory metaplasia of the olfactory epithelium) in male rats	Kociba et al. (1974) Kasai et al. (2009)

Exposure Route	Endpoint Type	Hazard POD/HEC/Slope Factor ^a	Value	Units	Benchmark MOE ^b	Basis for Selection	Key Study
		Human Equivalent Dose (HED) extrapolated from oral studies	2.6	mg/kg/day	30 (UFA = 3; UFH = 10)	PODs for hepatocellular and renal toxicity (degeneration and necrosis of renal tubular cells and hepatocytes; hepatocellular mixed cell foci) following drinking water exposure in male rats ^c	Kano et al. (2009) ; Kociba et al. (1974)
	Cancer	Cancer Slope Factor (CSF) extrapolated from an oral study	1.2E-01	(mg/kg-d) ¹	N/A	Cancer model for liver tumors in female mice (the most sensitive sex/species);	Kano et al. (2009)
		Cancer Slope Factor (CSF) extrapolated from an inhalation study	1.4E-02	(mg/kg-d) ¹	N/A	Result of combined cancer modeling for male rats (including liver)	Kasai et al. (2009)
			1.2E-02	(mg/kg-d) ¹	N/A	Result of combined cancer modeling for male rats (excluding liver)	Kasai et al. (2009)
^a HECs are adjusted from the study conditions as described above in Section 3.2.6.2. ^b UF _S = subchronic to chronic UF; UF _A = interspecies UF; UF _H = intraspecies UF; UF _L = LOAEL to NOAEL UF (U.S. EPA, 2002) ^c Data from both drinking water studies independently arrived at the same POD for liver effects N/A is shown in the benchmark MOE column for cancer endpoints because EPA did not use MOEs for cancer risks, see Section 4.2 for more information.							

Primary Strengths

There is a robust set of high quality chronic and sub-chronic studies in rats and mice. Available evidence demonstrates consistent systemic toxicity and tumor formation in rats exposed via inhalation and in both rats and mice exposed via drinking water. While data on 1,4-dioxane toxicity from acute exposures are limited, the acute PODs are supported by no effect levels reported in acute inhalation exposure studies in human volunteers.

Where possible, dose-response information used to identify PODs is based on BMD modeling. To calculate cancer risk, EPA assumed that different tumor types are independent and applied cancer models that integrate risk from all tumor types to calculate total cancer risk.

The systemic liver toxicity, nasal lesions and cancer endpoints that serve as the basis for the selected PODs are assumed to be relevant to humans. Inhalation studies that are used as the basis for PODs demonstrate that these effects occur through an exposure route that is relevant to the occupational exposure scenarios. Furthermore, toxicokinetic studies described in Section 3.2.2 demonstrate that systemic absorption and metabolism following inhalation exposure is similar in rats and humans.

The quality of the studies, consistency of effects, relevance of effects for human health, coherence of the effects observed and biological plausibility of the observed effects of 1,4-dioxane contribute to the overall confidence in the PODs.

Primary Limitations

Several limitations contribute to uncertainty around the selected PODs. For example, there are limited data on reproductive and developmental endpoints. There are no multi-generation reproduction studies or developmental neurotoxicity studies. There is a single developmental study that finds evidence of delayed ossification at high doses in the presence of maternal toxicity. EPA does not know if the selected PODs are adequately protective of sensitive endpoints that have not yet been tested.

There is limited information about dermal toxicity of 1,4-dioxane. In the absence of dermal toxicity studies, EPA relied on extrapolation from inhalation and oral exposure studies to derive dermal PODs. While route-to-route extrapolation introduces some additional uncertainty around dermal PODs, the primary sources of uncertainty are likely to underestimate the POD rather than overestimate the POD. For example, a primary source of uncertainty related to extrapolation from inhalation to dermal exposure is the relative efficiency of absorption through the lungs vs. absorption through the skin. Absorption through lungs is generally expected to be more efficient for solvents. Extrapolation from inhalation or oral to dermal exposure is therefore expected to be a relatively conservative approach. Similarly, a primary source of uncertainty related to extrapolation from oral studies is the presence of first-pass metabolism. In this risk evaluation, oral-to-dermal extrapolation was based on liver toxicity. Given first pass metabolism, it is unlikely that dermal exposure would result in greater exposure to the liver than oral exposures.

There is also uncertainty around the MOA of 1,4-dioxane carcinogenicity at all tumor sites. A MOA consistent with a threshold model has been proposed for liver tumors, but EPA concluded that there is insufficient evidence to identify an MOA. Sensitivity analysis demonstrates that inclusion or exclusion of liver tumors does not have a substantial impact on inhalation unit risk.

This suggests that MOA conclusions for liver tumors have a relatively small impact on overall inhalation cancer risk estimates.

Overall Confidence in Selected PODs

EPA qualitatively evaluated overall confidence in each of the selected PODs based on the quality of the key studies, the confidence in the dose-response models, the consistency of effects across studies, species and exposure routes, the relevance of effects for human health, and the coherence and biological plausibility of the effects observed.

Acute Non-Cancer

EPA has medium confidence in the acute inhalation POD. This POD is based on liver toxicity reported in a high quality study that evaluated effects of short-term (rather than acute) inhalation exposure. The POD is based on a LOAEC because the data were not amenable to BMD modeling and a UF of 10 was applied to the benchmark MOE to account for LOAEC to NOAEC extrapolation. The selected POD is below no effect levels identified for neurological effects reported in a medium quality short-term inhalation exposure study in rats ([Goldberg et al., 1964](#)). No effect levels reported in acute inhalation exposure studies in humans ([Ernstgard et al. \(2006\)](#); [Young et al. \(1977\)](#)) also indicate that the selected POD, in combination with the benchmark MOE of 300, is protective of acute irritation or inflammatory effects in humans.

EPA has medium confidence in the acute oral and dermal PODs which are extrapolated from the acute inhalation POD. The systemic liver toxicity identified in short-term inhalation studies is a systemic effect that is relevant for systemic toxicity from oral and dermal exposures. While there are uncertainties related to dosimetric extrapolation from an inhalation study, the approach is more likely to overestimate risk than underestimate risk. For example, absorption through lungs is generally expected to be more efficient for solvents. The oral and dermal PODs derived under the assumption of 100% absorption may therefore be artificially low, but are unlikely to be artificially high.

Chronic Non-Cancer

EPA has high confidence in the chronic inhalation POD. This POD is derived from BMD modeling of respiratory metaplasia in the olfactory epithelium in a high quality chronic inhalation study in rats ([Kasai et al., 2009](#)). The lesions in the olfactory epithelium reported in this chronic study are relevant to humans and are consistent with effects observed in the subchronic inhalation study and in drinking water exposure studies.

EPA has high confidence in the chronic dermal POD. This POD is derived from the chronic inhalation POD. Based on the systemic uptake of 1,4-dioxane following inhalation exposure, the uniform distribution of nasal lesions observed, and the observation of nasal lesions following both inhalation and oral exposures, the nasal lesions are believed to be primarily due to systemic exposure and therefore relevant for systemic toxicity from dermal exposure. While there is some uncertainty around the extent to which portal of entry effects may contribute to these nasal lesions, the selected POD is also strongly supported by very similar PODs derived from systemic effects observed in oral studies. Two oral exposure studies independently served as the basis for derivation of PODs of 2.6 mg/kg/day based on hepatocellular toxicity in male rats ([Kano et al., 2009](#); [Kociba et al., 1974](#)). The selected chronic dermal POD of 1.6 mg/kg/day was therefore considered protective of all observed systemic effects.

Cancer

EPA has high confidence in the cancer inhalation unit risk based on results of a high quality study in male rats. Tumors observed in this study are consistent with tumor types reported in drinking water studies in rats and mice. EPA evaluated inhalation cancer risk using the MS-Combo model to integrate risk of all tumor types reported in this study. A sensitivity analysis demonstrates that excluding liver tumors from this analysis does not substantially change overall cancer risk estimates. This means that applying a threshold model based on alternate MOA conclusions for liver tumors would not substantially alter overall inhalation cancer risk conclusions.

EPA has medium-high confidence in the oral and dermal cancer slope factors. These cancer slope factors are derived from tumors in female mice observed in a high quality drinking water cancer bioassay. Because liver tumor incidence in female mice was high even at the lowest dose tested, data were not readily amenable to EPA's standard modeling approaches. EPA therefore modeled dose-response using a time-to-tumor analysis that incorporates individual animal data. To avoid excess extrapolation, EPA applied an Extra Risk of 50% as the BMR.

4 RISK CHARACTERIZATION

4.1 Environmental Risk

The purpose of the environmental risk characterization is to determine whether there are risks above benchmarks to the aquatic environment from levels of 1,4-dioxane found in surface water based on the fate properties, relatively high potential for release, and the availability of environmental monitoring data and hazard data, and to describe any uncertainties or other considerations relevant to the risk estimate. EPA estimated risks based on a qualitative assessment of the physical-chemical properties and fate of 1,4-dioxane in the environment for sediment and land-applied biosolids, and a quantitative comparison of hazards and exposures for aquatic organisms. These analyses were conducted as part of problem formulation, and reassessed based on SACC recommendations on the risk evaluation. The results of the analyses are presented in Sections 2.3.1 and 4.1, Appendix E, and Appendix F.

The environmental exposure of 1,4-dioxane is summarized in Section 2.3 and Appendix E. As previously stated, only the aquatic pathway was quantitatively evaluated. For this assessment, a first-tier ecological aquatic exposure assessment was conducted using release estimates and measured effluent concentrations from EPA's Toxics Release Inventory (TRI) and Discharge Monitoring Report (DMR) Pollutant Loading Tool, respectively to predict surface water concentrations near a discharge facility (see section 2.3.1). The first-tier approach uses conservative assumptions and readily available data and models.

Summary of the Environmental Hazard of 1,4-Dioxane:

An environmental hazard assessment is summarized in Section 3.1 of this document. A total of nine acceptable aquatic environmental hazard studies were identified for 1,4-dioxane. EPA's evaluation of these studies was mostly high or medium during data quality evaluation (see Table 3-1. in Section 3.1 and "*Systematic Review Supplemental File: Data Quality Evaluation of Environmental Hazard Studies CASRN: 123-91-1*"). The *1,4-Dioxane (123-91-1) Systematic Review: Supplemental File for the TSCA Risk Evaluation Document* provides details of the data evaluations for each study, including scores for each metric and the overall study score.

Acceptable aquatic toxicity studies show that acute exposure to aquatic invertebrates are low. The 48-hour LC₅₀ values range from 4,269 mg/L to 8,450 mg/L. In addition, acute exposure of 1,4-dioxane to fish is low. The 96-hour LC₅₀ values range from 1,236 mg/L to 13,000 mg/L. The chronic toxicity of 1,4-dioxane to fish is low. The chronic values range from >145 mg/L to 565 mg/L, based on growth, weight hatchability, survival, and developmental endpoints.

In algae species, the toxicity of 1,4-dioxane is low with values ranging from 575 mg/L to 5,600 mg/L (with the more sensitive value of 575 mg/L used to represent algal species as a whole).

Summary of Concentrations of Concern Level of 1,4-Dioxane:

In section 3.1.2, EPA evaluated the environmental hazard data by applying a weight of scientific evidence approach (WoE). After weighing the evidence and selecting the appropriate toxicity values from the integrated data to calculate an acute and chronic COC, an assessment factor (AF)

is applied according to EPA methods ([Suter, 2016](#); [U.S. EPA, 2013c](#), [2012d](#)). The application of AFs provides a lower bound effect level that would likely encompass more sensitive species not specifically represented by the available experimental data. These concentrations of concern for acute and chronic ecotoxicity are summarized in Table 3-2. of this assessment.

For 1,4-dioxane, the algae endpoint was the most biological and environmental relevant species for short-term exposure to the chemical. The short-term or acute COC for the algae endpoint is 57,500 µg/L. The chronic COC was derived from a 32-day LOEC fish study of 14,500 µg/L.

Given 1,4-dioxane's conditions of use under TSCA outlined in problem formulation ([U.S. EPA, 2018d](#)), EPA determined that environmental exposures are expected for aquatic species and risk estimations are discussed in the following section.

4.1.1 Risk Estimation Approach of 1,4-Dioxane

To assess the environmental risk of 1,4-dioxane, EPA evaluated the environmental hazard (Section 3.1) and environmental exposure data (Section 2.3). EPA used modeled exposure data from Exposure and Fate Assessment Screening Tool (E-FAST) to characterize the exposure of 1,4-dioxane to aquatic species. Environmental risks are estimated by calculating a risk quotients (RQ). Modeled data were used to represent surface water concentrations near facilities actively releasing 1,4-dioxane to surface water. RQs were calculated using surface water concentrations and the COCs calculated in the hazard section of this document (see Section 4.1.2). The RQ is defined as:

$$RQ = \text{Predicted Environmental Concentration} / \text{Effect Level or COC}$$

For this assessment, RQ values that are equal to 1 ($RQ = 1$) indicates that environmental exposures are the same as the COC. If the RQ is above 1 (*i.e.*, $RQ > 1$), the exposure is greater than the COC. If the RQ is below 1 (*i.e.*, $R < 1$), the exposure is less than the COC. The COCs for aquatic organisms shown in Table 3-2. and the environmental concentrations shown in Section 2.3.1 and Appendix E, were used to calculate RQs ([U.S. EPA, 1998](#)).

EPA considered the biological relevance of the species that the COCs were based on when integrating the COCs with surface water concentration data to produce RQs. For example, certain biological factors affect the potential for adverse effects in aquatic organisms. Life-history and the habitat of aquatic organisms influences the likelihood of exposure above the hazard benchmark in an aquatic environment.

Frequency and duration of exposure also affect potential for adverse effects in aquatic organisms, especially for chronic exposures.

4.1.2 Risk Estimation for the Aquatic Environment

To characterize potential environmental risk of 1,4-dioxane to aquatic organisms, EPA calculated RQs based on modeled data from E-FAST for sites that had surface water discharges of 1,4-dioxane according to Toxic Release Inventory (TRI) and Discharge Monitoring Report (DMR) release information to model predicted surface water concentrations near discharging

facilities. EPA employed a first-tier aquatic exposure assessment. Based on the top ten DMR discharging facilities in 2015 and 2016, predicted surface water concentrations, which were based on the 7Q10 stream flow, ranged from 18.8 to 11,500 µg/L for acute release scenarios and 0.095 to 5,762 µg/L for chronic release scenarios. Based on the top TRI discharging facilities in 2014 and 2015 (including direct and indirect dischargers), predicted surface water concentrations ranged from 1.26 to 9,734 µg/L for acute release scenarios and 2.37E-08 to 4,879 µg/L for chronic release scenarios. The estimated surface water concentrations derived from chronic release scenarios (*i.e.*, those assuming 20 days or more of annual release days) were compared against the chronic COC of 14,500 µg/L using E-FAST's high-end Probabilistic Dilution Model (PDM).

The environmental exposure assessment predicts conservative surface water concentrations for a set of facilities that reports recent releases of 1,4-dioxane via DMR and/or TRI (see Appendix E). The dataset of facilities were queried from the Enforcement and Compliance History Online (ECHO) [Water Pollutant Loading Tool](#). The DMR includes pollutant loading information for more than 60,000 DMR reporting facilities (industrial and municipal point source dischargers) regulated under the Clean Water Act. It contains wastewater monitoring and other facility data, as reported on facility specific DMRs. TRI contains reporting information on facilities in specific industry sectors which employ more than 10 full-time equivalent employees and manufacture, process, or use more than 25,000 lbs. per year of a TRI-listed chemical.

The analysis was conducted using the top direct and indirect dischargers of 1,4-dioxane from DMR and TRI covering the two most current and complete reporting years available at the time of problem formulation (*i.e.*, 2015 and 2016 for DMR and 2014 and 2015 for TRI). As many of the facilities overlapped between the DMR and TRI sets, and between the assessment years, a total of 39 unique facilities were assessed. Detailed information on the selected facilities are summarized in Table E-2.

Estimation of Environmental Concentrations of 1,4-Dioxane in Surface Water:

The estimation of environmental concentrations of 1,4-dioxane in surface water underlying this aquatic risk characterization is discussed in Section 2.3.1 and Appendix E. Tables E-3, E-4, and E-5 presents the results of the first-tier aquatic exposure assessment. Based on the top ten DMR discharging facilities in 2015 and 2016, predicted surface water concentrations, which were based on the 7Q10 stream flow, ranging from 18.8 to 11,500 µg/L for acute release scenarios and 0.095 to 5,762 µg/L for chronic release scenarios. Based on the top TRI discharging facilities in 2014 and 2015 (including direct and indirect dischargers), predicted surface water concentrations ranged from 1.26 to 9,734 µg/L for acute release scenarios and 2.37E-08 to 4,879 µg/L for chronic release scenarios. The estimated surface water concentrations derived from chronic release scenarios (*i.e.*, those assuming 20 days or more of annual release days) were compared against the chronic COC of 14,500 µg/L using E-FAST's high-end Probabilistic Dilution Model (PDM).

The environmental releases of 1,4-dioxane into the aquatic environment occur from industrial use and are discharged directly to surface water or indirectly to wastewater treatment plants. Table 4-1., Table 4-2., and Table 4-3. summarize the modeled or estimated exposure scenarios and the RQ values from facilities that manufacture and release of 1,4-dioxane into surface water. Only the minimum and maximum concentrations of 1,4-dioxane from these facilities are summarized in the tables. All facilities from this analysis are provided in Appendix F of this assessment.

Environmental Risk Estimation of 1,4-Dioxane from Industrial Releases into Surface Water from DRM Reporting:

Table 4-1., Table 4-2., and Table 4-3. below, summarize the estimated surface water concentrations of 1,4-dioxane. In this section, only the maximum predicted environmental concentrations (PNEC) values of 1,4-dioxane in surface water were calculated to derive risk for acute and chronic exposures for aquatic organisms. For acute exposure, algae represent the most relevant and sensitive species that is susceptible to 1,4-dioxane exposures and fish for chronic exposures.

Table 4-1. summarizes the estimated surface water concentrations of 1,4-dioxane due to discharge from DMR facilities in 2015 and 2016. The parameters in this table are identical to the values that are reported in Table E1 in Appendix E. The calculated RQ values in the tables are included.

The data provided in the table was collected from 10 facilities in 2015 and 2016. Eastman Kodak in New York reported the lowest concentrations of 1,4-dioxane that resulted in acute exposures to algae and chronic exposure to fish in 2015 and 2016. DAK Americas, LLC in South Carolina, reported the maximum concentrations of 1,4-dioxane that resulted in acute and chronic exposures for the same years. Therefore, risk from acute exposure to the aquatic species from releases to surface water were not identified because predicted concentrations did not exceed the acute COC of 57,500 µg/L. Risk from chronic exposures to aquatic species were not identified despite the 20 days of exceedences (20/365 days/year during use) because the predicted environmental concentration (surface water concentrations) of 5,762 µg/L did not exceed the chronic COC of 14,500 µg/L (RQ<1).

Table 4-1. Environmental Risk Estimation of 1,4-Dioxane from Industrial Releases into Surface Water from DMR Facilities in Year 2015 and 2016

Name, Location, and ID of Active Releaser Facility	E-FAST Inputs and Results				RQ	
	Days of Release ^a	Release ^a (kg/day)	10 th Percentile 7Q10 Concentration (µg/L)	Days Exceedance (days/yr)	Algae (Acute) COC = 57,500 µg/L	Fish (Chronic) COC = 14,500 µg/L
<i>Minimum Acute and Chronic Risk Quotient Values Reported from 10 DMR Facilities Reported in 2015</i>						
Eastman Kodak NY0001643 (SIC 3861)	1	20	18.78	NA	6.90E-05	1.74E-05
	20	1	0.95	0	6.90E-06	1.74E-06
	250	0.1	0.0949	0	0	0
<i>Maximum Acute and Chronic Risk Quotient Values Reported from 10 DMR Facilities in 2015</i>						
Dak Americas LLC SC0026506 (SIC 2821)	10 ^b	920	10,900^b	NA	0.031731	0.0080017
	20	460	5,428.91	0	0.0025379	0.00064
	250	37	434.22	0	0.0002966	7.48E-05
<i>Minimum Acute and Chronic Risk Quotient Values Reported from 10 DMR Facilities Reported in 2016</i>						
Eastman Kodak NY0001643 (SIC 3861)	1	79	74.46	NA	0.001295	0.0051352
	20	3.9	3.7	0	6.43478 E-05	0.0002552
	250	0.3	0.28	0	4.86957 E-06	1.93103 E-05
<i>Maximum Acute and Chronic Risk Quotient Values Reported from 10 DMR Facilities in 2016</i>						
Dak Americas LLC SC0026506 (SIC 2821)	10 ^b	977	11,500	NA	0.2	0.7931034
	20	488	5,761.65	0	0.1002026	0.3973552
	250	39	461.36	0	0.0080237	0.0318179
<p>a. Days of release (1, 20, or 250) are EPA assumptions that provide a range of potential surface water concentrations; days of release were not reported in DMR. The release (kg/day) is based on the per day based on total annual loading (lbs/yr), as reported in DMR Pollutant Loading Tool, and is divided by the assumed number of release days prior to modeling.</p> <p>b. The Dak chemicals site acute scenario was re-run for a 10-day acute scenario based on input from EPA engineers related to the lowest number of operating days assumed for facilities falling within this standard industrial category (<i>i.e.</i>, 10 days per year). Therefore, maximum surface water concentrations based on this site reflect an assumed 10 days per year of release instead of 1 day.</p>						

Environmental Risk Estimation of 1,4-Dioxane from Direct Industrial Releases into Surface Water:

Table 4-2. summarizes the estimation of direct releases of 1,4-dioxane into surface water from industrial use from facilities during 2014 and 2015. There were 10 facilities reporting per year. The Dow Chemical Company in Louisiana reported the minimum acute and chronic concentrations of 1,4-dioxane in 2015 and 2016. The minimum acute exposure concentrations were 1.26 µg/L (2014) and 1.36 µg/L (2015). The minimum chronic exposure concentrations were 0.004 µg/L for 2014 and 2015. DAK Americas, LLC in South Carolina, reported the maximum acute and chronic concentrations of 1,4-dioxane for the 2014 and 2015. The maximum acute exposure concentrations were 9,734 µg/L (2014) and 9,557 µg/L (2015). The maximum chronic exposure concentrations were 4,861 µg/L (2014) and 4,779 µg/L (2015). As previously stated, the maximum estimated surface water concentrations that was reported for 2014 to 2015 for acute and chronic exposure to aquatic organisms will be used to derive the risks of 1,4-dioxane in surface water.

Risk from acute exposures to the aquatic species from releases to surface water were not identified because concentrations did not exceed the acute COC of 57,500 µg/L. Risk from chronic exposures to the environment were not identified despite the 20 days of exceedences (20/365 days/year during use) because the predicted environmental concentration (surface water concentrations) of 0.49 µg/L does not exceed the chronic COC of 14,500 µg/L (RQ<1).

Table 4-2. Environmental Risk Estimation of 1,4-Dioxane from Direct Industrial Releases into Surface Water from TRI Facilities in Year 2014 and 2015

Name, Location, and ID of Active Releaser Facility	E-FAST Inputs and Results				RQ	
	Days of Release ^a	Release ^a (kg/day)	10 th Percentile 7Q10 Concentration (µg/L)	Days Exceedance (days/yr)	Algae COC = 57,500 µg/L	Fish Chronic COC = 14,500 µg/L
<i>Minimum Acute and Chronic Risk Quotient Values Reported from 10 TRI Facilities in 2014a</i>						
The DOW Chemical Co. Louisiana Operations LA0003301 ^b	1	312	1.26	NA	2.19E-05	8.69E-05
	20	16	0.0648	0	1.13E-06	4.47E-06
	250	1	0.00405	0	7.04E-08	2.79E-07
<i>Maximum Acute and Chronic Risk Quotient Values Reported from 10 TRI Facilities in 2014a</i>						
DAK Americas LLC Cooper River Plant SC0026506	10 ^c	825	9,734	NA	1.69E-01	6.71E-01
	20	412	4,861.36	0	8.45E-02	3.35E-01
	250	33	389.4	0	6.77E-03	2.69E-02
<i>Minimum Acute and Chronic Risk Quotient Values Reported from 10 TRI Facilities in 2015</i>						
The DOW Chemical Co. Louisiana Operations LA0003301 ^b	1	337	1.36	NA	2.37E-05	9.38E-05
	20	17	0.0688	0	1.20E-06	4.74E-06
	250	1	0.00405	0	7.04E-08	2.79E-07
<i>Maximum Acute and Chronic Risk Quotient Values Reported from 10 TRI Facilities in 2015</i>						
DAK Americas LLC Cooper River Plant SC0026506	10 ^c	810	9,557	NA	1.66E-01	6.59E-01
	20	405	4778.76	0	8.31E-02	3.30E-01
	250	32	377.58	0	6.57E-03	2.60E-02
<p>a. Days of release (1, 20, or 250) are EPA assumptions that provide a range of potential surface water concentrations; days of release were not reported to TRI. The release (kg/day) is based on the per day based on annual releases to surface water (lbs/yr), as reported to TRI, and is divided by the assumed number of release days prior to modeling.</p> <p>b. The NPDES provided in DMR's Pollutant Loading Tool for the facility THE DOW CHEMICAL CO - LOUISIANA OPERATIONS (NPDES LA0116602) was not found in E-FAST 2014; however, a facility name and location search within E-FAST 2014 returned a different NPDES (LA0003301) associated with this facility name and location, so it was applied for modeling.</p> <p>c. ARKEMA Inc (KY0003603), Dow Chemical Co Freeport (TX0006483), Honeywell International (LA0000329), and Westlake Vinyls Inc (KY0003484) facilities, which were included in the risk evaluation based on previous data extraction, did not have reported surface water discharges in TRI explorer per 2015 release report and were therefore removed.</p>						

Environmental Risk Estimation of 1,4-Dioxane from Indirect Industrial Releases into Surface Water from TRI Reporting:

Table 4-3. summarizes the estimation of indirect releases of 1,4-dioxane concentration into surface water from industrial use from TRI facilities during 2014 and 2015. There were six facilities in 2014 and 10 facilities in 2015. Evonik Materials Corp., in Wisconsin and Heritage Thermal Services in Ohio, reported the minimum chronic environmental concentrations in 2014 and 2015, respectively. SUEZ WTS Solutions USA, Inc., in Indiana reported the maximum chronic environmental concentrations in during 2014 and 2015. There were no acute

environmental concentrations reported for indirect surface water releases of 1,4-dioxane during 2014 and 2015.

The minimum chronic environmental concentration was 2.37 E-08 µg/L and the maximum environmental concentration was 3789 µg/L. For this assessment, the maximum surface water concentrations that was reported from 2014 to 2015 for acute and chronic exposures will be used to derive the risks of 1,4-dioxane in surface water.

Risks from acute exposures to aquatic species were not identified because there were no indirect releases of 1,4-dioxane to surface water. Risk from chronic exposures to the environment were not identified despite the 250 days of exceedences (250/365 days/year during use) because the predicted environmental concentration (surface water concentrations) of 3,789 µg/L does not exceed the chronic COC of 14,500 µg/L (RQ<1).

Table 4-3. Environmental Risk Estimation of 1,4-Dioxane from Indirect Industrial Releases into Surface Water from TRI Facilities in Year 2014 and 2015

Name, Location, and ID of Active Releaser Facility NPDES Used in E-FAST	Receiving POTW	E-FAST Inputs and Results				RQ	
		Days of Release ^a	Release ^a (kg/day)	7Q10 Concentration (µg/L)	Days Exceedance (days/yr) COC = 14,500 µg/L	Algae COC = 57,500 µg/L	Fish Chronic COC = 14,500 µg/L
<i>Minimum Acute and Chronic Risk Quotient Values Reported from 6 TRI Facilities in 2014</i>							
Evonik Materials Corp. WI0060453	Milton Waterworks	250	0.001	0.00586	0	1.02E-07	4.04E-07
<i>Maximum Acute and Chronic Risk Quotient Values Reported from 6 TRI Facilities in 2014a</i>							
SUEZ WTS Solutions USA Inc. Ind. POTW (SIC 4952) ^b	Blue Lake WWTP	250	30	3788.66	4	6.59E-02	2.61E-01
<i>Minimum Acute and Chronic Risk Quotient Values Reported from 10 TRI Facilities in 2015</i>							
Heritage Thermal Services OH0024970	East Liverpool WWTP	250	2.39E-07	2.37E-08	0	4.12E-13	1.63E-12
<i>Maximum Acute and Chronic Risk Quotient Values Reported from 10 TRI Facilities in 2015</i>							
SUEZ WTS Solutions USA Inc. Ind. POTW (SIC 4952) ^b	Blue Lake WWTP	250	27	3409.79	3	5.93E-02	2.35E-01

a. Days of release (250) are EPA assumptions that provide a range of potential surface water concentrations; days of release were not reported to TRI. The release (kg/day) is based on the per day based on annual releases to surface water (lbs/yr), as reported to TRI, and is divided by the assumed number of release days prior to modeling.

b. SIC for industrial POTWs was used for the facility because the facility was not found in E-FAST 2014.

4.1.3 Risk Estimation for the Sediment Environment

EPA did not quantitatively assess exposure of 1,4-dioxane to sediment-dwelling organisms because the chemical is expected to remain in aqueous phases and has low potential to sorb to sediment due to its water solubility (> 800 g/L) and organic matter partition coefficient (log K_{OC} = 0.4). Sediment monitoring data suggest that 1,4-dioxane is present in sediments, but because 1,4-dioxane has low partitioning to organic matter (log K_{OC} = 0.4) it is likely that 1,4-dioxane detected in sediment is in the pore water and rather than sorbed to the sediment solids. It is expected that the concentrations of 1,4-dioxane in sediment pore water from environmental releases is similar to the concentrations of the overlying water.

4.1.4 Risk Estimation for the Terrestrial Environment

EPA did not quantitatively assess exposure of 1,4-dioxane to terrestrial organisms through soil, water or land-applied biosolids. Because activated sludge and biosolids (processed sludge) have high water content and 1,4-dioxane has low potential to sorb to sludge solids, most of the 1,4-dioxane in biosolids is expected to be in the aqueous phase of the biosolids as opposed to sorbed to the solids. Further, 1,4-dioxane released from wastewater treatment via biosolids is expected to be negligible compared to the 1,4-dioxane released with effluents: of the 1,4-dioxane in influent wastewater, it is expected that < 2% will be removed with biosolids and associated water and > 95% will be present in the effluent. Concentrations of 1,4-dioxane during biosolids processing may decrease through volatilization to air during transport, processing (including dewatering and digestion), handling, and application to soil (which may include spraying). 1,4-Dioxane released to the terrestrial pathway via land-applied biosolids has low potential to sorb to soil due to its low partitioning to organic matter (estimated log K_{OC} = 0.4). 1,4-Dioxane is thus expected to be mobile in soil and migrate to surface waters and groundwater or volatilize to air.

4.2 Human Health Risk

4.2.1 Human Health Risk Estimation Approach

1,4-Dioxane hazard and dose-response assessments were developed based on EPA, National Research Council (NRC), and European Chemicals Agency (ECHA) risk assessment guidance. Studies conducted via the inhalation and oral routes of exposure were evaluated in this assessment. The dose-response assessment used for selection of PODs for non-cancer and cancer endpoints and the benchmark dose analyses used in the risk characterization are described in Section 3.2.6.

The use scenarios, populations of interest and toxicological endpoints that were selected for determining potential risks from acute and chronic exposures are presented in Table 4-4..

Table 4-4. Summary of Parameters for Risk Characterization

Populations and Toxicological Approach	Occupational Exposure Scenarios for 1,4-Dioxane Uses at Industrial or Commercial Facilities (see Section G.6)
Population of Interest and Exposure Scenario:	<p><i>Users:</i> <u>Acute</u>- Healthy female and male adult workers (>16 years old) exposed to 1,4-dioxane for a single 8-hour exposure</p> <p><u>Chronic</u>- Healthy female and male adult workers (>16 years old) exposed to 1,4-dioxane for the entire 8-hour workday for 260 days per year for 40 working years</p>
	<p><i>Occupational Non-User:</i> <u>Acute or Chronic</u>- Healthy female and male adult workers (>16 years old) exposed to 1,4-dioxane indirectly by being in the same work area of the building</p>

Populations and Toxicological Approach	Occupational Exposure Scenarios for 1,4-Dioxane Uses at Industrial or Commercial Facilities (see Section G.6)
<p>Health Effects of Concern, Concentration and Time Duration</p>	<p>Acute/Short-term PODs: Short-term inhalation HEC is 78.7 ppm (284 mg/m³) Based on liver toxicity following short-term inhalation exposure in rats; 2-Week duration of study is relevant to typical short-term worker exposures</p> <p>Short-term dermal HED is 35.4 mg/kg-d Extrapolated from short-term inhalation HEC based on systemic liver toxicity</p> <p>Short-term oral HED is 35.4 mg/kg-d Extrapolated from short-term inhalation HEC based on systemic liver toxicity</p> <hr/> <p>Chronic Non-Cancer PODs: Inhalation 8-hour HEC: 12.8 mg/m³ (olfactory epithelium effects (<i>i.e.</i>, metaplasia and atrophy) from Table 3-14.)</p> <p>Dermal 8-hour HED: 1.6 mg/kg-d Extrapolated from inhalation POD based on olfactory epithelium effects attributed to systemic delivery</p>
<p>Health Effects of Concern, Concentration and Time Duration (cont.)</p>	<p>Cancer Health Effects: Inhalation Unit Risk (from Table 3-10.): 1.0E-06 (µg/m³)⁻¹ Based on consistent results of MS-Combo models for combined tumor risk in male rats including liver tumors (1.18E-6 (µg/m³)⁻¹) and excluding liver tumors (1.0E-6 (µg/m³)⁻¹)</p> <p>Dermal cancer slope factor^a (from Table 3-13.): 1.2E-01(mg/kg-d)⁻¹ Extrapolated from an oral cancer slope factor based on female mouse liver tumors in a drinking water study; An alternate CSF of 1.2E-02 was extrapolated from inhalation studies.</p>
<p>Non-Cancer Margin of Exposure (MOE) Uncertainty Factors (UF)^b</p>	<p>Acute/Short-term Inhalation Benchmark MOE = 300 UF_A = 3; UF_H = 10; UF_L = 10</p> <p>Acute/Short-term Dermal Benchmark MOE = 300 UFA = 3; UFH = 10; UFL = 10</p> <p>Acute/Short-term Oral Benchmark MOE = 300 UFA = 3; UFH = 10; UFL = 10</p> <p>Chronic Inhalation Benchmark MOE = 30 UF_A = 3; UF_H = 10</p> <p>Chronic Dermal Benchmark MOE = 30 UF_A = 3; UF_H = 10</p>

Populations and Toxicological Approach	Occupational Exposure Scenarios for 1,4-Dioxane Uses at Industrial or Commercial Facilities (see Section G.6)
Cancer Benchmark^c	<i>Inhalation and Dermal:</i> 1 x 10 ⁻⁴ excess cancer risk for worker populations 1 x 10 ⁻⁶ excess cancer risk for consumers

^a A route-to-route extrapolation was performed on the oral and inhalation cancer slope factors as described above in Section 3.2.6.2.

^b UF_A=interspecies uncertainty/variability; UF_H=intraspecies uncertainty/variability; UF_L=LOAEL-to-NOAEL uncertainty; See Section 3.2.6 for more detailed rationale for selection of uncertainty factors applied to each POD and Section 5.1.1.1 for additional explanation of the benchmark MOE approach.

^c See Section 5.1.1.2 for rationale for selection of the cancer benchmark

EPA used a Margin of Exposure (MOE) approach to identify potential non-cancer risks. The MOE is the ratio of the non-cancer POD divided by a human exposure dose.

The acute and chronic MOE (MOE_{acute} or MOE_{chronic}) for non-cancer inhalation and dermal risk were calculated using Equation 4.2.1-1.

Equation 4.2.1-1 Equation to Calculate Margin of Exposure for Non-Cancer Risks Following Acute or Chronic Exposures

$$MOE_{acute\ or\ chronic} = \frac{\text{Non – cancer Hazard value (POD)}}{\text{Human Exposure}}$$

Where:

MOE	= Margin of exposure (unitless)
Hazard value (POD)	= HEC (mg/m ³) or HED (mg/kg-d)
Human Exposure	= Exposure estimate (in mg/m ³ or mg/kg-d) from occupational exposure assessment

MOEs allow for the presentation of a range of risk estimates. EPA used MOEs¹⁵ to estimate non-cancer risks from acute and chronic exposures based on the following: the HECs/HEDs identified for each health effects domain; the endpoint/study-specific UFs applied to the HECs/HEDs per the review of the EPA [Reference Dose and Reference Concentration Processes \(U.S. EPA, 2002\)](#); and the exposure estimates calculated for 1,4-dioxane conditions under the conditions of use (see Section 2).

The Acute Exposure Concentration (AEC) was used to estimate acute/short-term inhalation risks, whereas the Average Daily Concentration/Dose (ADC)/D) was used to estimate chronic non-cancer inhalation/dermal. For occupational exposure calculations, the 8-hour TWA was used to calculate MOEs for risk estimates for acute and chronic exposures. Evaluation of non-cancer

¹⁵ Margin of Exposure (MOE) = (Non-cancer hazard value, POD) ÷ (Human Exposure). Equation 4.2.1-1. The benchmark MOE is used to interpret the MOEs and consists of the total UF shown in Table 4-4.

risks from acute consumer and general population exposures were also based on an 8-hour exposure.

For acute and chronic non-cancer effects, potential risks for adverse effects were based on liver toxicity and effects in the olfactory epithelium. Risk estimates for effects in the liver and olfactory epithelium were calculated from studies that were rated under the data quality criteria as “Medium” or “High.” The liver and olfactory epithelium endpoints used as the basis from which to estimate risks were chosen based on the quality of the key studies, the confidence in the dose-response models, the consistency of effects across studies, species and exposure routes, the relevance of effects for human health, and the coherence and biological plausibility of the effects observed, as discussed in Section 3.2.7.

EPA interpreted the MOE risk estimates for each use scenario in reference to benchmark MOEs. Benchmark MOEs are the total UF for each non-cancer POD. The MOE estimate was interpreted as a human health risk if the MOE estimate was less than the benchmark MOE (*i.e.*, the total UF). On the other hand, the MOE estimate indicated negligible concerns for adverse human health effects if the MOE estimate was equal to or exceeded the benchmark MOE. Typically, the larger the MOE, the more unlikely it is that a non-cancer adverse effect would occur.

Extra cancer risks for repeated exposures to 1,4-dioxane were estimated using Equation 4.2.1-2. Estimates of extra cancer risks are interpreted as the incremental probability of an individual developing cancer over a lifetime following exposure to 1,4-dioxane (*i.e.*, incremental or extra individual lifetime cancer risk).

Equation 4.2.1-2 Equation to Calculate Cancer Risks

$$\begin{aligned} \text{Inhalation Cancer Risk} &= \text{Human Exposure} \times \text{IUR} \\ \text{or} \\ \text{Dermal Cancer Risk} &= \text{Human Exposure} \times \text{CSF} \end{aligned}$$

Where:

Risk	= Extra cancer risk (unitless)
Human exposure	= Occupational exposure estimate (LADC in $\mu\text{g}/\text{m}^3$)
IUR	= Inhalation unit risk (1×10^{-6} per $\mu\text{g}/\text{m}^3$)
CSF	= Cancer slope factor (1.2×10^{-1} per $\text{mg}/\text{kg}\text{-d}$)

The range of IURs considered in Table 4-4. were 1.18×10^{-6} to 1.0×10^{-6} ($\mu\text{g}/\text{m}^3$)⁻¹. Therefore, a rounded value of 1×10^{-6} per $\mu\text{g}/\text{m}^3$ was used for calculation of inhalation cancer risks. The range of CSFs considered in Table 4-4. were 1.2×10^{-2} to 1.2×10^{-1} ($\text{mg}/\text{kg}\text{-d}$)⁻¹ for the different extrapolations from inhalation or oral studies and for different combinations of tumor types. The CSF 1.2×10^{-1} ($\text{mg}/\text{kg}\text{-d}$)⁻¹ was used for calculation of dermal cancer risks.

To determine the level of personal protection needed by workers to reduce the high-end exposures to below the level of concern, EPA evaluated the impact of respirator and glove use on risks from inhalation and dermal exposure. Typical APF values of 1, 10 and 50 and glove PF values of 1, 5, 10, and 20 were compared to the calculated MOEs and benchmark MOE to

determine the level of APF or glove PF required to reduce exposure so that risk is below the benchmark MOE.

4.2.2 Risk Estimate for Exposures for Occupational Use of 1,4-Dioxane

4.2.2.1 Occupational Risk Estimation for Effects of Acute/Short-term Inhalation Exposures

1,4-Dioxane exposure is associated with acute effects. Based on the weight of the scientific evidence analysis of the reasonably available toxicity studies from humans and animals, the key acute/short-term exposure effect is liver toxicity (*i.e.*, single cell necrosis).

The study that serves as the basis for acute/short-term health concerns ([Mattie et al., 2012](#)) is of high data quality. Risk estimates for acute inhalation exposures to 1,4-dioxane were determined for the occupational exposure scenarios. Based on the POD reported by Mattie *et al.* ([2012](#)) (*i.e.*, LOAEC = 378 mg/m³), EPA calculated an acute HEC of 283.5 mg/m³ and an acute inhalation benchmark MOE of 300.

Comparing the 8-hour acute exposures (AEC concentrations) for the use scenarios to the acute/short-term HEC for liver effects gives the calculated MOEs shown in Table 4-5. for workers and Table 4-6. for ONUs.

Table 4-5. Acute/Short-term Inhalation Exposure Risk to Workers; Benchmark MOE = 300

Exposure Scenario	Full Shift (8hr) AEC (mg/m ³)		Calculated MOE (no respirator)		Calculated MOE (APF 10) ^b		Calculated MOE (APF 50) ^b	
	Central Tendency	High-End	Central Tendency	High-End	Central Tendency	High-End	Central Tendency	High-End
Manufacturing	0.42	7.73	684	37	6,843	367	34,217	1,836
Import/Repackaging (Bottle)	9.28	33.1	30.6	8.6	306	86	1,529	429
Import/Repackaging (Drum)	10.6	38.2	26.7	7.4	267	74	1,334	372
Industrial Use	5.0	20	56.8	14.2	568	142	2,840	710
Open System Functional Fluids	0.0011	0.0038	266,475	74,906	2,664,753	749,065	13,323,767	3,745,324
Spray Foam Application	0.0097	0.012	29,194	24,030	291,939	240,300	1,459,696	1,201,501
Lab Chemicals	0.11	5.7	2,582	49.4	25,818	494	129,091	2,470
Film Cement	1.52	2.81	187	101	1,866	1,012	9,331	5,058
Use of Printing Inks (3D)	0.097 ^a		2,922		29,218		146,091	
Dry Film Lubricant	0.47	1.60	607	177	6,068	1,773	30,342	8,864
Disposal	1.87	6.64	152	42.8	1,517	428	7,586	2,138

Bold: Calculated MOEs were below the benchmark MOE.
^a EPA cannot determine the statistical representativeness of the values given the small sample size.
^b MOEs with respirator use were calculated by multiplying the MOE without a respirator by the respirator APF

Table 4-6. Acute/Short-term Inhalation Exposure Risk to Occupational Non-Users: Non-Cancer; Benchmark MOE = 300

Exposure Scenario	ADC (mg/m ³)		Calculated MOE	
	Central Tendency	High-end	Central Tendency	High-end
Manufacturing	-	-	-	-
Import/Repackaging	-	-	-	-
Industrial Use	-	-	-	-
Open System Functional Fluids	0.00015	0.00025	1,903,645	1,128,664
Spray Application	0.0019 ^a		151,467	
Lab Chemicals	-	-	-	-
Film Cement ^c	0.10 ^a		2,726	
Use of Printing Inks (3D)	-	-	-	-
Disposal	-	-	-	-

^a EPA cannot separately determine a central tendency and high-end estimate.
^c - EPA does not have ONU-specific estimates for these exposure scenarios and relies on central tendency worker exposure scenarios without PPE to predict risk to ONUs

4.2.2.2 Occupational Risk Estimation for Non-Cancer Effects Following Chronic Inhalation Exposures

Chronic non-cancer risk estimates for inhalation exposures to 1,4-dioxane were derived for occupational scenarios using estimated inhalation average daily concentrations (ADCs). The central and high-end ADC exposure estimates were compared to the inhalation hazard POD of 12.8 mg/m³ using a benchmark MOE of 30. Table 4-7. and Table 4-8. show the exposure estimates used for workers and ONUs and the resulting MOEs. The definition of high-end exposures varies by exposure scenario as to the percentile of the distribution. EPA calculated MOEs for workers with and without respirators.

Table 4-7. Chronic Inhalation Exposure Risk to Workers: Non-Cancer; benchmark MOE=30

Exposure Scenario	ADC (mg/m ³)		Calculated MOE (no respirator) ^a		Calculated MOE (APF 10) ^f		Calculated MOE (APF 50) ^f	
	Central Tendency	High-end	Central Tendency	High-end	Central Tendency	High-end	Central Tendency	High-end
Manufacturing	0.40	7.44	32.1	1.7	321	17	1,604	86.1
Import/Repackaging (Bottle)	0.46	3.39	27.6	3.8	276	38	1,381	189
Import/Repackaging (Drum)	0.46	3.39	27.6	3.8	276	38	1,381	189
Industrial Use	4.8	19.2 ^c	2.66	0.67	26.6	6.7	133.1	33.3
Open System Functional Fluids	0.0010	0.0038	12,491	3,511	124,906	35,111	624,528	175,555
Spray Application	0.0094	0.011	1,368	1,126	11,264	13,684	68,421	56,318
Lab Chemicals	0.11	5.53 ^d	121	2.32	1,210	23.15	6,051	116
Film Cement	1.46	2.70 ^e	8.75	4.74	87.5	47.4	437	237
Use of Printing Inks (3D)	0.093 ^b		137		1,370		6,848	
Dry Film Lubricant	0.1	0.35	127	37.1	1,270	371	6,349	1,855
Disposal	1.80	6.39	7.1	2.0	71	20	356	100

Bold: Calculated MOEs were below the benchmark MOE.

^a MOEs were calculated with Equation 5-1 briefly that is: “Central Tendency ADC (µg/m³)” or “High-end ADC (µg/m³)” ÷ POD (µg/m³)

^b EPA cannot determine the statistical representativeness of the values given the small sample size.

^c The risk assessment did not provide details about how these values were calculated, therefore, it is unclear what percentile is represented when an exposure is described as “reasonable worst case.”

^d For this scenario the high-end was the 90th percentile.

^e For this scenario the high-end was the maximum value.

^f MOEs with respirator use were calculated by multiplying the MOE without a respirator by the respirator APF

Table 4-8. Chronic Inhalation Exposure Risk to Occupational Non-Users: Non-Cancer; Benchmark MOE = 30

Exposure Scenario	ADC (mg/m ³)		Calculated MOE	
	Central Tendency	High-end	Central Tendency	High-end
Manufacturing	-	-	-	-
Import/Repackaging	-	-	-	-
Industrial Use	-	-	-	-
Open System Functional Fluids	0.00014	0.00024	89,230	52,904
Spray Application	0.0018 ^a		7,100	
Lab Chemicals	-	-	-	-
Film Cement ^c	0.10 ^a		128	
Use of Printing Inks (3D)	-	-	-	-
Disposal	-	-	-	-

^a EPA cannot separately determine a central tendency and high-end estimate.
^c EPA does not have ONU-specific estimates for these exposure scenarios and relies on central tendency worker exposure scenarios without PPE to predict risk to ONUs

4.2.2.3 Occupational Risk Estimation for Cancer Effects Following Chronic Inhalation Exposures

Chronic cancer risk estimates for inhalation exposures to 1,4-dioxane were derived for occupational scenarios using estimated inhalation lifetime average dose concentrations (LADC). Cancer risk was calculated for the central and high-end LADC exposure estimates. Table 4-9. shows the calculated cancer risks for central and high-end exposures. The definition of high-end percentile of the exposure distribution varies by exposure scenario. EPA calculated cancer risk for workers with and without respirators.

Table 4-9. Inhalation Exposure Risk Estimates to Workers: Cancer; Benchmark Risk = 1 x 10⁻⁴

Exposure Scenario	LADC (µg/m ³)		Cancer Risk (no respirator) ^a		Cancer Risk (APF 10) ^b		Cancer Risk (APF 50) ^b	
	Central Tendency	High-end	Central Tendency	High-end	Central Tendency	High-end	Central Tendency	High-end
Manufacturing	159	3814	1.6E-04	3.8E-03	1.6E-05	3.8E-04	3.2E-06	7.6E-05
Import/Repackaging	175	1,319	1.8E-04	1.3E-03	1.8E-05	1.3E-04	3.5E-06	2.6E-05
Industrial Use	1,911	9,862	1.9E-03	9.9E-03^d	1.9E-04	9.9E-04	3.8E-05	2.0E-04
Open System Functional Fluids	0.39	1.5	3.9E-07	1.5E-06	3.9E-08	1.5E-07	7.8E-09	2.9E-08
Spray Foam Application	3.6	5.3	3.6E-06	5.3E-06	3.6E-07	5.3E-07	7.3E-08	1.1E-07
Lab Chemicals	42	2,835	4.2E-05	2.8E-03^e	4.2E-06	2.8E-04	8.4E-07	5.7E-05
Film Cement	582	1,384	5.8E-04	1.4E-03^f	5.82E-05	1.38E-04	1.16E-05	2.77E-05
Use of Printing Inks (3D)	37	48	3.7E-05	4.8E-05 ^c	3.7E-06	4.8E-06	7.4E-07	9.6E-07
Dry Film Lubricant	40	177	4.0E-05	1.8E-04	4.0E-06	1.8E-05	8.0E-07	3.5E-06
Disposal	680	2,540	6.8E-04	2.5E-03	6.8E-05	2.5E-04	1.4E-05	5.1E-05

Bold: Cancer risk exceeds the benchmark of 1 x 10⁻⁴.

^a Cancer risk was calculated as follows: “Central Tendency LADC (µg/m³)” or “High-end LADC (µg/m³)” × IUR (*i.e.*, 1 × 10⁻⁶ per µg/m³)

^b Cancer risk with a respirator use was calculated by dividing the cancer risk by the APF

^c EPA cannot determine the statistical representativeness of the values given the small sample size.

^d The risk assessment did not provide details about how these values were calculated, therefore, it is unclear what percentile is represented when an exposure is described as “reasonable worst case.”

^e For this scenario the high-end was the 90th percentile.

^f For this scenario the high-end was the maximum value.

Table 4-10. Inhalation Exposures to Occupational Non-Users: Cancer; Benchmark Risk = 1×10^{-4}

Risk Scenario	ONU population	Central Tendency LADC ($\mu\text{g}/\text{m}^3$)	High-End LADC ($\mu\text{g}/\text{m}^3$)	Central Tendency Cancer Risk ^a	High-End Cancer Risk ^a
Manufacturing	-	-	-	-	-
Import/Repackaging	-	-	-	-	-
Industrial Use	-	-	-	-	-
Open System Functional Fluids	178,000	0.06	0.12	5.7E-08	1.2E-07
Spray Foam Application	15627	0.72	0.92	7.2E-07	9.2E-07
Lab Chemicals	-	-	-	-	-
Film Cement	10	40	50	3.98E-05	5.14E-05
Use of Printing Inks (3D)	-	-	-	-	-
Dry Film Lubricant	-	-	-	-	-
Disposal	-	-	-	-	-

^a Cancer risk was calculated as follows: “Central Tendency LADC ($\mu\text{g}/\text{m}^3$)” or “High-end LADC ($\mu\text{g}/\text{m}^3$)” \times IUR (*i.e.*, 1×10^{-6} per $\mu\text{g}/\text{m}^3$)
 - EPA does not have ONU-specific estimates for these exposure scenarios and relies on worker exposure scenarios without PPE to predict risk to ONUs.

4.2.2.4 Occupational Risk Estimation for Non-Cancer Effects Following Acute/Short-term Dermal Exposures

1,4-Dioxane exposure is associated with acute effects. Based on the weight of the scientific evidence analysis of the reasonably available toxicity studies from humans and animals, the key acute/short-term exposure effect is liver toxicity (*i.e.*, single cell necrosis).

The study that serves as the basis for acute/short-term health concerns from dermal exposures is an inhalation study (Mattie *et al.*, 2012). EPA extrapolated from the inhalation POD reported by Mattie *et al.* (2012) (*i.e.*, LOAEC = 378 mg/m³), to calculate an acute dermal HED of 35.4 mg/kg/day and an acute dermal benchmark MOE of 300.

EPA calculated risk estimates for acute dermal exposures to 1,4-dioxane by comparing the 8-hour acute retained dose (ARD) for each exposure scenario to the acute/short-term HED for liver effects. The resulting MOEs are shown in Table 4-11..

Wearing gloves could have important consequences for dermal uptake. EPA calculated MOEs for each worker exposure scenario with and without glove use by applying glove protection factors of 1, 5, 10, and 20. Glove protection factors are based on the ratio of uptake through the unprotected skin to the corresponding uptake through the hands when protective gloves are worn. The protection factor provided by gloves is unlikely to be constant for a glove type but could be influenced by the work situation and the duration of the exposure (see Table 2-32. for a summary of the conditions corresponding to each glove protection factor).

Table 4-11. Dermal Exposure Risk Estimates to Workers for Acute/Short-term Exposures Non-Cancer; Liver Toxicity; Benchmark MOE = 300

Exposure Scenario	Central Tendency/ High-End	No Gloves	Protective Gloves	Protective Gloves, Commercial Users	Protective Gloves, Industrial Users
		(PF = 1)	(PF = 5)	(PF = 10)	(PF = 20)
Manufacturing	CT	4.8	24.1	48.3	96.6
	HE	1.6	8.0	16.1	32.2
Import/Repackaging (Bottle)	CT	4.8	24.1	48.3	96.6
	HE	1.6	8.0	16.1	32.2
Import/Repackaging (Drum)	CT	4.8	24.1	48.3	96.6
	HE	1.6	8.0	16.1	32.2
Industrial Use	CT	4.8	24.1	48.3	96.6
	HE	1.6	8.0	16.1	32.2
Functional Fluids (Open System)	CT	4,830	24,149	48,299	96,598
	HE	1,610	8,050	16,100	32,199
Lab Chemical Use	CT	4.4	22.1	44.2	88.3
	HE	1.5	7.4	14.7	29.4
Use of Printing Inks (3D)	CT	4.4	22.1	44.2	88.3
	HE	1.5	7.4	14.7	29.4

Spray Foam Application	CT	4,415	22,075	44,151	88,301
	HE	1,472	7,358	14,717	29,434
Film Cement	CT	8.8	44.2	88.3	177
	HE	2.9	14.8	29.4	58.9
Dry Film Lubricant	CT	4.8	24.1	48.3	96.6
	HE	1.6	8.0	16.1	32.2
Disposal	CT	4.8	24.1	48.3	96.6
	HE	1.6	8.0	16.1	32.2
Bold: The MOE is below the benchmark MOE					

4.2.2.5 Occupational Risk Estimation for Non-Cancer Effects Following Chronic Dermal Exposures

The dermal 8-hour HED is extrapolated from the inhalation HEC based on effects in the olfactory epithelium attributed to systemic delivery following inhalation exposure. The POD of 12.8 mg/m³ for inhalation exposures was extrapolated to estimate a dermally absorbed dose of 1.6 mg/kg-d by adjusting for the differences between the inhalation and dermal routes. Table 4-12. outlines the non-cancer dermal risk estimates to workers with and without gloves.

**Table 4-12. Dermal Exposure Risk Estimates to Workers: Non-Cancer; Liver Toxicity
Benchmark MOE = 30**

Exposure Scenario	Central Tendency/ High-End	No Gloves	Protective Gloves	Protective Gloves, Commercial Users	Protective Gloves, Industrial Users
		(PF = 1)	(PF = 5)	(PF = 10)	(PF = 20)
Manufacturing	CT	0.23	1.1	2.3	4.5
	HE	0.08	0.38	0.76	1.5
Import/Repackaging (Bottle)	CT	18.92	94.60	189.19	378.39
	HE	0.59	2.96	5.91	11.82
Import/Repackaging (Drum)	CT	9.46	47.30	94.60	189.19
	HE	0.33	1.63	3.26	6.52
Industrial Use	CT	0.23	1.1	2.3	4.5
	HE	0.08	0.38	0.76	1.5
Functional Fluids (Open System)	CT	227	1,135	2,270	4,451
	HE	75.7	378	757	1,514
Lab Chemical Use	CT	0.21	1.0	2.1	4.2
	HE	0.07	0.35	0.69	1.4
Use of Printing Inks (3D)	CT	0.21	1.0	2.1	4.2
	HE	0.07	0.35	0.69	1.4
Spray Foam Application	CT	208	1,038	2,075	4,151
	HE	69.2	346	692	1,384
Film Cement	CT	0.42	2.1	4.2	8.3

Exposure Scenario	Central Tendency/ High-End	No Gloves	Protective Gloves	Protective Gloves, Commercial Users	Protective Gloves, Industrial Users
		(PF = 1)	(PF = 5)	(PF = 10)	(PF = 20)
	HE	0.14	0.69	1.4	2.8
Dry Film Lubricant	CT	1.0	5.1	10.1	20.3
	HE	0.34	1.7	3.4	6.8
Disposal	CT	0.23	1.1	2.3	4.5
	HE	0.08	0.38	0.76	1.5

Bold: The MOE is below the benchmark MOE

4.2.2.6 Occupational Risk Estimation for Cancer Effects Following Dermal Exposures

To estimate cancer risks from dermal exposure, EPA considered the exposure in all use scenarios for dermal exposure. For each of these scenarios, exposure under conditions with varying levels of PPE were used. Dermal exposure is assumed to decrease after volatilization of 1,4-dioxane from the skin. The degree of volatilization was predicted to be 22% based on the physical chemical properties of 1,4-dioxane. EPA also accounted for dermal absorption as described above in the risk estimates for chronic non-cancer effects following dermal exposures. The results of the cancer risk analysis for dermal exposures is presented in Table 4-13..

Table 4-13. Dermal Exposure Risk Estimates to Workers: Cancer; Benchmark Cancer Risk = 1×10^{-4}

Exposure Scenario	Central Tendency/ High-End	No Gloves	Protective Gloves	Protective Gloves, Commercial Users	Protective Gloves, Industrial Users
		(PF = 1)	(PF = 5)	(PF = 10)	(PF = 20)
Manufacturing	CT	0.34	0.07	0.03	0.02
	HE	1.33	0.27	0.13	0.07
Import/ Repackaging (Bottle)	CT	4.13E-3	8.27E-4	4.13E-4	2.07E-4
	HE	0.17	0.03	0.02	0.01
Import/ Repackaging (Drum)	CT	8.27E-3	1.65E-3	8.27E-4	4.13E-4
	HE	0.31	0.06	0.03	0.02
Industrial Use	CT	0.34	0.07	0.03	0.02
	HE	1.33	0.27	0.13	0.07
Functional Fluids (Open System)	CT	3.4E-4	6.9E-5	3.4E-5	1.7E-5
	HE	1.3E-3	2.7E-4	1.3E-4	6.7E-5
Lab Chemical Use	CT	0.38	0.08	0.04	0.02
	HE	1.5	0.29	0.15	0.07
Use of Printing Inks (3D)	CT	0.38	0.08	0.04	0.02
	HE	1.5	0.29	0.15	0.07
	CT	3.8E-4	7.5E-5	3.8E-5	1.9E-5

Exposure Scenario	Central Tendency/ High-End	No Gloves	Protective Gloves	Protective Gloves, Commercial Users	Protective Gloves, Industrial Users
		(PF = 1)	(PF = 5)	(PF = 10)	(PF = 20)
Spray Foam Application	HE	1.5E-3	2.9E-4	1.5E-4	7.3E-5
Film Cement	CT	0.19	0.04	0.02	9.4E-3
	HE	0.73	0.15	0.07	0.04
Dry Film Lubricant	CT	0.08	0.02	7.7E-3	3.9E-3
	HE	0.30	0.06	0.03	0.01
Disposal	CT	0.34	0.07	0.03	0.02
	HE	1.33	0.27	0.13	0.07

Bold: Cancer risk exceeds the benchmark of 1×10^{-4}

4.2.3 Risk Estimates for Exposures from Consumer Use of 1,4-Dioxane

The following sections present risk estimates for acute and chronic dermal and inhalation exposures following consumer use of products containing 1,4-dioxane.

4.2.3.1 Risk Estimation for Inhalation Exposures to 1,4-Dioxane in Consumer Products

Risks from acute and chronic inhalation exposure to 1,4-dioxane in consumer products are shown in Table 4-14., and Table 4-15., respectively.

EPA evaluated risk from acute inhalation exposure using a POD of 283.5 mg/m³ based on liver toxicity reported in Mattie *et al.* (2012).

Table 4-14. Risks from Acute Inhalation Exposure to 1,4-Dioxane in Consumer Products; Benchmark MOE= 300

Consumer Condition of Use	Scenario	Receptor	8 hr Max TWA (mg/m3)	MOE
Surface Cleaner	High-Intensity User	User	5.0E-03	5.7E+04
		Bystander	9.5E-04	3.0E+05
Antifreeze	High-Intensity User	User	1.6E-02	1.8E+04
		Bystander	4.0E-03	7.2E+04
Dish Soap	High-Intensity User	User	3.0E-02	9.3E+03
		Bystander	5.4E-03	5.2E+04
Dishwasher Detergent	High-Intensity User	User	6.9E-04	4.1E+05
		Bystander	1.2E-04	2.3E+06
Laundry Detergent		User	1.5E-03	1.9E+05

	High-Intensity User	Bystander	2.7E-04	1.1E+06
Paint and Floor Lacquer	High-Intensity User	User	2.1E-02	1.4E+04
		Bystander	7.5E-03	3.8E+04
Textile Dye	High-Intensity User	User	8.5E-04	3.3E+05
		Bystander	1.5E-04	1.9E+06
Spray Polyurethane Foam	Basement	User	8.9E-01	317
		Bystander	7.4E-01	384
	Attic	User	1.9E-01	1.5E+03
		Bystander	7.1E-02	4.0E+03
	Garage	User	1.6E-01	1.7E+03
		Bystander	1.2E-01	2.5E+03

For consumer products that are used regularly, EPA also evaluated chronic cancer risks. EPA evaluated cancer risk from chronic inhalation exposure using an inhalation unit risk of 1.0E-06 ($\mu\text{g}/\text{m}^3$)⁻¹. Calculated MOE values for chronic exposure above the cancer benchmark for consumers (1×10^{-6}) would indicate a consumer safety concern.

Table 4-15. Risks from Chronic Inhalation Exposure to 1,4-Dioxane in Consumer Products. Benchmark Cancer Risk = 1×10^{-6}

Consumer Condition of Use	Scenario	Lifetime Average Daily Concentration (LADC, mg/m^3)	Cancer Risk
Surface Cleaner	High-Intensity User	1.0E-03	1.0E-06
	Moderate-Intensity User	5.6E-04	5.6E-07
Dish Soap	High-Intensity User	7.1E-04	7.1E-07
	Moderate-Intensity User	3.3E-04	3.3E-07
Dishwasher Detergent	High-Intensity User	7.1E-05	7.1E-08
	Moderate-Intensity User	2.9E-05	2.9E-08
Laundry Detergent	High-Intensity User	1.3E-04	1.3E-07
	Moderate-Intensity User	7.1E-05	7.1E-08

Bold: Cancer risk exceeds the benchmark of 1×10^{-6} .

4.2.3.2 Risk Estimation for Dermal Exposure to 1,4-Dioxane in Consumer Products

Risks from acute and chronic dermal exposure to 1,4-dioxane in consumer products are shown in Table 4-16., and Table 4-17., respectively.

EPA evaluated risk from acute dermal exposure using a POD of 35.4 mg/kg/day based on liver toxicity reported in Mattie *et al.* (2012). Calculated MOE values below the benchmark MOE of 300 would indicate a risk concern for acute exposures.

Table 4-16. Risks from Acute Dermal Exposure to 1,4-Dioxane in Consumer Products; Benchmark MOE=300

Consumer Condition of Use	Scenario	Receptor	Acute Dose Rate (mg/kg/day)	MOE
Surface Cleaner	High-Intensity User	Adult (≥21 years)	7.7E-06	4.6E+06
		Child (16-20 years)	7.2E-06	4.9E+06
		Child (11-15 years)	7.9E-06	4.5E+06
Antifreeze	High-Intensity User	Adult (≥21 years)	5.1E-04	6.9E+04
		Child (16-20 years)	4.8E-04	7.4E+04
		Child (11-15 years)	5.2E-04	6.8E+04
Dish Soap	High-Intensity User	Adult (≥21 years)	3.1E-06	1.2E+07
		Child (16-20 years)	2.9E-06	1.2E+07
		Child (11-15 years)	3.1E-06	1.1E+07
Dishwasher Detergent	High-Intensity User	Adult (≥21 years)	3.2E-06	1.1E+07
		Child (16-20 years)	3.0E-06	1.2E+07
		Child (11-15 years)	3.3E-06	1.1E+07
Laundry Detergent	High-Intensity User	Adult (≥21 years)	4.8E-07	7.4E+07
		Child (16-20 years)	4.5E-07	7.9E+07
		Child (11-15 years)	4.9E-07	7.2E+07
Paint and Floor Lacquer	High-Intensity User	Adult (≥21 years)	2.0E-03	1.8E+04
		Child (16-20 years)	1.9E-03	1.9E+04
		Child (11-15 years)	2.0E-03	1.7E+04
Textile Dye	High-Intensity User	Adult (≥21 years)	6.4E-07	5.6E+07
		Child (16-20 years)	6.0E-07	5.9E+07
		Child (11-15 years)	6.5E-07	5.4E+07
Spray Polyurethane Foam	Basement, Attic or Garage	Adult (≥21 years)	1.0E-03	3.5E+04
		Child (16-20 years)	9.7E-04	3.7E+04

		Child (11-15 years)	1.1E-03	3.3E+04
--	--	---------------------	---------	---------

For consumer products that are used regularly, EPA also evaluated chronic cancer risks. EPA evaluated cancer risk from chronic inhalation exposure using a dermal cancer slope factor of 0.12 (mg/kg-d)⁻¹. Calculated MOE values for chronic exposure that are above the cancer benchmark for consumers (1 x 10⁻⁶) would indicate a risk concern.

Table 4-17. Risks from Chronic Dermal Exposure to 1,4-Dioxane in Consumer Products. Benchmark Cancer Risk = 1 x 10⁻⁶

Consumer Condition of Use	Scenario	Lifetime Average Daily Dose (mg/kg/day)	Cancer Risk (Cancer Slope Factor = 0.12)
Surface Cleaner	High-Intensity User	5.6E-06	6.7E-07
	Moderate-Intensity User	2.3E-06	2.8E-07
Dish Soap	High-Intensity User	2.6E-07	3.2E-08
	Moderate-Intensity User	1.1E-07	1.3E-08
Dishwasher Detergent	High-Intensity User	1.2E-06	1.4E-07
	Moderate-Intensity User	9.9E-07	1.2E-07
Laundry Detergent	High-Intensity User	1.5E-07	1.8E-08
	Moderate-Intensity User	6.2E-08	7.4E-09

4.2.4 Risk Estimates for Exposures from Incidental Exposure to 1,4-Dioxane in Surface Water

The following sections present the risk estimates for acute dermal and inhalation exposures that may occur from incidental contact with surface water. Calculated MOE values below the benchmark MOE (300) would indicate a potential safety concern.

Risks from acute oral exposure through incidental ingestion of surface water are shown in Table 4-18. and risks from acute dermal exposure through swimming in surface water are shown in Table 4-19..

Table 4-18. Risk from Acute Oral Exposure Through Incidental Ingestion of Water; Benchmark MOE = 300

OES	Facility/Data Source	Surface Water Concentration (µg/L)	Drinking Water Acute Dose, Child 11-15 (mg/kg/day) ^a	MOE (Oral POD 35.4 mg/kg/day)
Site-Specific Modeling – Estimated Surface Water Concentrations				
Manufacturing	BASF	9.7E+01	5.2E-04	6.8E+04
Industrial Uses	Ineos Oxide	2.2E+02	1.2E-03	3.0E+04
Industrial Uses	Microdyn-Nadir Corp	7.2E+00	3.9E-05	9.1E+05

OES	Facility/Data Source	Surface Water Concentration (µg/L)	Drinking Water Acute Dose, Child 11-15 (mg/kg/day) ^a	MOE (Oral POD 35.4 mg/kg/day)
Industrial Uses	St Charles Operations (Taft/Star) Union Carbide Corp	1.1E-02	5.9E-08	6.0E+08
Industrial Uses	SUEZ Water Technologies & Solutions	5.1E+03	2.7E-02	1.3E+03
Industrial Uses	The Dow Chemical Co - Louisiana Operations	8.7E-03	4.7E-08	7.6E+08
Industrial Uses	Union Carbide Corp Institute Facility	3.3E+00	1.8E-05	2.0E+06
Industrial Uses	Union Carbide Corp Seadrift Plant	2.4E+01	1.3E-04	2.7E+05
Industrial Uses	BASF Corp	3.4E-01	1.8E-06	2.0E+07
Industrial Uses	Cherokee Pharmaceuticals LLC	2.6E-03	1.4E-08	2.5E+09
Industrial Uses	DAK Americas LLC	2.8E+01	1.5E-04	2.4E+05
Industrial Uses	Institute Plant	5.3E+00	2.8E-05	1.3E+06
Industrial Uses	Kodak Park Division	1.7E-01	9.1E-07	3.9E+07
Industrial Uses	Pharmacia & Upjohn (Former)	2.7E-02	1.5E-07	2.4E+08
Industrial Uses	Philips Electronics Plant	1.0E-01	5.4E-07	6.6E+07
Industrial Uses	Sanderson Gulch Drainage Improvements	1.0E-02	5.4E-08	6.6E+08
Open System Functional Fluids	Ametek Inc. U.S. Gauge Div	4.0E-01	2.1E-06	1.7E+07
Open System Functional Fluids	Lake Reg Med/Collegeville	1.3E-02	7.0E-08	5.1E+08
Open System Functional Fluids	Pall Life Sciences Inc	4.3E-02	2.3E-07	1.5E+08
Open System Functional Fluids	Modeled Release Estimates	2.9E+00	1.5E-05	2.3E+06
Spray Foam Application	Modeled Release Estimates	2.7E-01	1.5E-06	2.5E+07
Disposal	Beacon Heights Landfill	5.3E-01	2.8E-06	1.3E+07

OES	Facility/Data Source	Surface Water Concentration (µg/L)	Drinking Water Acute Dose, Child 11-15 (mg/kg/day) ^a	MOE (Oral POD 35.4 mg/kg/day)
Disposal	Ingersoll Rand/Torrington Fac	3.5E+00	1.9E-05	1.9E+06
High-End of Submitted Monitoring Data – Measured Surface Water Concentrations				
---	STORET	1.0E+02	5.4E-04	6.6E+04
---	Sun et al. 2016	1.4E+03	7.5E-03	4.7E+03
---	North Carolina Department of Environmental Quality	1.0E+03	5.5E-03	6.4E+03
---	Minnesota Department of Environmental Quality	4.4E+00	2.4E-05	1.5E+06
^a Dose is based on high end incidental intake rate				

Table 4-19. Risk from Acute Dermal Exposure from Swimming; Benchmark MOE = 300

OES	Facility/Data Source	Surface Water Concentration (µg/L)	Dermal Acute Dose, Adult (mg/kg/day)	MOE (Dermal POD 35.4 mg/kg/day)
Site-Specific Modeling – Estimated Surface Water Concentrations				
Manufacturing	BASF	9.7E+01	3.6E-05	9.9E+05
Industrial Uses	Ineos Oxide	2.8E+02	8.0E-05	4.4E+05
Industrial Uses	Microdyn-Nadir Corp	7.2E+00	2.7E-06	1.3E+07
Industrial Uses	St Charles Operations (Taft/Star) Union Carbide Corp	1.1E-02	4.1E-09	8.6E+09
Industrial Uses	SUEZ Water Technologies & Solutions	5.1E+03	1.9E-03	1.9E+04
Industrial Uses	The Dow Chemical Co - Louisiana Operations	8.7E-03	3.2E-09	1.1E+10
Industrial Uses	Union Carbide Corp Institute Facility	3.3E+00	1.2E-06	2.9E+07
Industrial Uses	Union Carbide Corp Seadrift Plant	2.4E+01	8.9E-06	4.0E+06
Industrial Uses	BASF Corp	3.4E-01	1.3E-07	2.8E+08

OES	Facility/Data Source	Surface Water Concentration (µg/L)	Dermal Acute Dose, Adult (mg/kg/day)	MOE (Dermal POD 35.4 mg/kg/day)
Industrial Uses	Cherokee Pharmaceuticals LLC	2.6E-03	9.7E-10	3.6E+10
Industrial Uses	DAK Americas LLC	2.8E+01	1.0E-05	3.4E+06
Industrial Uses	Institute Plant	5.3E+00	2.0E-06	1.8E+07
Industrial Uses	Kodak Park Division	1.7E-01	6.3E-08	5.6E+08
Industrial Uses	Pharmacia & Upjohn (Former)	2.7E-02	1.0E-08	3.5E+09
Industrial Uses	Philips Electronics Plant	1.0E-01	3.7E-08	9.6E+08
Industrial Uses	Sanderson Gulch Drainage Improvements	1.00E-02	3.7E-09	9.6E+09
Open System Functional Fluids	Ametek Inc. U.S. Gauge Div	4.0E-01	1.5E-07	2.4E+08
Open System Functional Fluids	Lake Reg Med/Collegeville	1.3E-02	4.8E-09	7.3E+09
Open System Functional Fluids	Pall Life Sciences Inc	4.3E-02	1.6E-08	2.2E+09
Open System Functional Fluids	Modeled Release Estimates	2.9E+00	1.1E-06	3.4E+07
Spray Foam Application	Modeled Release Estimates	2.7E-01	10.0E-08	3.6E+08
Disposal	Beacon Heights Landfill	5.3E-01	2.0E-07	1.8E+08
Disposal	Ingersoll Rand/Torrington Fac	3.5E+00	1.3E-06	2.8E+07
High-End of Submitted Monitoring Data – Measured Surface Water Concentrations				
---	STORET	1.0E+02	3.7E-05	9.6E+05
---	Sun et al. 2016	1.4E+03	5.2E-04	6.8E+04
---	North Carolina Department of Environmental Quality	1.0E+03	3.8E-04	9.3E+04
---	Minnesota Department of Environmental Quality	4.4E+00	1.6E-06	2.2E+07

4.3 Assumptions and Key Sources of Uncertainty

There were uncertainties related to environmental risk for 1,4-dioxane, with some leading to potentially underestimating risk and some leading to potentially overestimating risk. As mentioned in Section 3.1.7, there were uncertainties regarding the hazard data for aquatic species; however, some of the uncertainty was mitigated by the use of multiple lines of evidence supporting the assessment of hazard.

There were also uncertainties around surface water concentrations used to determine the environmental risk. EPA used E-FAST. In some ways the E-FAST estimates are underestimating exposure, because data used in E-FAST only included TRI and DMR data and no monitoring data. DMR data are submitted by NPDES permit holders to states or directly to the EPA according to the monitoring requirements of the facility's permit. States are only required to load major discharger data into DMR and may or may not load minor discharger data. The definition of major vs. minor discharger is set by each state and could be based on discharge volume or facility size. Due to these limitations, some sites that discharge may not be included in the DMR dataset.

The characterization of assumptions, variability and uncertainty may raise or lower the confidence of the risk estimates. This section describes the assumptions and uncertainties in the exposure assessment, hazard/dose-response and risk characterization.

4.3.1 Key Assumptions and Uncertainties in the Occupational Exposure Assessment

EPA addressed variability in the occupational exposure models by identifying key model parameters to apply a statistical distribution that mathematically defines the parameter's variability. EPA defined statistical distributions for parameters using documented statistical variations where available. Uncertainty is "*the imperfect knowledge or lack of precise knowledge of the real world either for specific values of interest or in the description of the system*" (40 CFR § 702.33). It can be described qualitatively or quantitatively ([U.S. EPA, 2001](#)). The following sections discuss uncertainties in each of the assessed 1,4-dioxane use scenarios.

Number of Workers and ONUs

There are several uncertainties surrounding the estimated number of workers potentially exposed to 1,4-dioxane, as outlined below.

First, BLS OES employment data for each industry/occupation combination are only available at the 3-, 4-, or 5-digit NAICS level, rather than the full 6-digit NAICS level. This lack of granularity could result in an overestimation of the number of exposed workers if some 6-digit NAICS are included in the less granular BLS estimates but are not, in reality, likely to use 1,4-dioxane for the assessed applications. EPA addressed this issue by refining the OES estimates using total employment data from the U.S. Census SUBS. However, this approach assumes that the distribution of occupation types (SOC codes) in each 6-digit NAICS is equal to the distribution of occupation types at the parent 5-digit NAICS level. If the distribution of workers in occupations with 1,4-dioxane exposure differs from the overall distribution of workers in each NAICS, then this approach will result in uncertainty. Furthermore, market penetration data were unavailable, therefore, EPA was unable to estimate the number of establishments within each

NAICS code that used 1,4-dioxane instead of other chemicals. This would result in a systematic overestimation of the count of exposed workers. For manufacturing and import/re-packaging, CDR data provided information to better estimate the number of workers.

Second, EPA's judgments about which industries (represented by NAICS codes) and occupations (represented by SOC codes) are associated with the uses assessed in this report are based on EPA's understanding of how 1,4-dioxane is used in each industry. Designations of certain industries/occupations with few exposures might erroneously be included, or some industries/occupations with exposures might erroneously be excluded. This is not expected to systematically either overestimate or underestimate the count of exposed workers.

Analysis of Exposure Monitoring Data

This risk evaluation uses existing worker exposure monitoring data to assess exposure to 1,4-dioxane during manufacturing, industrial use, open system functional fluid, laboratory chemical, film cement, and 3D printing ink applications. To analyze the exposure data, EPA categorized each PBZ and area data point as either "worker" or "occupational non-user." The categorizations are based on descriptions of worker job activity as provided in literature and EPA's judgment. In general, PBZ samples are categorized as "worker" and area samples are categorized as "occupational non-user."

Exposure data for ONUs were not available for most scenarios. EPA assumes that these exposures are expected to be lower than worker exposures, since ONUs do not typically directly handle the 1,4-dioxane nor are they in the immediate proximity of 1,4-dioxane.

Some data sources may be inherently biased, such as data directly from industry or in response to reported issues. For example, NIOSH HHEs for the open system functional fluids and film cement uses were conducted to address concerns regarding adverse human health effects reported following exposures during use. Both HHEs were requested by the United Paperworkers International Union and Film Technicians Union, respectively.

Some monitoring data are incomplete and required assumptions to fill in the gaps. For example, the monitoring data from BASF for the manufacturing condition of use required EPA to make assumptions on worker activities and sampling rates for certain datapoints similar to others mentioned in the data set.

The 2002 EU Risk Assessment ([ECJRC, 2002](#)), did not provide complete datasets. This assessment provided limited summary statistics for different datasets, *i.e.*, a range of the monitoring data, an arithmetic average or median, and the 90th percentile. The EU report provided limited information about processes involved in each dataset with corresponding worker activities. Finally, this report provided recommendations for "typical" and "reasonable worst case" exposures but did not provide details for how these values were calculated.

Because of these limitations, EPA acknowledges that the reported inhalation exposure concentrations for the industrial scenario uses may not be representative for the exposures in all industries within that group.

Some scenarios have limited exposure monitoring data in literature, if any (*i.e.*, use in 3D printing inks). Where there are few data points available, it is unlikely the results will be representative of worker exposure across the industry depending on the sample collection location (PBZ or source zone), monitoring time and other conditions to represent the work situation and the duration of the exposure.

The 95th and 50th percentile exposure concentrations were calculated using reasonably available data. The 95th percentile exposure concentration is intended to represent a high-end exposure level, while the 50th percentile exposure concentration represents typical exposure level. The underlying distribution of the data, and the representativeness of the available data, are not known.

EPA calculated ADC values assuming a high-end exposure duration of 260 days per year over 40 years and LADC values assuming a high-end exposure duration of 260 days per year over 78 years. Repackaging and import is an exception, since the exposure duration depends on the number of containers being unloaded. The high-end exposure duration value for this exposure scenario is 90 days (one container unloaded per day). See Section 2.4.1.1.2 for more information. This assumes the workers and occupational non-users are regularly exposed during their entire working lifetime, which likely results in an overestimate. Individuals may change jobs during their career such that they are no longer exposed to 1,4-dioxane, and that actual ADC and LADC values become lower than the estimates presented.

Modeling Dermal Exposures





The *EPA Dermal Exposure to Volatile Liquids Model* used for modeling dermal exposures offers an improvement over the existing *EPA 2-Hand Dermal Exposure* models by accounting for the effect of evaporation on dermal absorption for volatile chemicals and the potential exposure reduction due to glove use. The passage of a chemical through the skin barrier is dependent on many factors. The skin is not uniform in terms of thickness. For example, epidermis to dermis ratio, density of hair follicles, and many other parameters could affect permeability. Other factors that could influence the dermal uptake include temperature and the presence of other materials on the skin. A detailed description of dermal exposure assessment method is shown in Appendix G.7. To address the uncertainty due to lack of monitoring data, a film-thickness approach was used. This approach considered a thin film of product on a defined skin area. A multiplicative factor was incorporated to the EPA model to include the proportion of 1,4-dioxane remaining on the skin after the bulk liquid has fallen from the hand that cannot be removed by wiping the skin. The model assumes an infinite dose scenario and does not consider the transient exposure and exposure duration effect.



Uncertainties of Occupational Exposure of 1,4-dioxane for Various Conditions of Use

The summary and uncertainty rating of occupational exposure of 1,4-dioxane indicating strengths, challenges, whether modelling or monitoring preformed, representativeness and confidence of data assessed, and overall rating for various conditions of use are shown in Table 4-20..

Table 4-20. Summary and Uncertainty Rating of Occupational Exposure of 1,4-dioxane for Various Conditions of Use

Occupational Exposure Scenario	Strength	Challenge	Inhalation Exposure						Representativeness	Dermal Exposure Modeling		Overall Rating
			Monitoring				Modeling			Worker ^a	ONU ^b	
			Data (#)	Surrogate	Worker	ONU	Worker	ONU				
Manufacturing	PBZ sampling	Data is provided from one source	✓ (32)	✗	✓ (30 ^c)	✗	✗	✗	Routine monitoring data available for work environment	✓	✗	
	High data quality											
	Source of information available directly from manufacturer											
	CDR provided employee counts for specific manufacturing site											
	Data from multiple facilities											
Import and Repackaging	CDR provided employee counts for specific Import and Repackaging sites	No Monitoring Data	✗	✗	✗	✗	✓	✗	Assesses exposure based on loading and unloading only. Assumes controlled and closed systems for all other operations.	✓	✗	
		EPA models are not specific to Import and Repackaging										
	Monte Carlo simulation of models to vary specific parameters	Relies on process and protection assumptions										
		May underestimate worker exposure										
Industrial Use	Aggregated data points	No monitoring data for this CoU; Surrogate data from manufacturing	✓ (~294)	✗	✓ (~294)	✗	✗	✗	Routine monitoring data available for work environment	✓	✗	
	PBZ Sampling											
	Data from multiple facilities	Data is provided from one source										
	CDR provided employee counts for specific manufacturing sites	Many data points were at or below the limit of detection										
Functional Fluids (Open System)	PBZ sampling	All data points are at or below the limit of detection	✗	✓ (19)	✓ (6)	✓ (4)	✗ ^d	✗	Model assesses exposure based on loading and unloading only. Assumes controlled and closed systems for all other operations.	✓	✗	
	Source of information available directly from manufacturer								Samples representative of metalworking fluid, but not necessarily metalworking fluid with 1,4-dioxane content			
	Specific worker activities for each sample	Sampling data is from one facility							Routine monitoring data available for work environment			
Laboratory Chemicals	CDR provided employee counts for	Dataset is limited, lacking specific	✓	✗	✓	✗	✗	✗	Assesses exposure based on loading and unloading			

Occupational Exposure Scenario	Strength	Challenge	Inhalation Exposure						Representativeness	Dermal Exposure Modeling		Overall Rating
			Monitoring				Modeling			Worker ^a	ONU ^b	
			Data (#)	Surrogate	Worker	ONU	Worker	ONU				
	specific industrial processing agent/aid sites	descriptions of worker tasks and exposure sources	(335)		(335)				only. Assumes controlled and closed systems for all other operations.	✓	✗	 Higher Lower
		Comparison with other laboratories is not possible due to lack of information										
	PBZ samples	Most datasets provided in a range May underestimate worker exposure										
Film Cement	Job operations are provided	Three of the six samples were non-detects							Three of the six samples were non-detects			 Higher Lower
	Source of information includes data from multiple film cement users	Data is only from one reference Lack of statistical representativeness due to the small dataset: 5 PBZ and 1 Area samples	✓ (6)	✗	✓ (5)	✓ (1)	✗	✗	Assesses exposure based on loading and unloading only. Assumes controlled and closed systems for all other operations.	✓	✗	
	PBZ sampling											
Spray Foam Application	Utilizes the GS on the Application of Spray Polyurethane Foam insulation	No monitoring data										 Higher Lower
	Combines established models with Monte Carlo simulations	Relies on models, surrogate data, and general industry data which may not be representative Estimation does not account for the potential evaporation of 1,4-dioxane from the mist particles and resulting inhalation exposure	✗	✓ ^e	✗	✗	✓	✓	Model is based on a relevant generic scenario	✓	✗	
Use of printing inks	One data point exists	Lack of statistical representativeness due to the small dataset: 1 Area sample	✓ (1)	✗	✓ (1)	✗	✗	✗	Sample pulled from inner-workings of equipment that is a part of the routine work environment	✓	✗	 Higher Lower

Occupational Exposure Scenario	Strength	Challenge	Inhalation Exposure						Representativeness	Dermal Exposure Modeling		Overall Rating
			Monitoring				Modeling			Worker ^a	ONU ^b	
			Data (#)	Surrogate	Worker	ONU	Worker	ONU				
Dry Film Lubrication	PBZ samples are 8-hour TWAs	Captures 100% of known users, but unclear if other DOE facilities are also 1,4-dioxane dry film lubricant users							Direct conversation with hygienists regarding sample data			Higher 
	Source of information available directly from manufacturer and user		✓ (7)	✗	✓ (7)	✗	✗	✗	Routine monitoring data available for work environment	✓	✗	
Disposal	Combines established models with Monte Carlo simulations	No process details were available for disposal sites							Relies on models, surrogate data, and general industry data which may not be representative			Higher 
		EPA models are not specific to disposal/recycling	✗	✗	✗	✗	✓	✗	Assesses exposure based on loading and unloading only. Assumes controlled and closed systems for all other operations.	✓	✗	
		EPA assumptions may be overly conservative										

a: Dermal exposure estimates, which are based on high-end/central tendency parameters and commercial/industrial settings, have medium level of confidence.

b: ONU exposure estimates, which are based on central tendency parameters, have low levels of confidence.

c: Two data points were short term samples.

d: A monte carlo model was performed on this to determine fit of data.

e: Surrogate data were used to determine foam thickness and input to models.

4.3.2 Key Assumptions and Uncertainties in the Consumer Exposure Estimation

EPA's approach recognizes the need to include uncertainty analysis. One important distinction for such an analysis is variability versus uncertainty – both aspects need to be addressed. Variability refers to the inherent heterogeneity or diversity of data in an assessment. It is a quantitative description of the range or spread of a set of values and is often expressed through statistical metrics, such as variance or standard deviation, that reflect the underlying variability of the data. Uncertainty refers to a lack of data or an incomplete understanding of the context of the risk evaluation decision. Variability cannot be reduced, but it can be better characterized. Uncertainty can be reduced by collecting more or better data. Quantitative methods to address uncertainty include non-probabilistic approaches such as sensitivity analysis and probabilistic or stochastic methods. Uncertainty can also be addressed qualitatively, by including a discussion of factors such as data gaps and subjective decisions or instances where professional judgment was used. Uncertainties associated with approaches and data used in the evaluation of consumer exposures are described below.

Deterministic vs. Stochastic

With deterministic approaches like the one applied in this evaluation of consumer exposure, the output of the model is fully determined by the choices of parameter values and initial conditions. Stochastic approaches feature inherent randomness, such that a given set of parameter values and initial conditions can lead to an ensemble of different model outputs.

Aggregate Exposure

Background levels of 1,4-dioxane in indoor and outdoor air are not considered or aggregated in this analysis; therefore, there is a potential for underestimating consumer inhalation exposures, particularly for populations living near a facility emitting 1,4-dioxane or living in a home with other sources of 1,4-dioxane, such as other 1,4-dioxane-containing products stored and/or used in the home such as personal care products that are not covered under TSCA. Similarly, inhalation and dermal exposures were evaluated on a product-specific basis and are based on use of a single product type within a day, not multiple products. There was no aggregation of dermal and inhalation exposure to single products either.

Dermal Exposure Approach

For dermal exposure scenarios using the permeability model that may involve dermal contact with impeded evaporation based on professional considerations of the formulation type and likely use pattern, there is uncertainty surrounding the application of exposure durations for such scenarios. The exposure durations modeled are based on reported durations of product use, unless otherwise specified, and may not reflect reasonable durations of dermal contact with impeded evaporation. The exposure duration modeled could exceed a reasonable duration of such dermal contact with a wet rag, for example.

For scenarios using the absorption fraction model that are less likely to involve dermal contact with impeded evaporation, there is uncertainty surrounding the assumption that the entire mass present in the thin film is absorbed and retained in the stratum corneum following a use event. The fractional absorption factor estimated based on Frasch and Bunge (2015) is intended to be applied to the mass retained in the stratum corneum after exposure; it does not account for evaporation from the skin surface during the exposure event. Therefore, the assumption that the entire amount of chemical present in the thin film on the skin surface is retained in the stratum corneum may lead to uncertainty in the absorbed dose estimate.

Product Concentration Data

The products evaluated are largely based on EPA's 2015 TSCA Work Plan Chemical Problem Formulation and Initial Assessment of 1,4-Dioxane (U.S. EPA, 2015). EPA conducted an additional systematic review focused on identifying data on 1,4-dioxane presence in consumer products and associated exposures and/or emissions. Because 1,4-dioxane is present in consumer products as a byproduct and not as an ingredient, there is more uncertainty than typical when identifying and using concentration information. Unlike other chemicals that are ingredients in consumer products with readily available reported concentration ranges in SDSs for each product category, 1,4-dioxane concentrations have been sourced from a variety of primary and secondary sources such as governmental risk assessments, SDSs, literature reviews, emission studies, etc. There are limited reasonably available data and they are not necessarily complete or consistently updated and general internet searches cannot guarantee entirely comprehensive product identification. According to reasonably available information, there may be uncertainty in the range of weight fractions modeled for consumer dish soap and laundry detergent. Therefore, it is possible that the entire universe of products that contain 1,4-dioxane as a byproduct may not have been identified, or that certain changes in the universe of products may not have been captured, due to market changes or research limitations. Maximum identified weight fractions

were used in acute high-intensity user scenarios and mean weight fractions were used in chronic high-intensity and moderate-intensity user scenarios, where possible. While weight fractions are described as “maximum” in tables, these reflect only the maximum levels identified from available literature and other sources and may not capture the true maximum in specific products or batches. There is uncertainty about how these means and maximums broadly reflect typical products and there is also uncertainty about whether the true upper end is captured in the ranges identified through the available sources. For the range of weight fractions identified, see the Supplemental File [*Consumer Exposure Assessment Modeling Input Parameters*].

Emission Rate

The higher-tier Multi-Chamber Concentration and Exposure Model (MCCEM) is used in the estimation of inhalation exposures from SPF application only. For other product scenarios, key data (*i.e.*, chamber emission data) were not reasonably available. Therefore, the model used (CEM 2.1) estimates emission rate based on chemical properties and emission profiles matching the formulation type and use method.

The emission rate data derived from Karlovich et al. (2011b) is based on occupational-grade products, so there is some uncertainty surrounding the application to consumers. High-pressure SPF may not be available to consumers, unlike one-component or low-pressure foams. Each foam type is anticipated to have unique exposure profiles and therefore there is uncertainty surrounding how the emission and exposure profile may have differed, had EPA identified and used emission rate data from low-pressure or one-component SPF products. The product for which 1,4-dioxane emission data were collected is an open-cell foam. The initial emission rate and decay constant estimates were based on a modeled relationship, as measured emission data were not available during application.

Dilution Factor

For most product scenarios, the dilution factor is not considered. For dish soap, laundry detergent, and textile dye, all of which are expected to be used in aqueous solutions during hand washing or dyeing activities, dilution factors are incorporated. For dish soap, a dilution factor of 0.7% is applied based on assuming a mass of 28 g (~1 oz) is used in one gallon of water for hand washing of dishes. For laundry detergent, a dilution factor of 1.6% is applied based on assuming a high-end mass of 60 g (oz) is used in one gallon of water for hand washing of laundry. These estimations incorporate a conservative water use assumption.

Chronic Exposure Estimations

Chronic (lifetime) inhalation and dermal exposures were estimated for four product scenarios: surface cleaner, dish soap, dishwasher detergent, and laundry detergent. The inclusion of lifetime exposure estimates for these conditions of use is based on the anticipated daily or near-daily use of these products. This differs from expected intermittent exposure pattern associated with the other evaluated consumer conditions of use. Lifetime exposure estimates are calculated assuming the exposure event occurs for 365 or 300 days per year for high-end or central tendency frequencies, respectively, for an exposure duration 57 years. The exposure scenarios still assume one exposure event per day and therefore may not capture users that continuously use products throughout the day. This exposure is averaged over a period of 78 years (*i.e.*, averaging time). The models employed (CEM 2.1 and CEM) typically utilize central tendency inputs for

weight fraction, duration, frequency, and mass when estimating lifetime exposures ([U.S. EPA, 2019a](#); [U.S. EPA, 2007](#)). Central tendency inputs for weight fraction were used in estimating chronic exposures, across high- and moderate-intensity user scenarios.

4.3.2.1 Confidence in Consumer Exposure Estimates

The considerations and overall confidence ratings for the inhalation consumer exposure scenarios are displayed in **Table 4-21**. Ratings are based on the strength of the models employed, as well as the quality and relevance of the modeling parameterization. CEM, CEM 2.1, and MCCEM are peer reviewed, publicly available, and were designed to estimate inhalation and dermal exposures from household uses of products and articles.

Systematic review identified several studies reporting emission rates or chamber concentrations of 1,4-dioxane from spray foam and paint products and findings as they relate to the current evaluation are summarized in Appendix H.3. Although measured chamber or test room concentrations are not directly comparable to the 8-hr TWAs estimated for the various consumer exposure scenarios, on the whole, these emission studies bolster confidence in the predicted air concentrations for the SPF and paint and floor lacquer conditions of use.

The predicted 8-hr TWAs for SPF range from 160 to 890 $\mu\text{g}/\text{m}^3$ for users. These predicted estimates fall within the range predicted in Karlovich et al. ([2011b](#)) for samples measured at four and 12 hours. Peppendieck et al. ([2017](#)) also reported measured air concentrations that encompass the modeled consumer exposure estimates, with concentrations from non-ideal closed-cell spray foam ranging from 500 to 1,000 $\mu\text{g}/\text{m}^3$ over the first 48 hours. Won et al. ([2014](#)) reported levels of 1,4-dioxane well below the CEM 2.1 predictions, from 0.25 to 44.68 $\mu\text{g}/\text{m}^3$ at six hours for various insulation products including foam board and two-component open- and closed-cell spray foams.

The predicted 8-hr TWAs for paint and floor lacquer is 20 $\mu\text{g}/\text{m}^3$ for users, which is roughly one order of magnitude greater than concentrations measured in Won et al. ([2014](#)) (0.8 – 1.74 $\mu\text{g}/\text{m}^3$ at six hours), but aligns with the measured air concentration five hours after application of the two-component epoxy floor paint (21 $\mu\text{g}/\text{m}^3$). The predicted TWA also falls within the range of air concentrations taken five hours after application in the Danish EPA's 2020 Follow-Up study, which reported levels from 7 to 460 $\mu\text{g}/\text{m}^3$ at five hours.

The considerations and overall confidence ratings for the dermal consumer exposure scenarios are displayed in **Table 4-22**. Ratings are based on the strength of the models employed, as well as the quality and relevance of the modeling parameterization. CEM 2.1 is peer reviewed, publicly available, and was designed to estimate inhalation and dermal exposures from household uses of products and articles.

Table 4-21 Overall Confidence Ratings for Consumer Inhalation Exposure Estimates

Consumer Product Scenario	Overall Confidence Acute	Overall Confidence Chronic	Scenario-Specific Considerations	Overarching Considerations
Surface Cleaner	Moderate to High	Moderate	<ul style="list-style-type: none"> Duration and mass inputs obtained from the Westat Survey from its solvent-type cleaning fluids and degreasers category. Weight fraction range obtained from few sources. 	<ul style="list-style-type: none"> There is uncertainty regarding how the maximum and mean from identified weight fraction sources reflects the existing range or captures actual maximum concentrations. Use of CEM (not CEM 2.1) to estimate lifetime inhalation exposures (LADCs) did not estimate exposure to bystanders; however, bystanders would be exposed to lower levels than the presented user exposures based on their placement in the home during use (Zone 2). Use of central tendency weight fractions for chronic exposure scenarios bolsters confidence, as it does not assume use of the highest identified concentration daily or near-daily intervals over 57 years.
Antifreeze	Moderate to High	NA	<ul style="list-style-type: none"> Duration and mass inputs obtained from CEM 2.1 scenario-specific defaults. Weight fraction range obtained from few sources. 	
Dish Soap	Moderate to High	Moderate	<ul style="list-style-type: none"> Duration and mass inputs obtained from CEM 2.1 scenario-specific defaults. Weight fraction range obtained from several sources. 	
Dishwasher Detergent	Moderate to High	Moderate	<ul style="list-style-type: none"> Duration and mass inputs obtained from CEM 2.1 scenario-specific defaults. Exposure duration assumes user is in the room of use (kitchen) during the machine's run time (50 min). Weight fraction range obtained from several sources. 	
Laundry Detergent	Moderate to High	Moderate	<ul style="list-style-type: none"> Duration and mass inputs obtained from CEM 2.1 scenario-specific defaults. Exposure duration assumes user is in the room of use (utility) during the machine's run time (50 min). Weight fraction range obtained from several sources. 	
Paint and Floor Lacquer	High	NA	<ul style="list-style-type: none"> Duration and mass inputs obtained from the Westat Survey from its latex paint category. Weight fraction data obtained from American Coatings Association public submission (Nekoomaram and Wieroniewy, 2015). 	

Consumer Product Scenario	Overall Confidence Acute	Overall Confidence Chronic	Scenario-Specific Considerations	Overarching Considerations
			<ul style="list-style-type: none"> Measured emission data align with 8-hr TWA for users. 	
Textile Dye	Moderate	NA	<ul style="list-style-type: none"> Duration and mass inputs obtained from CEM 2.1 scenario-specific defaults. Single weight fraction source. 	
SPF	High	NA	<ul style="list-style-type: none"> Initial emission rate and decay constant are based on a modeled relationship. No emission or concentration data were available for 1,4-dioxane during application. Emission data on 1,4-dioxane from Karlovich et al., (2011b) is from open cell foam. Duration inputs based on the SPF occupational exposure assessment. Application area specific air exchange rates and ventilation rates applied. Product and chemical specific emission rate applied. Used higher-tier MCCEM model to estimate air concentrations. Weight fraction based on occupational exposure assessment. Measured and predicted emission data encompass predicted range of 8-hr TWAs for users. 	

Table 4-22 Overall Confidence Ratings for Consumer Dermal Exposure Estimates

Consumer Product Scenario	Overall Confidence Acute	Overall Confidence Chronic	Scenario-Specific Considerations	Overarching Considerations
Surface Cleaner	Moderate	Low to Moderate	<ul style="list-style-type: none"> Duration input obtained from the Westat Survey from its solvent-type cleaning fluids and degreasers category. Exposure duration assumes dermal contact may occur during the entire activity duration. Weight fraction range obtained from few sources. 	<ul style="list-style-type: none"> There is uncertainty regarding how the maximum and mean from identified weight fraction sources reflects the existing range or captures actual maximum concentrations. An estimated permeability coefficient is used in dermal modeling. There are uncertainties associated with both dermal models applied (see Section 2.4.3.6). Use of central tendency weight fractions for chronic exposure scenarios bolsters confidence, as it does not assume use of the highest identified concentration daily or near-daily intervals over 57 years.
Antifreeze	Moderate	NA	<ul style="list-style-type: none"> Duration input obtained from CEM 2.1 scenario-specific defaults. Exposure duration assumes dermal contact may occur during the entire activity duration. Weight fraction range obtained from few sources. 	
Dish Soap	Moderate	Low to Moderate	<ul style="list-style-type: none"> Duration input obtained from CEM 2.1 scenario-specific defaults. Dilution fraction of 3% may be a conservative assumption. Weight fraction range obtained from several sources. 	
Dishwasher Detergent	Moderate	Low to Moderate	<ul style="list-style-type: none"> Duration input obtained from CEM 2.1 scenario-specific defaults. Exposure duration adjusted to one minute to approximate contact time during loading of liquid detergent. Weight fraction range obtained from several sources. 	
Laundry Detergent	Moderate	Low to Moderate	<ul style="list-style-type: none"> Duration input obtained from CEM 2.1 scenario-specific defaults. Exposure duration adjusted to equal dish soap exposure durations to approximate contact time during hand washing of laundry. 	

Consumer Product Scenario	Overall Confidence Acute	Overall Confidence Chronic	Scenario-Specific Considerations	Overarching Considerations
			<ul style="list-style-type: none"> Chronic exposure scenario assumes hand washing of laundry daily or near daily. Weight fraction range obtained from several sources. 	
Paint and Floor Lacquer	Moderate	NA	<ul style="list-style-type: none"> Duration and mass inputs obtained from the Westat Survey from its latex paint category. Exposure duration assumes dermal contact may occur during the entire activity duration. Weight fraction data obtained from American Coatings Association public comment submission (Nekoomaram and Wieroniewy, 2015). 	
Textile Dye	Moderate	NA	<ul style="list-style-type: none"> Duration and mass inputs obtained from CEM 2.1 scenario-specific defaults. Dilution fraction of 10% likely a conservative assumption. Single weight fraction source. 	
SPF	Moderate	NA	<ul style="list-style-type: none"> Duration inputs based on the SPF occupational exposure assessment. Exposure duration assumes dermal contact may occur during the entire activity duration. Weight fraction based on occupational exposure assessment. 	

4.3.3 Key Assumptions and Uncertainties in the General Population Exposure

EPA's approach recognizes the need to include uncertainty analysis. One important distinction for such an analysis is variability versus uncertainty – both aspects need to be addressed. Variability refers to the inherent heterogeneity or diversity of data in an assessment. It is a quantitative description of the range or spread of a set of values and is often expressed through statistical metrics, such as variance or standard deviation, that reflect the underlying variability of the data. Uncertainty refers to a lack of data or an incomplete understanding of the context of the risk evaluation decision. Variability cannot be reduced, but it can be better characterized. Uncertainty can be reduced by collecting more or better data. Quantitative methods to address uncertainty include non-probabilistic approaches such as sensitivity analysis and probabilistic or stochastic methods. Uncertainty can also be addressed qualitatively, by including a discussion of factors such as data gaps and subjective decisions or instances where professional judgment was used. Uncertainties associated with approaches and data used in the evaluation of general population exposures are described below.

Modeling Inputs and Assumptions

Releases modeled using E-FAST 2014 were predicted based on engineering site-specific estimates based on DMR and TRI reporting databases. These data that form the basis for engineering estimates are self-reported by facilities subject to minimum reporting thresholds; therefore, they may not capture releases from certain facilities not meeting reporting thresholds (*i.e.*, environmental releases may be underestimated). The modeled releases are based on occupational exposure scenarios (*i.e.*, industrial and/or commercial conditions of use) and are not intended to reflect contributions from the use and/or disposal of consumer products. These release estimates, however, are described as having a medium level of confidence in Section 2.2.1.3.1.

E-FAST 2014 estimates surface water concentrations at the point of release, without accounting for post-release environmental fate or degradation processes such as volatilization, biodegradation, photolysis, hydrolysis, or partitioning. Additionally, E-FAST does not estimate stream concentrations based on the potential for downstream transport and dilution. These considerations tend to lead to higher predicted surface water concentrations. Dilution is incorporated, but it is based on the stream flow applied. Therefore, there is uncertainty regarding the level of 1,4-dioxane that would be predicted downstream of a releasing facility or after accounting for potential volatilization from the water surface, which is dependent on the degree of mixing in a receiving water body.

The ambient water analysis assumes that members of the general population are incidentally exposed via swimming in ambient waters, but there is uncertainty surrounding the likelihood that such recreation and contact would occur at or near the point of release. If such activities occurred further from the point of release, this analysis may overestimate the water concentrations that swimmers would be exposed to.

EPA's SWIMODEL was used as the source for exposure duration. This model is intended to assess exposure from swimming in pools, not ambient water bodies, so there is uncertainty about the application of swimming pool duration data in this analysis.

Monitoring Data

The surface water monitoring data that were submitted during the draft's public comment period and SACC review were utilized but relative contributions from specific industrial and/or consumer sources of 1,4-dioxane are unknown.

Aggregate Exposure

Background levels of 1,4-dioxane from other sources are not considered or aggregated in this analysis; therefore, there is a potential for underestimating exposures, particularly for populations living near a facility emitting 1,4-dioxane or living in a home with other sources of 1,4-dioxane, such as other 1,4-dioxane-containing products stored and/or used in the home such as personal care products that are not covered under TSCA. Similarly, there was no aggregation of incidental oral and dermal exposures from swimming, which would be expected to be concurrent.

4.3.3.1 Confidence in General Population Exposure Estimates

Confidence ratings for general population ambient water exposure scenarios are informed by uncertainties surrounding inputs and approaches used in modeling surface water concentrations and estimating incidental oral and dermal doses. In Section 2.2.1.3.1, confidence ratings are assigned to these estimated daily releases (kg/site-day) on a per occupational exposure scenario (OES) basis and reflect moderate confidence.

Other considerations that impact confidence in the ambient water exposure scenarios include the model used (E-FAST 2014) and its associated default and user-selected values and related uncertainties. As described, there are uncertainties related to the ability of E-FAST 2014 to incorporate downstream fate and transport. Of note, as stated on the EPA's [E-FAST 2014 website](#), "modeled estimates of concentrations and doses are designed to reasonably overestimate exposures, for use in an exposure assessment in the absence of or with reliable monitoring data." Regarding the assumption that members of the general population could reasonably be expected to swim at or near the point of release, there is relatively low confidence due to uncertainty.

EPA utilized the SWIMODEL default duration parameters to estimate incidental dermal and oral exposures to the general population from swimming in ambient water bodies. The model's default duration inputs were based on swimming pool use patterns rather than freshwater bodies, so there is low to moderate confidence that these parameters accurately reflect the ambient water body recreation activities covered in this supplemental analysis.

There are surface water monitoring data available that reflect ambient water exposure levels in the United States (see Section 2.4.2.3). These data were submitted from only two states (NC and MN) and may reflect multiple sources of 1,4-dioxane in surface water that may or may not be related to within-scope occupational exposure scenarios. Because these monitoring data reflect surface water conditions at specific sampling sites during a specific sampling period, they may not reflect current levels of 1,4-dioxane in surface water. The modeled surface water concentration ranges obtained from E-FAST modeling (2.63E-03 - 5.09E+03 $\mu\text{g/L}$) encompass the full range of the surface water monitoring data submitted during public comment period.

Based on the above considerations, the general population ambient water exposure assessment scenarios have an overall low to moderate confidence.

4.3.4 Key Assumptions and Uncertainties in Environmental Risk

The available environmental toxicity data for 1,4-dioxane indicate that the hazard to aquatic organisms is low. While the EPA has determined that sufficient data are available to characterize the overall environmental hazards of 1,4-dioxane, there are limited chronic toxicity studies available for assessing the long-term effects of 1,4-dioxane to aquatic species that may create some uncertainty associated with this assessment.

National-scale monitoring data from EPA's STOrage and RETreival (STORET) and National Water Information System (NWIS) for the past ten years, shows that 1,4-dioxane is detected in surface water. The data points show a detection rate of approximately 6% for this media, with detections ranging from 0.568 to 100 µg/L. However, some samples within this dataset have method detection limits above the highest detection level of 100 µg/L. Public commenters pointed out that some of these MDLs may exceed the chronic COC of 14,500 µg/L [[EPA-HQ-OPPT-2019-0238-0058](#)]. Non-detects from this dataset were not considered, so there is some uncertainty surrounding potential levels of 1,4-dioxane from such samples.

As described in Appendix E and Section 2.3.1, a screening-level aquatic exposure assessment was undertaken during problem formulation to evaluate ecological exposures in the U.S. that may be associated with releases of 1,4-dioxane to surface waters.

This assessment was intended as a first-tier, or screening-level, evaluation. Discharging or releasing facilities were chosen from two data sources: EPA's Discharge Monitoring Report (DMR) and Toxic Release Inventory (TRI). The top ten (by annual release/discharge amount) facilities were selected for use in exposure modeling; therefore, not all reporting sites were modeled, and the selected sites were not cross-walked with the conditions of use included in the occupational engineering assessment. These top dischargers were selected from two recent complete years of TRI and DMR reporting, which at the time of modeling included 2014-2015 for TRI and 2015-2016 for DMR.

EPA's Exposure and Fate Assessment Screening Tool, Version 2014 ([U.S. EPA, 2014c](#)) was used for predicting stream concentrations resulting from the selected releasers. The predicted stream concentrations reflect concentrations in the receiving water body at the point of the release, incorporating any immediate dilution based on stream flow. Downstream transport and/or dilution are not modeled, nor are any post-release fate or removal processes such as degradation, photolysis, hydrolysis, or volatilization.

For the purposes of this assessment, the number of release days was based on conservative assumptions. The reported annual release amounts from TRI and DMR were converted to kg and divided by the assumed number of release days (1, 20, or 250) to obtain the necessary kg/site-day release input. These assumptions are not based on associated industry-specific data or standards, but on screening-level assumptions to capture worst-case environmental concentrations for acute and chronic release scenarios. One day of release is the worst-case release assumption for an acute scenario, appropriate for comparison against an acute COC, while 20 days of release is the worst-case release assumption for a chronic scenario, appropriate for comparison against a chronic COC. 250 days of release may be more typical for facilities that operate and release effluent frequently, such as POTWs or treatment plants.

4.3.5 Key Assumptions and Uncertainties in Human Health Hazards

Data are limited for some chronic toxicological endpoints. While not required here, there is no multi-generation reproductive/developmental study. In the only available developmental study in mammals ([Giavini et al., 1985](#)), effects of 1,4-dioxane included delayed ossification of the sternebrae and reduced fetal body weight. These effects only reached statistical significance at the highest dose tested (1000 mg/kg-day) in the presence of slight maternal toxicity. Although there is some limited evidence of developmental toxicity, there is a lack of data for several reproductive and developmental endpoints, including neurodevelopmental effects.

There is also a lack of data on toxicity of 1,4-dioxane from dermal exposures. EPA therefore extrapolated from evidence from oral and inhalation studies to derive dermal PODs. As described in Section 3.2.7, route-to-route extrapolation introduces several sources of uncertainty, including differences in absorption through different routes of exposure (*e.g.*, first-pass metabolism following oral exposure) and uncertainty related to exposure methods (*e.g.*, whole body inhalation exposure in animal studies may result in additional exposure via dermal and oral exposure routes that are unaccounted for in POD derivation). EPA did not apply additional uncertainty factors to address uncertainties related to route-to-route extrapolation because these sources of uncertainty are likely to underestimate rather than overestimate the POD for 1,4-dioxane.

One source of uncertainty for cancer risk estimates is the mode of action (MOA) for 1,4-dioxane carcinogenicity. EPA concluded that there is insufficient information to support a specific MOA for any of the tumor types associated with 1,4-dioxane exposure. A clearer understanding of the MOA for carcinogenesis at each tumor location could inform selection of linear or non-linear models for BMD modeling to determine the dose-response relationship at low doses. For example, there is uncertainty on whether the toxic moiety is 1,4-dioxane or one or more metabolites and whether cytotoxicity is a necessary key event in the progression to observed liver tumors. Additionally, cancer dose-response was performed on a set of tissue types that are not all present in humans (*i.e.*, Zymbal gland). However, in the absence of information to indicate otherwise, and considering similar cell types are prevalent throughout the respiratory tract of rats and humans, nasal, liver, renal, peritoneal, mammary gland, Zymbal gland, and subcutis tumors were all considered relevant to humans. Inclusion of Zymbal gland tumors is consistent with EPA's *Guidelines for Carcinogenic Risk Assessment* ([U.S. EPA, 2005a](#)), which does not always require site concordance between humans and animals.

In the reasonably available studies for inhalation and oral cancer hazard, there were issues such as mortality at the high doses ([NCI, 1978](#); [Kociba et al., 1974](#)). EPA was unable to use the data from male rats in the NCI ([1978](#)) study due to high levels of mortality, and the doses were too close together due to drinking water intake.

EPA performed BMD modeling for all non-cancer data that were amenable to modeling. EPA made several assumptions related to modeling, including selection of BMRs and appropriate model fits. The assumptions and uncertainties related to BMD modeling for each endpoint are described in detail in Appendix K. The acute liver toxicity as well as some of the chronic respiratory and olfactory effects were not able to be estimated with BMD modeling and were instead based on a LOAEC or a NOAEC. This resulted in greater uncertainty and a higher

benchmark MOE for those endpoints. The endpoint EPA selected as the basis for the acute PODs relies on a LOAEC and therefore requires an additional uncertainty factor of LOAEC and NOAEC extrapolation. The endpoint EPA ultimately selected as the basis for the chronic inhalation POD was evaluated with BMD modeling.

EPA performed BMD modeling for data on all cancer endpoints ([Kano et al., 2009](#); [Kasai et al., 2009](#)) as relevant to humans. EPA ran the multi-tumor BMD models with and without liver tumors to determine the sensitivity of the result to the inclusion of liver tumors. For some tumors, the human relevance and/or pathology is not well understood such as subcutis fibroma, which is a skin tumor that occurred following both inhalation and oral exposure.

Subcutis fibromas were observed in both oral and inhalation studies of chronic duration. The high concentration group for subcutis fibroma inhalation data ([Kasai et al., 2009](#)) was omitted from the dose-response analysis ([U.S. EPA, 2013b](#)). The incidence data were monotonic non-decreasing functions of dose for the control (0 ppm), low (50 ppm), and mid-dose (250 ppm); however, the incidence rate at the high dose (1,250 ppm) was lower than observed at the mid-dose. No BMDS model exhibited reasonable fit to the data without dropping the high dose. The need to drop the high dose creates uncertainty regarding the endpoint.

Nasal tumors were seen in both oral and inhalation studies of chronic duration. The MOA for nasal tumors is uncertain. It has been suggested that direct exposure of the nasal tissues to liquid during drinking water studies of 1,4-dioxane where sipper tubes have been used may have confounded findings at the portal of entry in the nose ([Sweeney et al., 2008](#)). However, nasal tumors occurred in both oral and inhalation studies. 1,4-dioxane is a volatile chemical and it is unknown how much drinking water exposure may be due to liquid, vapor, or aerosols.

There are a number of datasets where effect incidence was only observed in the highest exposure group [zymbal gland adenomas and renal cell carcinomas from the inhalation data by [Kasai et al. \(2009\)](#), cortical tubule degeneration from the oral data by [NCI \(1978\)](#), and nasal tumors from the oral data by [Kano et al. \(2009\)](#) and [Kociba et al. \(1974\)](#)].

As described in Section 3.2.7, EPA has medium-high confidence in hazard PODs used as the basis for risk characterization.

4.3.6 Key Assumptions and Uncertainties in the Human Health Risk Characterization

The uncertainty factors that are the basis of benchmark MOEs used in the risk evaluation account for some sources of uncertainty for non-cancer hazards.

For chronic non-cancer risks, EPA used a benchmark MOE of 30, based on an uncertainty factor of 3 for interspecies variability and an uncertainty factor of 10 for interindividual variability. Chronic non-cancer risk estimates from inhalation exposures were based on effects in the olfactory epithelium and respiratory epithelium. These effects were attributed to systemic delivery of 1,4-dioxane and are therefore assumed to be relevant to both inhalation and dermal exposures.

For acute non-cancer risks, EPA used a benchmark MOE of 300 based on uncertainty factors of 3 for interspecies variability, 10 for interindividual variability, and 10 for extrapolation from a LOEAL to a NOAEL.

For cancer risk estimates, in the absence of a known MOA for liver tumors or other tumor types, a linear low-dose extrapolation approach was used to estimate the dose-response at doses below the observable range. There was a high degree of uncertainty in any of the MOA hypotheses considered in this evaluation (e.g., mutagenic mode of action or threshold response to cytotoxicity and regenerative hyperplasia for liver tumors). Linear extrapolation is the default approach when there is uncertainty about the MOA. 1,4-Dioxane is a multi-site carcinogen and may have more than one MOA. EPA estimates for excess cancer risk were based on the assumption of linearity in the relationship between 1,4-dioxane exposure and the probability of cancer. To understand the impact of assuming a linear dose-response for liver tumors, EPA presents combined cancer risk estimates that do not include the liver tumors. As seen in Table 3-10., excluding liver tumors from the combined linear model has a minimal impact on the overall inhalation cancer risk estimate.

Route-to-route extrapolation of dermal cancer and non-cancer PODs from oral and inhalation studies introduced several potential sources of uncertainty. There is a lack of information about how differences in absorption, metabolism and distribution to target tissues alter toxicity of 1,4-dioxane across routes of exposure. While EPA does not have data to quantify these uncertainties, they are expected to overestimate rather than underestimate dermal risk.

Dermal absorption and permeation could provide sources of uncertainty in the dermal risk assessment for both dermal cancer and noncancer estimates of risk. The transdermal flux parameters reported by researchers varied depending on the test conditions (Section 2.4.1.1.13 and Figure 2-2).

There is also some uncertainty related to the potential impact of 1,4-dioxane on potentially exposed and susceptible subpopulations. EPA applied an intraspecies uncertainty factor of 10 to all non-cancer PODs to account for variation in sensitivity across gender, age, health status, or genetic makeup, but the actual magnitude of the impact of these factors on susceptibility is unknown. Workers were identified as relevant potentially exposed or susceptible subpopulations, but EPA did not specifically identify women of reproductive age or pregnant women who may work with 1,4-dioxane or children ages 16 to 21 because EPA does not have information to indicate that 1,4-dioxane would preferentially affect women or developing children.

4.4 Potentially Exposed or Susceptible Subpopulations (PESS)

TSCA § 6(b)(4) requires that EPA conduct a risk evaluation to “*determine whether a chemical substance presents an unreasonable risk of injury to health or the environment, without consideration of cost or other non-risk factors, including an unreasonable risk to a potentially exposed or susceptible subpopulation identified as relevant to the risk evaluation by the Administrator, under the conditions of use.*” TSCA § 3(12) states that “*the term ‘potentially exposed or susceptible subpopulation’ means a group of individuals within the general population identified by the Administrator who, due to either greater susceptibility or greater*

exposure, may be at greater risk than the general population of adverse health effects from exposure to a chemical substance or mixture, such as infants, children, pregnant women, workers, or the elderly.” EPA believes that the statutory directive to consider potentially exposed or susceptible subpopulations (PESS) and the statutory definition of PESS inherently include environmental justice populations. Thus, EPA’s consideration of PESS in this risk evaluation addresses the requirements of the Executive Order 12898.

Previous EPA assessments for 1,4-dioxane found no direct evidence that specific populations and lifestages are more susceptible to 1,4-dioxane (EPA IRIS Assessments ([U.S. EPA, 2013d, 2010](#))). Information on induction of liver enzymes, genetic polymorphisms and gender differences is inadequate to quantitatively assess toxicokinetic or toxicodynamic differences in 1,4-dioxane hazard between animals and humans and the potential variability in human susceptibility.

As discussed in Section 3.2.6.1, some subpopulations may be more biologically susceptible to the effects of 1,4-dioxane due to genetic variability, pre-existing health conditions, lifestage, pregnancy, or other factors that alter metabolism or increase target organ susceptibility. For example, people with liver disease may be more susceptible due to reduced metabolism of 1,4-dioxane and increased susceptibility of a target organ. EPA does not have sufficient quantitative information about these potential sources of susceptibility to quantitatively incorporate them into the risk evaluation. Populations with liver sensitivities or other underlying health issues within the worker and ONU populations would be expected to have increased susceptibility to 1,4-dioxane.

In developing the risk evaluation, the EPA qualitatively analyzed the reasonably available information to ascertain whether some human receptor groups may have greater exposure or greater susceptibility than the general population to the hazard posed by a chemical. Exposures of 1,4-dioxane would be expected to be higher amongst workers and ONUs using 1,4-dioxane as compared to the general population. EPA’s decision for unreasonable risk are based on high-end exposure estimates for workers and high intensity use scenarios for consumers and bystanders in order to capture individuals who are PESS. Members of the general population incidentally exposed to 1,4-dioxane through recreational activities in ambient water containing 1,4-dioxane are also subject to greater exposure. The general population analysis considered and used the age group that resulted in the highest exposure estimates for the purposed of risk characterization and risk determination. For example, while recommended intake rates for oral ingestion during swimming were available for ages 6 years and greater, the 11-15 age class was selected for exposure and risk characterization based on the combination of intake, duration, and body weight for that age class resulting in the highest estimated exposures. Likewise, consumers and bystanders exposed to 1,4-dioxane through the use of household products that contain 1,4-dioxane as a byproduct are also considered PESS due to their greater exposure. Additionally, high-intensity users (*i.e.*, those using consumer products for longer durations or in great amounts) are evaluated. Consumers are considered to include children and adults, ages 11 and up, while bystanders in the home exposed via inhalation could include children and adults of all ages.

4.5 Aggregate and Sentinel Exposures

Section 2605(b)(4)(F)(ii) of TSCA requires the EPA, as a part of the risk evaluation, to describe whether aggregate or sentinel exposures under the conditions of use were considered and the basis for their consideration. The EPA has defined aggregate exposure as “*the combined exposures to an individual from a single chemical substance across multiple routes and across multiple pathways* (40 CFR § 702.33).”

For each COU, EPA evaluated risks from dermal and inhalation exposures independently. Inhalation and dermal exposures are assumed to occur simultaneously for workers and consumers. Dermal and oral exposures are assumed to occur simultaneously for general population exposures through swimming. EPA chose not to employ simple additivity of risk exposure pathways within a condition of use because of the uncertainties present in the current exposure estimation procedures. There is currently no PBPK model available to facilitate evaluation of aggregate exposure from simultaneous exposure through inhalation and dermal contact with 1,4-dioxane. Without a PBPK model containing a dermal compartment to account for toxicokinetic processes the true internal dose for any given exposure cannot be determined, and aggregating exposures by simply adding exposures from multiple routes could inappropriately overestimate total exposure. This lack of aggregation across exposure routes may lead to an underestimate of exposure.

EPA also did not consider aggregate exposure among individuals who may be exposed both in an occupational and consumer context because there is insufficient information reasonably available as to the likelihood of this scenario or the relative distribution of exposures from each pathway.

The EPA defines sentinel exposure as “*the exposure to a single chemical substance that represents the plausible upper bound of exposure relative to all other exposures within a broad category of similar or related exposures* (40 CFR § 702.33).” In terms of this risk evaluation, the EPA considered sentinel exposures by evaluating exposures to populations who may have upper bound exposures. EPA characterized high-end exposures using both monitoring data and modeling approaches. Where statistical data are available, EPA typically uses the 95th percentile value of the available dataset to characterize high-end exposure for a given condition of use. For consumer and bystander exposures, EPA characterized sentinel exposure through a “high-intensity use” category based on both product and user-specific. EPA’s decision for unreasonable risk are based on high-end exposure estimates to capture individuals with sentinel exposure.

4.6 Risk Conclusions

4.6.1 Summary of Environmental Risk

EPA’s analysis of environmental risk, in Section 4.1 identified risk to aquatic organisms (acute $RQ \geq 1$, or a chronic $RQ \geq 1$ and 20 days or more of exceedance for the chronic COC). EPA did not identify RQs greater than 1 for aquatic organisms near any facilities. These facilities are presented in Tables 4-1, 4-1 and 4-3.

EPA did not identify acute or chronic risks to fish, invertebrates or algae in the surface water where monitored data were reasonably available. There were no exceedances of the acute COC (57,000 ppb), or chronic COC (14,500 ppb) in surface water.

Table 4-1. Environmental Risk Estimation of 1,4-Dioxane from Industrial Releases into Surface Water from DMR Facilities in Year 2015 and 2016

Name, Location, and ID of Active Releaser Facility	E-FAST Inputs and Results				RQ	
	Days of Release ^a	Release ^a (kg/day)	10 th Percentile 7Q10 Concentration (µg/L)	Days Exceedance (days/yr)	Algae (Acute) COC = 57,500 µg/L	Fish (Chronic) COC = 14,500 µg/L
<i>Minimum Acute and Chronic Risk Quotient Values Reported from 10 DMR Facilities Reported in 2015</i>						
Eastman Kodak NY0001643 (SIC 3861)	1	20	18.78	NA	6.90E-05	1.74E-05
	20	1	0.95	0	6.90E-06	1.74E-06
	250	0.1	0.0949	0	0	0
<i>Maximum Acute and Chronic Risk Quotient Values Reported from 10 DMR Facilities in 2015</i>						
Dak Americas LLC SC0026506 (SIC 2821)	10 ^b	920	10,900^b	NA	0.031731	0.0080017
	20	460	5,428.91	0	0.0025379	0.00064
	250	37	434.22	0	0.0002966	7.48E-05
<i>Minimum Acute and Chronic Risk Quotient Values Reported from 10 DMR Facilities Reported in 2016</i>						
Eastman Kodak NY0001643 (SIC 3861)	1	79	74.46	NA	0.001295	0.0051352
	20	3.9	3.7	0	6.43478 E-05	0.0002552
	250	0.3	0.28	0	4.86957 E-06	1.93103 E-05
<i>Maximum Acute and Chronic Risk Quotient Values Reported from 10 DMR Facilities in 2016</i>						
Dak Americas LLC SC0026506 (SIC 2821)	10 ^b	977	11,500	NA	0.2	0.7931034
	20	488	5,761.65	0	0.1002026	0.3973552
	250	39	461.36	0	0.0080237	0.0318179

- a. Days of release (1, 20, or 250) are EPA assumptions that provide a range of potential surface water concentrations; days of release were not reported in DMR. The release (kg/day) is based on the per day based on total annual loading (lbs/yr), as reported in DMR Pollutant Loading Tool, and is divided by the assumed number of release days prior to modeling.
- b. The Dak chemicals site acute scenario was re-run for a 10-day acute scenario based on input from EPA engineers related to the lowest number of operating days assumed for facilities falling within this standard industrial category (*i.e.*, 10 days per year). Therefore, maximum surface water concentrations based on this site reflect an assumed 10 days per year of release instead of 1 day.

Table 4-2. Environmental Risk Estimation of 1,4-Dioxane from Direct Industrial Releases into Surface Water from TRI Facilities in Year 2014 and 2015

Name, Location, and ID of Active Releaser Facility	E-FAST Inputs and Results				RQ	
	Days of Release ^a	Release ^a (kg/day)	10 th Percentile 7Q10 Concentration (µg/L)	Days Exceedance (days/yr)	Algae COC = 57,500 µg/L	Fish Chronic COC = 14,500 µg/L
<i>Minimum Acute and Chronic Risk Quotient Values Reported from 10 TRI Facilities in 2014a</i>						
The DOW Chemical Co. Louisiana Operations LA0003301 b	1	312	1.26	NA	2.19E-05	8.69E-05
	20	16	0.0648	0	1.13E-06	4.47E-06
	250	1	0.00405	0	7.04E-08	2.79E-07

Name, Location, and ID of Active Releaser Facility	E-FAST Inputs and Results				RQ	
	Days of Release ^a	Release ^a (kg/day)	10 th Percentile 7Q10 Concentration (µg/L)	Days Exceedance (days/yr)	Algae COC = 57,500 µg/L	Fish Chronic COC = 14,500 µg/L
<i>Maximum Acute and Chronic Risk Quotient Values Reported from 10 TRI Facilities in 2014a</i>						
DAK Americas LLC Cooper River Plant SC0026506	10 ^c	825	9,734	NA	1.69E-01	6.71E-01
	20	412	4,861.36	0	8.45E-02	3.35E-01
	250	33	389.4	0	6.77E-03	2.69E-02
<i>Minimum Acute and Chronic Risk Quotient Values Reported from 10 TRI Facilities in 2015</i>						
The DOW Chemical Co. Louisiana Operations LA0003301 ^b	1	337	1.36	NA	2.37E-05	9.38E-05
	20	17	0.0688	0	1.20E-06	4.74E-06
	250	1	0.00405	0	7.04E-08	2.79E-07
<i>Maximum Acute and Chronic Risk Quotient Values Reported from 10 TRI Facilities in 2015</i>						
DAK Americas LLC Cooper River Plant SC0026506	10 ^c	810	9,557	NA	1.66E-01	6.59E-01
	20	405	4778.76	0	8.31E-02	3.30E-01
	250	32	377.58	0	6.57E-03	2.60E-02

- Days of release (1, 20, or 250) are EPA assumptions that provide a range of potential surface water concentrations; days of release were not reported to TRI. The release (kg/day) is based on the per day based on annual releases to surface water (lbs/yr), as reported to TRI, and is divided by the assumed number of release days prior to modeling.
- The NPDES provided in DMR's Pollutant Loading Tool for the facility THE DOW CHEMICAL CO - LOUISIANA OPERATIONS (NPDES LA0116602) was not found in E-FAST 2014; however, a facility name and location search within E-FAST 2014 returned a different NPDES (LA0003301) associated with this facility name and location, so it was applied for modeling.
- ARKEMA Inc (KY0003603), Dow Chemical Co Freeport (TX0006483), Honeywell International (LA0000329), and Westlake Vinyls Inc (KY0003484) facilities, which were included in the risk evaluation based on previous data extraction, did not have reported surface water discharges in TRI explorer per 2015 release report and were therefore removed from the list of assessed sites.

Table 4-3. Environmental Risk Estimation of 1,4-Dioxane from Indirect Industrial Releases into Surface Water from TRI Facilities in Year 2014 and 2015

Name, Location, and ID of Active Releaser Facility NPDES Used in E-FAST	Receiving POTW	E-FAST Inputs and Results				RQ	
		Days of Release ^a	Release ^a (kg/day)	7Q10 Concentration (µg/L)	Days Exceedance (days/yr) COC = 14,500 µg/L	Algae COC = 57,500 µg/L	Fish Chronic COC = 14,500 µg/L
<i>Minimum Acute and Chronic Risk Quotient Values Reported from 6 TRI Facilities in 2014</i>							
Evonik Materials Corp. WI0060453	Milton Waterworks	250	0.001	0.00586	0	1.02E-07	4.04E-07
<i>Maximum Acute and Chronic Risk Quotient Values Reported from 6 TRI Facilities in 2014a</i>							
SUEZ WTS Solutions USA Inc. Ind. POTW (SIC 4952) ^b	Blue Lake WWTP	250	30	3788.66	4	6.59E-02	2.61E-01
<i>Minimum Acute and Chronic Risk Quotient Values Reported from 10 TRI Facilities in 2015</i>							
Heritage Thermal Services OH0024970	East Liverpool WWTP	250	2.39E-07	2.37E-08	0	4.12E-13	1.63E-12
<i>Maximum Acute and Chronic Risk Quotient Values Reported from 10 TRI Facilities in 2015</i>							
SUEZ WTS Solutions USA Inc. Ind. POTW (SIC 4952) ^b	Blue Lake WWTP	250	27	3409.79	3	5.93E-02	2.35E-01

Name, Location, and ID of Active Releaser Facility NPDES Used in E-FAST	Receiving POTW	E-FAST Inputs and Results				RQ	
		Days of Release ^a	Release ^a (kg/day)	7Q10 Concentration (µg/L)	Days Exceedance (days/yr) COC = 14,500 µg/L	Algae COC = 57,500 µg/L	Fish Chronic COC = 14,500 µg/L

- a. Days of release (250) are EPA assumptions that provide a range of potential surface water concentrations; days of release were not reported to TRI. The release (kg/day) is based on the per day based on annual releases to surface water (lbs/yr), as reported to TRI, and is divided by the assumed number of release days prior to modeling.
- b. SIC for industrial POTWs was used for the facility because the facility was not found in E-FAST 2014.

4.6.2 Summary of Human Health Risk

4.6.2.1 Summary of Risk for Workers and ONUs

Table 4-23. summarizes the representative risk estimates for inhalation and dermal exposures for all occupational exposure scenarios. Risk estimates that indicate potential risk (*i.e.* MOEs less than the benchmark MOE or cancer risks greater than the cancer risk benchmark) are highlighted by bolding the number and shading the cell in gray. The occupational exposure assessment and risk characterization are described in more detail in Sections 2.4.1 and 4.2, respectively. Specific links to the relevant risk characterization sections are listed in Table 4-23. in the Occupational Exposure Scenario column.

Risk estimates for each inhalation and dermal exposure scenario for workers are presented both with and without PPE. EPA calculated risks based on respirator APFs of 1, 10, or 50 and glove PFs of 1, 5, 10 or 20. The lowest protection factor that results in no indication of risk relative to the benchmark is shown (*i.e.*, if risks do not exceed the benchmark for APF 10 and above, the risk estimate for APF 10 is shown).

Inhalation

Cancer risks for central tendency and high-end worker inhalation exposures exceed the cancer benchmark for manufacturing, import/repackaging, industrial use, film cement, and disposal. High-end inhalation exposures also exceed the cancer benchmark for lab chemicals and dry film lubricant. With respirator use (APF 50), cancer risk is reduced to below the benchmark for all worker exposure scenarios except for high-end industrial use exposures.

For acute and chronic inhalation exposures, MOEs indicate non-cancer risks to workers relative to the benchmarks for central tendency and high-end exposures predicted for import/repackaging (bottle and drum), industrial use, film cement, and disposal. MOEs also indicate risks relative to the benchmarks for high-end exposures predicted for manufacturing, lab chemicals, and dry film lubricant. MOEs calculated based on respirator use (APF 50), do not indicate non-cancer risk relative to the benchmarks for any acute or chronic worker inhalation exposures.

Occupational non-users are expected to have lower levels of exposure than workers in most instances, but exposures could not always be quantified. When separate ONU exposure estimates were not reasonably available, EPA provided risk estimates for ONUs based on central tendency exposures for workers without PPE. These instances are indicated with footnotes in Table 4-23.. MOEs for ONU-specific exposure scenarios for spray foam application, functional fluids, and film cement do not indicate risk relative to the benchmark. Upper-bound ONU exposure estimates based on central tendency exposures for workers indicate inhalation risks for ONUs in

manufacturing, import/repackaging (bottle and drum), industrial use, and disposal exposure scenarios. ONUs are assumed not to wear respirators.

Dermal

Cancer risk from central tendency and high end dermal exposures exceeds the cancer benchmark of 10^{-4} , indicating risk for all occupational exposure scenarios in the absence of glove use. With glove use (PF 5 and above), cancer risk is reduced to below the benchmark for functional fluids and spray foam application exposure scenarios. Glove use does not reduce cancer risk to below the cancer benchmark for any other worker exposure scenarios.

Noncancer risks for central tendency and high-end acute and chronic dermal exposures are below the benchmark MOEs, indicating risk for workers in the following exposure scenarios: manufacturing, import/repackaging (bottle and drum), industrial use, lab chemical use, use of 3D printing inks, film cement, dry film lubricant, and disposal. For most of these scenarios, glove use (up to PF 20) is not sufficient to reduce risks from acute or chronic exposures relative to the benchmark. Glove use would only be expected to reduce chronic non-cancer risk relative to the benchmark MOE for import/repackaging scenarios. No acute or chronic non-cancer risk is identified for dermal exposures associated with spray foam application or functional fluids, regardless of glove use. EPA did not calculate risks of dermal exposure for ONUs because ONUs are assumed to have no direct dermal contact with 1,4-dioxane.

Table 4-23. Summary of Human Health Risk From Occupational Exposures

Life Cycle Stage/ Category ^a	Subcategories	Occupational Exposure Scenario	Population	Exposure Route and Duration	Exposure Level	Risk Estimates for No PPE			Risk Estimates with PPE		
						Acute Non-cancer (benchmark MOE = 300)	Chronic Non-cancer (benchmark MOE = 30)	Cancer (benchmark = 10 ⁻⁴)	Acute Non-cancer (benchmark MOE = 300)	Chronic Non-cancer (benchmark MOE = 30)	Cancer (benchmark = 10 ⁻⁴)
Manufacture/ Domestic manufacture	Domestic manufacture	Section 2.4.1.1.1 and 4.2 – Manufacturing	Worker	Inhalation 8-hr TWA	Central Tendency	684	32.1	1.59E-04	6,843 (APF 10)	321 (APF 10)	1.59E-05 (APF 10)
					High-End	36.7	1.72	3.81E-03	367 (APF 10)	86.1 (APF 50)	7.63E-05 (APF 50)
				Dermal	Central Tendency	4.83	0.23	0.34	96.6 (PF 20)	4.54 (PF 20)	1.72E-02 (PF 20)
					High-End	1.61	7.57E-02	1.33	32.2 (PF 20)	1.51 (PF 20)	6.67E-02 (PF 20)
			ONU ^b	Inhalation 8-hr TWA	Central Tendency	684	32.1	1.59E-04	N/A	N/A	N/A
					High-End	--	--	--	N/A	N/A	N/A
Manufacture/ Import	Import	Section 2.4.1.1.2 and 4.2 – Import/	Worker	Inhalation 8-hr TWA	Central Tendency	30.6	27.6	1.75E-04	306 (APF 10)	276 (APF 10)	1.75E-05 (APF 10)

Life Cycle Stage/ Category ^a	Subcategories	Occupational Exposure Scenario	Population	Exposure Route and Duration	Exposure Level	Risk Estimates for No PPE			Risk Estimates with PPE		
						Acute Non-cancer (benchmark MOE = 300)	Chronic Non-cancer (benchmark MOE = 30)	Cancer (benchmark = 10 ⁻⁴)	Acute Non-cancer (benchmark MOE = 300)	Chronic Non-cancer (benchmark MOE = 30)	Cancer (benchmark = 10 ⁻⁴)
	Repackaging (Bottle)	Repackaging (Bottle)		Dermal	High-End	8.58	3.77	1.32E-03	429 (APF 50)	37.7 (APF 10)	2.64E-05 (APF 50)
					Central Tendency	4.83	18.9	4.13E-03	96.6 (PF 20)	94.6 (PF 5)	2.07E-04 (PF 20)
					High-End	1.61	0.59	0.17	32.2 (PF 20)	11.8 (PF 20)	8.54E-03 (PF 20)
			ONU ^b	Inhalation 8-hr TWA	Central Tendency	30.6	27.6	1.75E-04	N/A	N/A	N/A
					High-End	--	--	--	N/A	N/A	N/A
Manufacture/ Import	Import Repackaging (Drum)	Section 2.4.1.1.2 and 4.2 – Import/Repackaging (Drum)	Worker	Inhalation 8-hr TWA	Central Tendency	26.7	27.6	1.75E-04	1,334 (APF 50)	276 (APF 10)	1.75E-05 (APF 10)
					High-End	7.44	3.77	1.32E-03	372 (APF 50)	37.7 (APF 10)	2.64E-05 (APF 50)
				Dermal	Central Tendency	4.83	9.46	8.27E-03	96.6 (PF 20)	47.3 (PF 5)	4.13E-04 (PF 20)
					High-End	1.61	0.33	0.31	32.2 (PF 20)	6.52 (PF 20)	1.55E-02 (PF 20)
			ONU ^b	Inhalation 8-hr TWA	Central Tendency	26.7	27.6	1.75E-04	N/A	N/A	N/A
					High-End	--	--	--	N/A	N/A	N/A
Processing	Processing/ Repackaging (Bottle)	Section 2.4.1.1.2 and 4.2 – Import/	Worker	Inhalation 8-hr TWA	Central Tendency	30.6	27.6	1.75E-04	306 (APF 10)	276 (APF 10)	1.75E-05 (APF 10)

Life Cycle Stage/ Category ^a	Subcategories	Occupational Exposure Scenario	Population	Exposure Route and Duration	Exposure Level	Risk Estimates for No PPE			Risk Estimates with PPE		
						Acute Non-cancer (benchmark MOE = 300)	Chronic Non-cancer (benchmark MOE = 30)	Cancer (benchmark = 10 ⁻⁴)	Acute Non-cancer (benchmark MOE = 300)	Chronic Non-cancer (benchmark MOE = 30)	Cancer (benchmark = 10 ⁻⁴)
		Repackaging (Bottle)		Dermal	High-End	8.58	3.77	1.32E-03	429 (APF 50)	37.7 (APF 10)	2.64E-05 (APF 50)
					Central Tendency	4.83	18.9	4.13E-03	96.6 (PF 20)	94.6 (PF 5)	2.07E-04 (PF 20)
					High-End	1.61	0.59	0.17	32.2 (PF 20)	11.8 (PF 20)	8.54E-03 (PF 20)
			ONU ^b	Inhalation 8-hr TWA	Central Tendency	30.6	27.6	1.75E-04	N/A	N/A	N/A
					High-End	--	--	--	N/A	N/A	N/A
Processing	Processing/ Repackaging (Drum)	Section 2.4.1.1.2 and 4.2 – Import/Repackaging (Drum)	Worker	Inhalation 8-hr TWA	Central Tendency	26.7	27.6	1.75E-04	1,334 (APF 50)	276 (APF 10)	1.75E-05 (APF 10)
					High-End	7.44	3.77	1.32E-03	372 (APF 50)	37.7 (APF 10)	2.64E-05 (APF 50)
				Dermal	Central Tendency	4.83	9.46	8.27E-03	96.6 (PF 20)	47.3 (PF 5)	4.13E-04 (PF 20)
					High-End	1.61	0.33	0.31	32.2 (PF 20)	6.52 (PF 20)	1.55E-02 (PF 20)
			ONU ^b	Inhalation 8-hr TWA	Central Tendency	26.7	27.6	1.75E-04	N/A	N/A	N/A
					High-End	--	--	--	N/A	N/A	N/A
Processing/ Recycling	Recycling	Section 2.4.1.1.4 and 4.2 – Industrial Use	Worker	Inhalation 8-hr TWA	Central Tendency	56.8	2.66	1.91E-03	568 (APF 10)	133 (APF 50)	3.82E-05 (APF 50)
					High-End	14.2	0.67	9.86E-03	710 (APF 50)	33.3 (APF 50)	1.97E-04 (APF 50)

Life Cycle Stage/ Category ^a	Subcategories	Occupational Exposure Scenario	Population	Exposure Route and Duration	Exposure Level	Risk Estimates for No PPE			Risk Estimates with PPE					
						Acute Non-cancer (benchmark MOE = 300)	Chronic Non-cancer (benchmark MOE = 30)	Cancer (benchmark = 10 ⁻⁴)	Acute Non-cancer (benchmark MOE = 300)	Chronic Non-cancer (benchmark MOE = 30)	Cancer (benchmark = 10 ⁻⁴)			
				Dermal	Central Tendency	4.83	0.23	0.34	96.6 (PF 20)	4.54 (PF 20)	1.72E-02 (PF 20)			
					High-End	1.61	7.57E-02	1.33	32.2 (PF 20)	1.51 (PF 20)	6.67E-02 (PF 20)			
				ONU ^b	Inhalation 8-hr TWA	Central Tendency	56.8	2.66	1.91E-03	N/A	N/A	N/A		
					High-End	--	--	--	N/A	N/A	N/A			
			Processing/ Non-Incorporative	Basic organic chemical manufacturing (process solvent)	Section 2.4.1.1.4 and 4.2 – Industrial Use	Worker	Inhalation 8-hr TWA	Central Tendency	56.8	2.66	1.91E-03	568 (APF 10)	133 (APF 50)	3.82E-05 (APF 50)
								High-End	14.2	0.67	9.86E-03	710 (APF 50)	33.3 (APF 50)	1.97E-04 (APF 50)
Dermal	Central Tendency	4.83					0.23	0.34	96.6 (PF 20)	4.54 (PF 20)	1.72E-02 (PF 20)			
	High-End	1.61					7.57E-02	1.33	32.2 (PF 20)	1.51 (PF 20)	6.67E-02 (PF 20)			
ONU ^b	Inhalation 8-hr TWA	Central Tendency				56.8	2.66	1.91E-03	N/A	N/A	N/A			
	High-End	--				--	--	N/A	N/A	N/A				
Processing/ Processing as a reactant	Polymerization catalyst	Section 2.4.1.1.4 and 4.2 – Industrial Use				Worker	Inhalation 8-hr TWA	Central Tendency	56.8	2.66	1.91E-03	568 (APF 10)	133 (APF 50)	3.82E-05 (APF 50)
								High-End	14.2	0.67	9.86E-03	710 (APF 50)	33.3 (APF 50)	1.97E-04 (APF 50)
			Dermal	Central Tendency	4.83		0.23	0.34	96.6 (PF 20)	4.54 (PF 20)	1.72E-02 (PF 20)			
				High-End	1.61		7.57E-02	1.33	32.2 (PF 20)	1.51 (PF 20)	6.67E-02 (PF 20)			

Life Cycle Stage/ Category ^a	Subcategories	Occupational Exposure Scenario	Population	Exposure Route and Duration	Exposure Level	Risk Estimates for No PPE			Risk Estimates with PPE		
						Acute Non-cancer (benchmark MOE = 300)	Chronic Non-cancer (benchmark MOE = 30)	Cancer (benchmark = 10 ⁻⁴)	Acute Non-cancer (benchmark MOE = 300)	Chronic Non-cancer (benchmark MOE = 30)	Cancer (benchmark = 10 ⁻⁴)
			ONU ^b	Inhalation 8-hr TWA	Central Tendency	56.8	2.66	1.91E-03	N/A	N/A	N/A
					High-End	--	--	--	N/A	N/A	N/A
Industrial Use/ Intermediate Use	Agricultural chemical intermediate	Section 2.4.1.1.4 and 4.2 – Industrial Use	Worker	Inhalation 8-hr TWA	Central Tendency	56.8	2.66	1.91E-03	568 (APF 10)	133 (APF 50)	3.82E-05 (APF 50)
	High-End				14.2	0.67	9.86E-03	710 (APF 50)	33.3 (APF 50)	1.97E-04 (APF 50)	
	Dermal			Central Tendency	4.83	0.23	0.34	96.6 (PF 20)	4.54 (PF 20)	1.72E-02 (PF 20)	
				High-End	1.61	7.57E-02	1.33	32.2 (PF 20)	1.51 (PF 20)	6.67E-02 (PF 20)	
	Catalysts and reagents for anhydrous acid reactions, brominations and sulfonations		ONU ^b	Inhalation 8-hr TWA	Central Tendency	56.8	2.66	1.91E-03	N/A	N/A	N/A
					High-End	--	--	--	N/A	N/A	N/A
			Worker	Inhalation 8-hr TWA	Central Tendency	56.8	2.66	1.91E-03	568 (APF 10)	133 (APF 50)	3.82E-05 (APF 50)
					High-End	14.2	0.67	9.86E-03	710 (APF 50)	33.3 (APF 50)	1.97E-04 (APF 50)
Wood pulping	Section 2.4.1.1.4 and 4.2 – Industrial Use	Worker	Inhalation 8-hr TWA	Central Tendency	56.8	2.66	1.91E-03	568 (APF 10)	133 (APF 50)	3.82E-05 (APF 50)	
				High-End	14.2	0.67	9.86E-03	710 (APF 50)	33.3 (APF 50)	1.97E-04 (APF 50)	
		Dermal	Central Tendency	4.83	0.23	0.34	96.6 (PF 20)	4.54 (PF 20)	1.72E-02 (PF 20)		
			High-End	1.61	7.57E-02	1.33	32.2 (PF 20)	1.51 (PF 20)	6.67E-02 (PF 20)		
Extraction of animal and vegetable oils	Section 2.4.1.1.4 and 4.2 – Industrial Use	Worker	Inhalation 8-hr TWA	Central Tendency	56.8	2.66	1.91E-03	N/A	N/A	N/A	
				High-End	--	--	--	N/A	N/A	N/A	
		Dermal	Central Tendency	4.83	0.23	0.34	96.6 (PF 20)	4.54 (PF 20)	1.72E-02 (PF 20)		
			High-End	1.61	7.57E-02	1.33	32.2 (PF 20)	1.51 (PF 20)	6.67E-02 (PF 20)		
Wetting and dispersing agent in textile processing	Section 2.4.1.1.4 and 4.2 – Industrial Use	Worker	Inhalation 8-hr TWA	Central Tendency	56.8	2.66	1.91E-03	N/A	N/A	N/A	
				High-End	--	--	--	N/A	N/A	N/A	
		Dermal	Central Tendency	4.83	0.23	0.34	96.6 (PF 20)	4.54 (PF 20)	1.72E-02 (PF 20)		
			High-End	1.61	7.57E-02	1.33	32.2 (PF 20)	1.51 (PF 20)	6.67E-02 (PF 20)		
Purification of process intermediates Etching of fluoropolymers	Section 2.4.1.1.4 and 4.2 – Industrial Use	Worker	Inhalation 8-hr TWA	Central Tendency	56.8	2.66	1.91E-03	N/A	N/A	N/A	
				High-End	--	--	--	N/A	N/A	N/A	
		Dermal	Central Tendency	4.83	0.23	0.34	96.6 (PF 20)	4.54 (PF 20)	1.72E-02 (PF 20)		
			High-End	1.61	7.57E-02	1.33	32.2 (PF 20)	1.51 (PF 20)	6.67E-02 (PF 20)		

Life Cycle Stage/ Category ^a	Subcategories	Occupational Exposure Scenario	Population	Exposure Route and Duration	Exposure Level	Risk Estimates for No PPE			Risk Estimates with PPE		
						Acute Non-cancer (benchmark MOE = 300)	Chronic Non-cancer (benchmark MOE = 30)	Cancer (benchmark = 10 ⁻⁴)	Acute Non-cancer (benchmark MOE = 300)	Chronic Non-cancer (benchmark MOE = 30)	Cancer (benchmark = 10 ⁻⁴)
Industrial Use/ Functional Fluids, Open System	Metalworking fluid	Section 2.4.1.1.5 and 4.2 – Functional Fluids, Open System	Worker	Inhalation 8-hr TWA	Central Tendency	266,475	12,491	3.88E-07	2,664,753 (APF 10)	124,906 (APF 10)	3.88E-08 (APF 10)
					High-End	74,906	3,511	1.45E-06	749,065 (APF 10)	35,111 (APF 10)	1.45E-07 (APF 10)
	Dermal			Central Tendency	4,830	227	3.45E-04	24,149 (PF 5)	1,135 (PF 5)	6.89E-05 (PF 5)	
				High-End	1,610	75.7	1.33E-03	8,050 (PF 5)	378 (PF 5)	6.67E-05 (PF 20)	
	Polyalkylene glycol fluid		ONU ^c	Inhalation 8-hr TWA	Central Tendency	1,903,645	89,230	5.70E-08	N/A	N/A	N/A
					High-End	1,128,664	52,904	1.24E-07	N/A	N/A	N/A
Industrial Use, Potential Commercial Use/ Laboratory Chemicals	Chemical reagent	Section 2.4.1.1.7 and 4.2 – Lab Chemicals	Worker	Inhalation 8-hr TWA	Central Tendency	2,582	121	4.20E-05	25,818 (APF 10)	1,210 (APF 10)	4.20E-06 (APF 10)
	High-End				49.4	2.32	2.83E-03	494 (APF 10)	116 (APF 50)	5.67E-05 (APF 50)	
	Spectroscopic and photometric measurement			Dermal	Central Tendency	4.42	0.21	0.38	88.3 (PF 20)	4.15 (PF 20)	1.88E-02 (PF 20)
					High-End	1.47	6.92E-02	1.46	29.4 (PF 20)	1.38 (PF 20)	7.29E-02 (PF 20)
	Liquid scintillation counting medium		ONU ^b	Inhalation 8-hr TWA	Central Tendency	2,582	121	4.20E-05	N/A	N/A	N/A
					High-End	--	--	--	N/A	N/A	N/A
Stable reaction medium											

Life Cycle Stage/ Category ^a	Subcategories	Occupational Exposure Scenario	Population	Exposure Route and Duration	Exposure Level	Risk Estimates for No PPE			Risk Estimates with PPE		
						Acute Non-cancer (benchmark MOE = 300)	Chronic Non-cancer (benchmark MOE = 30)	Cancer (benchmark = 10 ⁻⁴)	Acute Non-cancer (benchmark MOE = 300)	Chronic Non-cancer (benchmark MOE = 30)	Cancer (benchmark = 10 ⁻⁴)
	Cryoscopic solvent for molecular mass determinations Preparation of histological sections for microscopic examination										
Industrial Use, Potential Commercial Use/ Adhesives and Sealants	Film cement	Section 2.4.1.1.8 and 4.2 – Film Cement	Worker	Inhalation 8-hr TWA	Central Tendency	187	8.75	5.82E-04	1,866 (APF 10)	87.5 (APF 10)	5.82E-05 (APF 10)
					High-End	101	4.74	1.38E-03	1,012 (APF 10)	47.4 (APF 10)	2.77E-05 (APF 50)
				Dermal	Central Tendency	8.83	0.42	0.19	177 (PF 20)	8.30 (PF 20)	9.42E-03 (PF 20)
					High-End	2.94	0.14	0.73	58.9 (PF 20)	2.77 (PF 20)	3.65E-02 (PF 20)
			ONU ^c	Inhalation 8-hr TWA	Central Tendency	2,726	128	3.98E-05	N/A	N/A	N/A
					High-End	2,726	128	5.14E-05	N/A	N/A	N/A
Industrial Use, Potential Commercial Use/ Other Uses	Spray polyurethane foam	Section 2.4.1.1.9 and 4.2 – Spray Foam Application	Worker	Inhalation 8-hr TWA	Central Tendency	29,194	1,368	3.63E-06	291,939 (APF 10)	13,684 (APF 10)	3.63E-07 (APF 10)
					High-End	24,030	1,126	5.25E-06	240,300 (APF 10)	11,264 (APF 10)	5.25E-07 (APF 10)
			Dermal	Central Tendency	4,415	208	3.77E-04	22,075 (PF 5)	1,038 (PF 5)	7.54E-05 (PF 5)	

Life Cycle Stage/ Category ^a	Subcategories	Occupational Exposure Scenario	Population	Exposure Route and Duration	Exposure Level	Risk Estimates for No PPE			Risk Estimates with PPE		
						Acute Non-cancer (benchmark MOE = 300)	Chronic Non-cancer (benchmark MOE = 30)	Cancer (benchmark = 10 ⁻⁴)	Acute Non-cancer (benchmark MOE = 300)	Chronic Non-cancer (benchmark MOE = 30)	Cancer (benchmark = 10 ⁻⁴)
					High-End	1,472	69.2	1.46E-03	7,358 (PF 5)	346 (PF 5)	7.29E-05 (PF 20)
			ONU ^c	Inhalation 8-hr TWA	Central Tendency	151,467	7,100	7.17E-07	N/A	N/A	N/A
					High-End	151,467	7,100	9.25E-07	N/A	N/A	N/A
Industrial Use, Potential Commercial Use/ Other Uses	Printing and printing compositions	Section 2.4.1.1.10 and 4.2 – Use of Printing Inks (3D)	Worker	Inhalation 8-hr TWA	Central Tendency	2,922	137	3.71E-05	29,218 (APF 10)	1,370 (APF 10)	3.71E-06 (APF 10)
					High-End	2,922	137	4.79E-05	29,218 (APF 10)	1,370 (APF 10)	4.79E-06 (APF 10)
				Dermal	Central Tendency	4.42	0.21	0.38	88.3 (PF 20)	4.15 (PF 20)	1.88E-02 (PF 20)
					High-End	1.47	6.92E-02	1.46	29.4 (PF 20)	1.38 (PF 20)	7.29E-02 (PF 20)
			ONU ^b	Inhalation 8-hr TWA	Central Tendency	2,922	137	3.71E-05	N/A	N/A	N/A
					High-End	--	--	--	N/A	N/A	N/A
Industrial Use, Potential Commercial Use/ Other Uses	Dry film lubricant	Section 2.4.1.1.11 and 4.2 – Dry Film Lubricant	Worker	Inhalation 8-hr TWA	Central Tendency	607	127	4.01E-05	6,068 (APF 10)	1,270 (APF 10)	4.01E-06 (APF 10)
					High-End	177	37.1	1.77E-04	1,773 (APF 10)	371 (APF 10)	1.77E-05 (APF 10)
				Dermal	Central Tendency	4.83	1.01	7.72E-02	96.6 (PF 20)	20.3 (PF 20)	3.86E-03 (PF 20)
					High-End	1.61	0.34	0.30	32.2 (PF 20)	6.76 (PF 20)	1.49E-02 (PF 20)
			ONU ^b	Inhalation 8-hr TWA	Central Tendency	607	127	4.01E-05	N/A	N/A	N/A
					High-End	--	--	--	N/A	N/A	N/A

Life Cycle Stage/ Category ^a	Subcategories	Occupational Exposure Scenario	Population	Exposure Route and Duration	Exposure Level	Risk Estimates for No PPE			Risk Estimates with PPE		
						Acute Non-cancer (benchmark MOE = 300)	Chronic Non-cancer (benchmark MOE = 30)	Cancer (benchmark = 10 ⁻⁴)	Acute Non-cancer (benchmark MOE = 300)	Chronic Non-cancer (benchmark MOE = 30)	Cancer (benchmark = 10 ⁻⁴)
Disposal/ Disposal	Wastewater	Section 2.4.1.1.12 and 4.2 – Disposal	Worker	Inhalation 8-hr TWA	Central Tendency	152	7.11	6.80E-04	1,517 (APF 10)	71.1 (APF 10)	6.80E-05 (APF 10)
					High-End	42.8	2.00	2.54E-03	428 (APF 10)	100 (APF 50)	5.08E-05 (APF 50)
	Dermal			Central Tendency	4.83	0.23	0.34	96.6 (PF 20)	4.54 (PF 20)	1.72E-02 (PF 20)	
				High-End	1.61	7.57E-02	1.33	32.2 (PF 20)	1.51 (PF 20)	6.67E-02 (PF 20)	
	Incineration		ONU ^b	Inhalation 8-hr TWA	Central Tendency	152	7.11	6.80E-04	N/A	N/A	N/A
					High-End	--	--	--	N/A	N/A	N/A

^a Details on whether modelling or monitoring performed, representativeness and confidence of data for various occupational exposure life cycle categories are shown in Table 4-13.

^b ONU-specific exposure estimates were not reasonably available. Risk estimates for ONUs are based on central tendency values for workers without PPE.

^c Based on ONU-specific exposure estimates. N/A = Not Applicable; ONUs are assumed to not wear respiratory protection.

4.6.2.2 Summary of Risk for Consumer Users and Bystanders

Table 4-24. summarizes risk estimates for inhalation and dermal exposures for all consumer exposure scenarios. Risk estimates that indicate potential risk (*i.e.* MOEs less than the benchmark MOE or cancer risks greater than the cancer risk benchmark) are highlighted by bolding the number and shading the cell in gray. The consumer exposure assessment and risk characterization are described in more detail in Sections 2.4.3 and 4.2.3, respectively.

Table 4-24. Summary of Human Health Risks from Consumer Exposures

Category	Assessed Condition of Use	Scenario Descriptor	Receptor	Dermal Risk Estimates		Inhalation Risk Estimates	
				Acute MOE <i>Benchmark = 300</i>	Chronic Cancer Risk ^a <i>Benchmark = 1E-06</i>	Acute MOE HEC = 284 mg/m ³ <i>Benchmark = 300</i>	Chronic Cancer Risk ^a <i>Benchmark = 1E-06</i>
Paints and Coatings	Paint and Floor Lacquer	High-Intensity User	Adult (≥21 years)	1.8E+04	NA	1.4E+04	NA
		High-Intensity User	Child (16-20 years)	1.9E+04	NA	NA	NA
		High-Intensity User	Child (11-15 years)	1.7E+04	NA	NA	NA
		High-Intensity User	Bystander	NA	NA	3.8E+04	NA
Cleaning and Furniture Care Products	Surface Cleaner	High-Intensity User	Adult (≥21 years)	4.6E+06	6.7E-07	5.7E+04	1.0E-06
		Moderate-Intensity User	Adult (≥21 years)	NA	2.8E-07	NA	5.6E-07
		High-Intensity User	Child (16-20 years)	4.9E+06	NA	NA	NA
		High-Intensity User	Child (11-15 years)	4.5E+06	NA	NA	NA
		High-Intensity User	Bystander	NA	NA	3.0E+05	NA
Laundry and Dishwashing Products	Dish Soap	High-Intensity User	Adult (≥21 years)	1.2E+07	3.2E-08	9.3E+03	7.1E-07
		Moderate-Intensity User	Adult (≥21 years)	NA	1.3E-08	NA	3.3E-07
		High-Intensity User	Child (16-20 years)	1.2E+07	NA	NA	NA
		High-Intensity User	Child (11-15 years)	1.1E+07	NA	NA	NA
		High-Intensity User	Bystander	NA	NA	5.2E+04	NA

Category	Assessed Condition of Use	Scenario Descriptor	Receptor	Dermal Risk Estimates		Inhalation Risk Estimates	
				Acute MOE <i>Benchmark = 300</i>	Chronic Cancer Risk ^a <i>Benchmark = 1E-06</i>	Acute MOE HEC = 284 mg/m ³ <i>Benchmark = 300</i>	Chronic Cancer Risk ^a <i>Benchmark = 1E-06</i>
	Dishwasher Detergent	High-Intensity User	Adult (≥21 years)	1.1E+07	1.4E-07	4.1E+05	7.1E-08
		Moderate-Intensity User	Adult (≥21 years)	NA	1.2E-07	NA	2.9E-08
		High-Intensity User	Child (16-20 years)	1.2E+07	NA	NA	NA
		High-Intensity User	Child (11-15 years)	1.1E+07	NA	NA	NA
		High-Intensity User	Bystander	NA	NA	2.3E+06	NA
	Laundry Detergent	High-Intensity User	Adult (≥21 years)	7.4E+07	1.8E-08	1.9E+05	1.3E-07
		Moderate-Intensity User	Adult (≥21 years)	NA	7.4E-09	NA	7.8E-08
		High-Intensity User	Child (16-20 years)	7.9E+07	NA	NA	NA
		High-Intensity User	Child (11-15 years)	7.2E+07	NA	NA	NA
		High-Intensity User	Bystander	NA	NA	1.1E+06	NA
Arts, Crafts, and Hobby Materials	Textile Dye	High-Intensity User	Adult (≥21 years)	5.6E+07	NA	3.4E+05	NA
		High-Intensity User	Child (16-20 years)	5.9E+07	NA	NA	NA
		High-Intensity User	Child (11-15 years)	5.4E+07	NA	NA	NA
		High-Intensity User	Bystander	NA	NA	1.9E+06	NA

Category	Assessed Condition of Use	Scenario Descriptor	Receptor	Dermal Risk Estimates		Inhalation Risk Estimates	
				Acute MOE <i>Benchmark = 300</i>	Chronic Cancer Risk ^a <i>Benchmark = 1E-06</i>	Acute MOE HEC = 284 mg/m ³ <i>Benchmark = 300</i>	Chronic Cancer Risk ^a <i>Benchmark = 1E-06</i>
Other Consumer Uses	Spray Polyurethane Foam	Basement	Adult (≥21 years)	3.5E+04	NA	317	NA
			Bystander	NA	NA	384	NA
			Child (16-20 years)	3.7E+04	NA	NA	NA
			Child (11-15 years)	3.3E+04	NA	NA	NA
		Attic	Adult (≥21 years)	3.5E+04	NA	1.5E+03	NA
			Bystander	NA	NA	4.0E+03	NA
			Child (16-20 years)	3.7E+04	NA	NA	NA
			Child (11-15 years)	3.3E+04	NA	NA	NA
		Garage	Adult (≥21 years)	3.5E+04	NA	1.7E+03	NA
			Bystander	NA	NA	2.5E+03	NA
			Child (16-20 years)	3.7E+04	NA	NA	NA
			Child (11-15 years)	3.3E+04	NA	NA	NA
	Antifreeze	High-Intensity User	Adult (≥21 years)	6.9E+04	NA	1.8E+04	NA
		High-Intensity User	Child (16-20 years)	7.4E+04	NA	NA	NA
		High-Intensity User	Child (11-15 years)	6.8E+04	NA	NA	NA
		High-Intensity User	Bystander	NA	NA	7.2E+04	NA

Category	Assessed Condition of Use	Scenario Descriptor	Receptor	Dermal Risk Estimates		Inhalation Risk Estimates	
				Acute MOE <i>Benchmark = 300</i>	Chronic Cancer Risk ^a <i>Benchmark = 1E-06</i>	Acute MOE HEC = 284 mg/m ³ <i>Benchmark = 300</i>	Chronic Cancer Risk ^a <i>Benchmark = 1E-06</i>
NA= Not Applicable							
Bold: Cancer risk exceeds the benchmark of 1×10^{-6}							
^a Risks from chronic exposure were evaluated only for consumer products that are used regularly							

4.6.2.3 Summary of Risk for the General Population

EPA considered reasonably available information to characterize general population exposures and risk.

Table 4-25. summarizes potential risks from acute exposures from incidental ingestion of or dermal contact with 1,4-dioxane in surface water. Calculated MOE values below the benchmark MOE (300) would indicate a potential safety concern. None of the surface water concentration estimates indicate risks from acute exposures to the general population. EPA did not identify releases to surface waters from OESs that are not included in this table (including for import/repackaging, recycling, film cement, printing inks, dry film lubricants, and laboratory chemical use).

Table 4-25. Summary of Human Health Risks from Incidental Exposure to 1,4-Dioxane in Surface Waters

OES	Facility/Data Source	Acute MOE Oral Exposure <i>Benchmark= 300</i>	Acute MOE Dermal Exposure <i>Benchmark = 300</i>
Site-Specific Modeling – Estimated Surface Water Concentrations			
Manufacturing	BASF	6.8E+04	9.9E+05
Industrial Uses	Ineos Oxide	3.0E+04	4.4E+05
Industrial Uses	Microdyn-Nadir Corp	9.1E+05	1.3E+07
Industrial Uses	St Charles Operations (Taft/Star) Union Carbide Corp	6.0E+08	8.6E+09
Industrial Uses	SUEZ Water Technologies & Solutions	1.3E+03	1.9E+04
Industrial Uses	The Dow Chemical Co - Louisiana Operations	7.6E+08	1.1E+10
Industrial Uses	Union Carbide Corp Institute Facility	2.0E+06	2.9E+07
Industrial Uses	Union Carbide Corp Seadrift Plant	2.7E+05	4.0E+06
Industrial Uses	BASF Corp	2.0E+07	2.8E+08
Industrial Uses	Cherokee Pharmaceuticals LLC	2.5E+09	3.6E+10
Industrial Uses	DAK Americas LLC	2.4E+05	3.4E+06
Industrial Uses	Institute Plant	1.3E+06	1.8E+07
Industrial Uses	Kodak Park Division	3.9E+07	5.6E+08
Industrial Uses	Pharmacia & Upjohn (Former)	2.4E+08	3.5E+09
Industrial Uses	Philips Electronics Plant	6.6E+07	9.6E+08
Industrial Uses	Sanderson Gulch Drainage Improvements	6.6E+08	9.6E+09
Open System Functional Fluids	Ametek Inc. U.S. Gauge Div	1.7E+07	2.4E+08
Open System Functional Fluids	Lake Reg Med/Collegeville	5.1E+08	7.3E+09
Open System Functional Fluids	Pall Life Sciences Inc	1.5E+08	2.2E+09

OES	Facility/Data Source	Acute MOE Oral Exposure Benchmark= 300	Acute MOE Dermal Exposure Benchmark = 300
Open System Functional Fluids	Modeled Release Estimates	2.3E+06	3.4E+07
Spray Foam Application	Modeled Release Estimates	2.5E+07	3.6E+08
Disposal	Beacon Heights Landfill	1.3E+07	1.8E+08
Disposal	Ingersoll Rand/Torrington Fac	1.9E+06	2.8E+07
High-End of Submitted Monitoring Data – Measured Surface Water Concentrations			
---	STORET	6.6E+04	9.6E+05
---	Sun et al. 2016	4.7E+03	6.8E+04
---	North Carolina Department of Environmental Quality	6.4E+03	9.3E+04
---	Minnesota Department of Environmental Quality	1.5E+06	2.2E+07

5 RISK DETERMINATION

5.1 Overview

In each risk evaluation under TSCA Section 6(b), EPA determines whether a chemical substance presents an unreasonable risk of injury to health or the environment, under the conditions of use. These determinations do not consider costs or other non-risk factors. In making these determinations, EPA considers relevant risk-related factors, including, but not limited to: the effects of the chemical substance on health and human exposure to such substance under the conditions of use (including cancer and non-cancer risks); the effects of the chemical substance on the environment and environmental exposure under the conditions of use; the population exposed (including any potentially exposed or susceptible subpopulations (PESS)); the severity of hazard (including the nature of the hazard, the irreversibility of the hazard); and uncertainties. EPA also takes into consideration the Agency's confidence in the data used in the risk estimate. This includes an evaluation of the strengths, limitations, and uncertainties associated with the information used to inform the risk estimate and the risk characterization. This approach is in keeping with the Agency's final rule, *Procedures for Chemical Risk Evaluation Under the Amended Toxic Substances Control Act* (82 FR 33726).¹⁶

This section describes the final unreasonable risk determinations of the conditions of use in the scope of the risk evaluation. The final unreasonable risk determinations are based on the risk estimates in the final risk evaluation, which may differ from the risk estimates in the draft risk

¹⁶ This risk determination is being issued under TSCA section 6(b) and the terms used, such as unreasonable risk, and the considerations discussed are specific to TSCA. Other statutes have different authorities and mandates and may involve risk considerations other than those discussed here.

evaluation due to peer review and public comments. Therefore, the final unreasonable risk determinations of some conditions of use may differ from those in the draft risk evaluation.

5.1.1 Human Health

EPA's risk evaluation identified cancer and non-cancer adverse effects from acute and chronic inhalation and dermal exposure to 1,4-dioxane. The health risk estimates for all conditions of use are in 4.6.2 (Table 4-23. and Table 4-24.).

EPA generally identified as Potentially Exposed or Susceptible Subpopulations: workers and ONUs, including men and women of reproductive age, and adolescents; and consumers and bystanders, including men, women, and children of any age.

EPA evaluated exposures to workers, ONUs, consumers, and bystanders using reasonably available monitoring and modeling data of inhalation and dermal exposures, as applicable. For example, EPA assumed that ONUs and bystanders do not have direct contact with 1,4-dioxane; therefore non-cancer effects and cancer from dermal exposures to 1,4-dioxane are not expected. The description of the data used for human health exposure is in Section 2.4. Uncertainties in the analysis are discussed in Section 4.3 and considered in the unreasonable risk determination for each condition of use presented below, including the fact that the dermal model used does not address variability in exposure duration and frequency.

As discussed in Section 1.4.2, EPA did not assess exposures from ambient air, drinking water, and sediment pathways because they fall under the jurisdiction of other environmental statutes administered by EPA, i.e., CAA, SDWA, RCRA, and CERCLA. However, EPA has not developed recommended ambient water quality criteria for the protection of human health for 1,4-dioxane. Exposure to the general population via surface water can occur through recreational activities (e.g., swimming) and through consuming fish. EPA considered reasonably available information and environmental fate properties to characterize general population exposure through the surface water pathway. EPA evaluated the human health risks of potential acute and chronic incidental exposures via oral and dermal routes from recreational swimming in bodies of water that receive discharges from the industrial and commercial conditions of use of 1,4-dioxane and determined that these risks are not unreasonable. In addition, because 1,4-dioxane has low bioaccumulation potential, EPA has determined that the human health risks from fish ingestion are not unreasonable.

5.1.1.1 Non-Cancer Risk Estimates

The risk estimates of non-cancer effects (MOEs) refers to adverse health effects associated with health endpoints other than cancer, including to the body's organ systems, such as reproductive/developmental effects, cardiac and lung effects, and kidney and liver effects. The MOE is the point of departure (POD) (an approximation of the no-observed adverse effect level (NOAEL) or benchmark dose level (BMDL)) for a specific health endpoint divided by the exposure concentration for the specific scenario of concern. Section 3.2.6 presents the PODs for non-cancer effects for 1,4-dioxane and Section 4.2 presents the MOEs for non-cancer effects.

The MOEs are compared to a benchmark MOE. The benchmark MOE accounts for the total uncertainty in a POD, including, as appropriate: (1) the variation in sensitivity among the members of the human population (*i.e.*, intrahuman/intraspecies variability); (2) the uncertainty

in extrapolating animal data to humans (*i.e.*, interspecies variability); (3) the uncertainty in extrapolating from data obtained in a study with less-than-lifetime exposure to lifetime exposure (*i.e.*, extrapolating from subchronic to chronic exposure); and (4) the uncertainty in extrapolating from a lowest observed adverse effect level (LOAEL) rather than from a NOAEL. A lower benchmark MOE (*e.g.*, 30) indicates greater certainty in the data (because fewer of the default UFs relevant to a given POD as described above were applied). A higher benchmark MOE (*e.g.*, 1000) would indicate more uncertainty for specific endpoints and scenarios. However, these are often not the only uncertainties in a risk evaluation. The benchmark MOE for 1,4-dioxane for acute exposures is 100 (accounting for interspecies and intraspecies variability and LOAEL-to-NOAEL uncertainty), while the benchmark MOE for chronic exposures is 30 (accounting for interspecies and intraspecies variability). Additional information regarding the benchmark MOE is in Section 4.2.

5.1.1.2 Cancer Risk Estimates

Cancer risk estimates represent the incremental increase in probability of an individual in an exposed population developing cancer over a lifetime (excess lifetime cancer risk (ELCR)) following exposure to the chemical. Standard cancer benchmarks used by EPA and other regulatory agencies are an increased cancer risk above benchmarks ranging from 1 in 1,000,000 to 1 in 10,000 (*i.e.*, 1×10^{-6} to 1×10^{-4}) depending on the subpopulation exposed.¹⁷ EPA used 1×10^{-6} as the benchmark for the cancer risk to consumers and bystanders from consumer use of cleaning and furniture care products and laundry and dishwashing products. EPA used 1×10^{-4} as the benchmark for the purposes of this unreasonable risk determination for individuals in industrial and commercial work environments. This cancer benchmark is consistent with the 2017 NIOSH chemical carcinogen policy.¹⁸ It is important to note these benchmarks are not bright lines and EPA has discretion to make unreasonable risk determinations based on other benchmarks as appropriate.

5.1.1.3 Determining Unreasonable Risk of Injury to Health

Calculated risk estimates (MOEs or cancer risk estimates) can provide a risk profile by presenting a range of estimates for different health effects for different conditions of use. A calculated MOE that is less than the benchmark MOE supports a determination of unreasonable risk of injury to health, based on non-cancer effects. Similarly, a calculated cancer risk estimate that is greater than the cancer benchmark supports a determination of unreasonable risk of injury to health from cancer. Whether EPA makes a determination of unreasonable risk depends upon other risk-related factors, such as the endpoint under consideration, the reversibility of effect,

¹⁷ As an example, when EPA's Office of Water in 2017 updated the Human Health Benchmarks for Pesticides, the benchmark for a "theoretical upper-bound excess lifetime cancer risk" from pesticides in drinking water was identified as 1 in 1,000,000 to 1 in 10,000 over a lifetime of exposure (EPA. Human Health Benchmarks for Pesticides: Updated 2017 Technical Document (pp.5). (EPA 822-R -17 -001). Washington, DC: U.S. Environmental Protection Agency, Office of Water. January 2017. <https://www.epa.gov/sites/production/files/2015-10/documents/hh-benchmarks-techdoc.pdf>). Similarly, EPA's approach under the Clean Air Act to evaluate residual risk and to develop standards is a two-step approach that "includes a presumptive limit on maximum individual lifetime [cancer] risk (MIR) of approximately 1 in 10 thousand" and consideration of whether emissions standards provide an ample margin of safety to protect public health "in consideration of all health information, including the number of persons at risk levels higher than approximately 1 in 1 million, as well as other relevant factors" (54 FR 38044, 38045, September 14, 1989).

¹⁸ NIOSH Current intelligence bulletin 68: NIOSH chemical carcinogen policy (Whittaker et al. 2016). Note that the NIOSH Recommended Exposure Limit (REL) for 1,4-dioxane was established prior to this guidance.

exposure-related considerations (*e.g.*, duration, magnitude, or frequency of exposure, or population exposed), and the confidence in the information used to inform the hazard and exposure values. A calculated MOE greater than the benchmark MOE or a calculated cancer risk estimate less than the cancer benchmark, alone do not support a determination of unreasonable risk, since EPA may consider other risk-based factors when making an unreasonable risk determination.

When making an unreasonable risk determination based on injury to health of workers (who are one example of PESS), EPA also makes assumptions regarding workplace practices and exposure controls, including engineering controls or use of PPE (see limitations and use practices under Respiratory Protection subheading in Section 2.4.1.1). EPA's decisions for unreasonable risk to workers are based on high-end exposure estimates, in order to capture not only exposures for PESS but also to account for the uncertainties related to whether or not workers are using PPE. However, EPA does not assume that ONUs use PPE. Once EPA has applied the appropriate PPE assumption for a particular condition of use in each unreasonable risk determination, in those instances when EPA assumes PPE is used, EPA also assumes that the PPE is used in a manner that achieves the stated APF or PF.

In the 1,4-dioxane risk characterization, liver toxicity was used as the most sensitive endpoint for non-cancer adverse effects from acute inhalation and dermal exposures. For chronic inhalation and dermal exposures to workers and ONUs, olfactory epithelium effects were used. However, additional risks associated with other adverse respiratory and liver effects were identified for chronic inhalation and dermal exposures. Determining unreasonable risk by using olfactory epithelium effects for workers and ONUs will also include the unreasonable risk from other endpoints resulting from chronic inhalation and dermal exposures.

The 1,4-dioxane unreasonable risk determination considers the uncertainties associated with the reasonably available information to justify the linear cancer dose-response model when compared to other available models. The cancer analysis is described in Section 3.2.4. EPA considered cancer risk estimates from chronic inhalation or dermal exposures in the unreasonable risk determination.

When making a determination of unreasonable risk, the Agency has a higher degree of confidence where uncertainty is low. Similarly, EPA has high confidence in the hazard and exposure characterizations when, for example, the basis for characterizations is measured or based on monitoring data or a robust model and the hazards identified for risk estimation are relevant for conditions of use. Where EPA has made assumptions in the scientific evaluation, whether or not those assumptions are protective is also a consideration. Additionally, EPA considers the central tendency and high-end exposure levels when determining the unreasonable risk. High-end risk estimates (*e.g.*, 95th percentile) are generally intended to cover individuals or sub-populations with greater exposure (*i.e.*, PESS) and central tendency risk estimates are generally estimates of average or typical exposure.

EPA may make a determination of no unreasonable risk for conditions of use where the substance's hazard and exposure potential, or where the risk-related factors described previously, lead the Agency to determine that the risks are not unreasonable.

5.1.2 Environment

EPA used environmental fate parameters, physical-chemical properties, modelling, and monitoring data to assess ambient water exposure to aquatic organisms. Further analysis was not conducted for biosolids, soil and sediment pathways based on a qualitative assessment of the physical-chemical properties and fate of 1,4-dioxane in the environment. However, a quantitative comparison of hazards and exposures for aquatic organisms in surface water was evaluated. EPA calculated a risk quotient (RQ) to compare environmental concentrations against an effect level in surface water for the most biological relevant species. Exposures of 1,4-dioxane to aquatic organisms from surface water are assessed and presented in this risk evaluation and used to inform the risk determination. These analyses are described in Sections 2.1, 2.3, and 4.1.

5.1.2.1 Determining Unreasonable Risk to Injury to the Environment

An RQ equal to 1 indicates that the exposures are the same as the concentration that causes effects. An RQ less than 1, when the exposure is less than the effect concentration, supports a determination that there is no unreasonable risk of injury to the environment. An RQ greater than 1, when the exposure is greater than the effect concentration supports a determination that there is unreasonable risk of injury to the environment. Consistent with EPA's human health evaluations, other risk-based factors may be considered (*e.g.*, confidence in the hazard and exposure characterization, duration, magnitude, uncertainty) for purposes of making an unreasonable risk determination.

EPA considered the effects on the aquatic, sediment dwelling and terrestrial organisms. EPA provides estimates for environmental risk in Section 4.1 and Table 4-2..

5.2 Detailed Unreasonable Risk Determinations by Condition of Use

Table 5-1. Categories and Subcategories of Conditions of Use Included in the Scope of the Risk Evaluation

Life Cycle Stage	Category ^a	Subcategory ^b	Unreasonable Risk	Detailed Risk Determination
Manufacture	Domestic manufacture	Domestic manufacture	Yes	Sections 5.2.1.1 and 5.2.2.
	Import/repackaging	Import/repackaging/bottle and drum	Yes	Sections 5.2.1.2 and 5.2.2.
Processing	Repackaging	Repackaging/bottle and drum	Yes	Sections 5.2.1.3 and 5.2.2.
	Recycling	Recycling	Yes	Sections 5.2.1.4 and 5.2.2.
	Non-incorporative	Basic organic chemical manufacturing (process solvent)	Yes	Sections 5.2.1.5 and 5.2.2.
	Processing as a reactant ^c	Polymerization catalyst	Yes	Sections 5.2.1.6 and 5.2.2.

Table 5-1. Categories and Subcategories of Conditions of Use Included in the Scope of the Risk Evaluation

Life Cycle Stage	Category ^a	Subcategory ^b	Unreasonable Risk	Detailed Risk Determination
Distribution in commerce	Distribution	Distribution	No	Sections 5.2.1.7 and 5.2.2.
Industrial/commercial use	Intermediate ^c	Agricultural chemical	Yes	Sections 5.2.1.8 and 5.2.2.
		Plasticizer		
		Catalysts and reagents for anhydrous acid reactions, brominations, and sulfonations		
	Processing aids, not otherwise listed ^c	Wood pulping	Yes	Sections 5.2.1.9 and 5.2.2.
		Extraction of animal and vegetable oils		
		Wetting and dispersing agent in textile processing		
		Polymerization catalyst		
		Purification of process intermediates		
		Etching of fluoropolymers		
	Functional fluids, open system	Metalworking fluid	No	Sections 5.2.1.10 and 5.2.2.
Cutting and tapping fluid				
Polyalkylene glycol fluid				

Table 5-1. Categories and Subcategories of Conditions of Use Included in the Scope of the Risk Evaluation

Life Cycle Stage	Category ^a	Subcategory ^b	Unreasonable Risk	Detailed Risk Determination
Industrial/ commercial use	Laboratory chemicals	Chemical reagent	Yes	Sections 5.2.1.11 and 5.2.2.
		Reference material		
		Spectroscopic and photometric measurement		
		Liquid scintillation counting medium		
		Stable reaction medium		
		Cryoscopic solvent for molecular mass determinations		
		Preparation of histological sections for microscopic examination		
Industrial/ commercial use	Adhesives and sealants	Film cement	Yes	Sections 5.2.1.12 and 5.2.2.
	Other uses	Spray polyurethane foam	No	Sections 5.2.1.13 and 5.2.2.
		Printing and printing compositions	Yes	Sections 5.2.1.14 and 5.2.2.
		Dry film lubricant	Yes	Sections 5.2.1.15 and 5.2.2.
Consumer users	Arts, crafts, and hobby materials	Textile dye	No	Sections 5.2.1.16 and 5.2.2.
	Automotive care products	Antifreeze	No	Sections 5.2.1.17 and 5.2.2.
	Cleaning and furniture care products	Surface cleaner	No	Sections 5.2.1.18 and 5.2.2.
	Laundry and dishwashing products	Dish soap	No	Sections 5.2.1.19 and 5.2.2.
		Dishwasher detergent	No	Sections 5.2.1.20 and 5.2.2.
		Laundry detergent	No	Sections 5.2.1.21 and 5.2.2.
	Paints and coatings	Paint and floor lacquer	No	Sections 5.2.1.22 and 5.2.2.
Other consumer uses	Spray polyurethane foam	No	Sections 5.2.1.23 and 5.2.2.	

Table 5-1. Categories and Subcategories of Conditions of Use Included in the Scope of the Risk Evaluation

Life Cycle Stage	Category ^a	Subcategory ^b	Unreasonable Risk	Detailed Risk Determination
Disposal	Disposal	Industrial pre-treatment	Yes	Sections 5.2.1.24 and 5.2.2.
		Industrial wastewater treatment		
		Publicly owned treatment works (POTW)		
		Underground injection		
		Municipal landfill		
		Hazardous landfill		
		Other land disposal		
		Municipal waste incinerator		
		Hazardous waste incinerator		
		Off-site waste transfer		

^a These categories of conditions of use appear in the Life Cycle Diagram, reflect CDR codes, and broadly represent additional information regarding all conditions of use of 1,4-dioxane.

^b These subcategories reflect more specific information regarding the conditions of use of 1,4-dioxane.

^c While use of 1,4-dioxane as a process solvent and as an intermediate in the manufacture of pharmaceuticals was included in the problem formulation and draft risk evaluation, upon further analysis of the details of these processes, EPA has determined that these uses fall outside TSCA’s definition of “chemical substance.” Under TSCA § 3(2)(B)(vi), the definition of “chemical substance” does not include any food, food additive, drug, cosmetic, or device (as such terms are defined in section 201 of the Federal Food, Drug, and Cosmetic Act) when manufactured, processed, or distributed in commerce for use as a food, food additive, drug, cosmetic, or device. EPA has concluded that 1,4-dioxane use as a process solvent and an intermediate during pharmaceutical manufacturing falls outside TSCA’s definition of a chemical substance when used for these purposes. As a result, the use of 1,4-dioxane as a process solvent and an intermediate during pharmaceutical manufacturing are not included in the scope of this risk evaluation.

5.2.1 Human Health

5.2.1.1 Manufacture – Domestic Manufacture – Domestic Manufacture

Section 6(b)(4)(A) unreasonable risk determination for domestic manufacture of 1,4-dioxane: Presents an unreasonable risk of injury to health (workers and ONUs).

For workers, EPA found that there was an unreasonable risk of non-cancer effects (liver toxicity and olfactory epithelium effects) from acute and chronic dermal exposures and cancer from chronic dermal exposures at the central tendency and high-end, even when

assuming use of PPE. For occupational non-users (ONUs), EPA found that there was an unreasonable risk of cancer from chronic inhalation exposures at the central tendency.

EPA's determination that the domestic manufacturing of 1,4-dioxane presents an unreasonable risk is based on the comparison of the risk estimates for non-cancer effects and cancer to the benchmarks (Table 4-23.). As explained in Section 5.1., EPA also considered the health effects of 1,4-dioxane, the exposures from the condition of use, and the uncertainties in the analysis (Section 4.3), including uncertainties related to the exposures for ONUs:

- For workers, when assuming the use of gloves with PF of 20, the risk estimates for acute and chronic non-cancer effects and cancer from dermal exposures at the high end and central tendency support an unreasonable risk determination.
- For workers, when assuming the use of respirators with APF of 50, the risk estimates of non-cancer effects from acute and chronic inhalation exposures at the high-end and the risk estimates for cancer from chronic inhalation exposures at the high-end do not support an unreasonable risk determination. Respirators with APF of 50 and gloves with PF of 20 are the maximum assumed personal protective equipment for workers at manufacturing facilities, based on process and work activity descriptions at a manufacturing facility.
- The inhalation exposure was assessed using full-shift personal breathing zone (PBZ) monitoring data reflective of current operations at one manufacturing facility, and there is uncertainty of how well the data represents activities at other manufacturing facilities.
- The dermal exposure was assessed using modeled data.
- Based on EPA's analysis, the data for worker and ONU inhalation exposure could not be distinguished; however, ONU inhalation exposures are assumed to be lower than inhalation exposures for workers directly handling the chemical substance. To account for this uncertainty, EPA considered the workers' central tendency estimate of inhalation exposures when determining ONU risk.

In summary, the risk estimates, the health effects of 1,4-dioxane, the exposures, and consideration of uncertainties support EPA's determination that there is an unreasonable risk of injury to health (workers and ONUs) from the domestic manufacture of 1,4-dioxane.

5.2.1.2 Manufacture – Import – Import/Repackaging (Bottle and Drum)

Section 6(b)(4)(A) unreasonable risk determination for import/repackaging of 1,4-dioxane (bottle and drum): Presents an unreasonable risk of injury to health (workers and ONUs).

For workers, EPA found that there was an unreasonable risk of non-cancer effects (liver toxicity and olfactory epithelium effects) from acute and chronic dermal exposures and cancer from chronic dermal exposures, even when assuming use of PPE. For occupational non-users (ONUs), EPA found that there was an unreasonable risk of non-cancer effects (liver toxicity) from acute inhalation exposures and cancer from chronic inhalation exposures at the central tendency.

EPA's determination that the import/repackaging of 1,4-dioxane presents an unreasonable risk is based on the comparison of the risk estimates for non-cancer effects and cancer to the

benchmarks (Table 4-23.). As explained in Section 5.1., EPA also considered the health effects of 1,4-dioxane, the exposures from the condition of use, and the uncertainties in the analysis (Section 4.3), including uncertainties related to the exposures for ONUs:

- For workers, when assuming the use of gloves with PF of 20, the risk estimates for non-cancer effects and cancer from dermal exposures support an unreasonable risk determination.
- For workers, when assuming the use of respirators with APF of 50, the risk estimates of non-cancer effects from acute and chronic inhalation exposures at the high-end and the risk estimates for cancer from chronic inhalation exposures at the high-end do not support an unreasonable risk determination. Respirators with APF of 50 and gloves with PF of 20 are the maximum assumed personal protective equipment for workers at import/repackaging facilities, based on professional judgment regarding practices at import/repackaging facilities.
- Inhalation and dermal exposures were assessed using modeled data.
- Based on EPA's analysis, the data for worker and ONU inhalation exposure could not be distinguished; however, ONU inhalation exposures are assumed to be lower than inhalation exposures for workers directly handling the chemical substance. To account for this uncertainty, EPA considered the workers' central tendency estimate of inhalation exposures when determining ONU risk.

In summary, the risk estimates, the health effects of 1,4-dioxane, the exposures, and consideration of uncertainties support EPA's determination that there is an unreasonable risk of injury to health (workers and ONUs) from the import/repackaging of 1,4-dioxane.

5.2.1.3 Processing – Repackaging – Repackaging (Bottle and Drum)

Section 6(b)(4)(A) unreasonable risk determination for repackaging (bottle and drum) of 1,4-dioxane: Presents an unreasonable risk of injury to health (workers and ONUs).

For workers, EPA found that there was an unreasonable risk of non-cancer effects (liver toxicity and olfactory epithelium effects) from acute and chronic dermal exposures at the central tendency and high-end and cancer from chronic inhalation exposures at the high-end and dermal exposures at the central tendency and high-end, even when assuming use of PPE. For ONUs, EPA found that there was an unreasonable risk of non-cancer effects (liver toxicity and olfactory epithelium effects) from acute and chronic inhalation exposures and cancer from chronic inhalation exposures at the central tendency.

EPA's determination that the repackaging of 1,4-dioxane presents an unreasonable risk based on the comparison of the risk estimates for non-cancer effects and cancer to the benchmarks (Table 4-23.). As explained in Section 5.1., EPA also considered the health effects of 1,4-dioxane, the exposures from the condition of use, and the uncertainties in the analysis (Section 4.3), including uncertainties related to the exposures for ONUs:

- For workers, when assuming the use of gloves with PF of 20, the risk estimates for non-cancer effects from acute and chronic dermal exposures and cancer from chronic dermal exposures at the central tendency and high-end support an unreasonable risk

determination. Similarly, for workers, even when assuming the use of respirators with APF of 50, the risk estimates for cancer from chronic inhalation exposures at the high-end support an unreasonable risk determination.

- For workers, when assuming use of respirators with APF of 50, the risk estimates of non-cancer effects from acute and chronic inhalation exposures at the high-end do not support an unreasonable risk determination. Respirators with APF of 50 and gloves with PF of 20 are the maximum assumed personal protective equipment for workers at repackaging facilities, based on professional judgment regarding practices at repackaging facilities.
- Inhalation exposures were assessed based on exposure data from the 2002 EU Risk Assessment for 1,4-dioxane. The data sets used were limited and mostly lacked specific descriptions of worker tasks, exposure sources, and possible engineering controls. The values were reported to be full-shift values, which EPA assumed to be 8-hour time-weighted average (TWA) values.
- Dermal exposures were assessed using modeled data.
- Based on EPA's analysis, the data for worker and ONU inhalation exposure could not be distinguished; however, ONU inhalation exposures are assumed to be lower than inhalation exposures for workers directly handling the chemical substance. To account for this uncertainty, EPA considered the workers' central tendency estimate of inhalation exposures when determining ONU risk.

In summary, the risk estimates, the health effects of 1,4-dioxane, the exposures, and consideration of uncertainties support EPA's determination that there is an unreasonable risk of injury to health (workers and ONUs) from the repackaging of 1,4-dioxane.

5.2.1.4 Processing – Recycling

Section 6(b)(4)(A) unreasonable risk determination for the recycling of 1,4-dioxane: Presents an unreasonable risk of injury to health (workers and ONUs).

For workers, EPA identified an unreasonable risk of non-cancer effects (liver toxicity and olfactory epithelium effects) from acute and chronic dermal exposures at the central tendency and high-end and cancer from chronic inhalation exposures at the high-end and dermal exposures at the central tendency and high-end, even when assuming use of PPE. For ONUs, EPA identified an unreasonable risk of non-cancer effects (liver toxicity and olfactory epithelium effects) from acute and chronic inhalation exposures and cancer from chronic inhalation exposures at the central tendency.

EPA's determination that the recycling of 1,4-dioxane presents an unreasonable risk based on the comparison of the risk estimates for non-cancer effects and cancer to the benchmarks (Table 4-23.). As explained in Section 5.1., EPA also considered the health effects of 1,4-dioxane, the exposures from the condition of use, and the uncertainties in the analysis (Section 4.3), including uncertainties related to the exposures for ONUs:

- For workers, when assuming the use of gloves with PF of 20, the risk estimates for non-cancer effects from acute and chronic dermal exposures and cancer from chronic dermal exposures at the central tendency and high-end support an unreasonable risk

determination. Similarly, for workers, even when assuming the use of respirators with APF of 50, the risk estimates for cancer from chronic inhalation exposures at the high-end support an unreasonable risk determination.

- For workers, when assuming use of respirators with APF of 50, the risk estimates of non-cancer effects from acute and chronic inhalation exposures at the high-end do not support an unreasonable risk determination. Respirators with APF of 50 and gloves with PF of 20 are the maximum assumed personal protective equipment for workers at recycling facilities, based on professional judgment regarding practices at a recycling facility.
- Inhalation exposures were assessed based on exposure data from the 2002 EU Risk Assessment for 1,4-dioxane. The data sets used were limited and mostly lacked specific descriptions of worker tasks, exposure sources, and possible engineering controls. The values were reported to be full-shift values, which EPA assumed to be 8-hour time-weighted average (TWA) values.
- Dermal exposures were assessed using modeled data.
- Based on EPA's analysis, the data for worker and ONU inhalation exposure could not be distinguished; however, ONU inhalation exposures are assumed to be lower than inhalation exposures for workers directly handling the chemical substance. To account for this uncertainty, EPA considered the workers' central tendency estimate of inhalation exposures when determining ONU risk.

In summary, the risk estimates, the health effects of 1,4-dioxane, the exposures, and consideration of uncertainties support EPA's determination that there is an unreasonable risk of injury to health (workers and ONUs) from the recycling of 1,4-dioxane.

5.2.1.5 Processing – Non-incorporative – Basic organic chemical manufacturing (process solvent)

Section 6(b)(4)(A) unreasonable risk determination for non-incorporative processing of 1,4-dioxane: Presents an unreasonable risk of injury to health (workers and ONUs).

For workers, EPA found that there was an unreasonable risk of non-cancer effects (liver toxicity and olfactory epithelium effects) from acute and chronic dermal exposures at the central tendency and high-end and cancer from chronic inhalation exposures at the high-end and dermal exposures at the central tendency and high-end, even when assuming use of PPE. For ONUs, EPA found that there was an unreasonable risk of non-cancer effects (liver toxicity and olfactory epithelium effects) from acute and chronic inhalation exposures and cancer from chronic inhalation exposures at the central tendency.

EPA's determination that the non-incorporative processing of 1,4-dioxane presents an unreasonable risk is based on the comparison of the risk estimates for non-cancer effects and cancer to the benchmarks (Table 4-23.). As explained in Section 5.1., EPA also considered the health effects of 1,4-dioxane, the exposures from the condition of use, and the uncertainties in the analysis (Section 4.3), including uncertainties related to the exposures for ONUs:

- For workers, when assuming the use of gloves with PF of 20, the risk estimates for non-cancer effects from acute and chronic dermal exposures and cancer from chronic dermal exposures at the central tendency and high-end support an unreasonable risk

determination. Similarly, for workers, even when assuming the use of respirators with APF of 50, the risk estimates for cancer from chronic inhalation exposures at the high-end support an unreasonable risk determination.

- For workers, when assuming use of respirators with APF of 50, the risk estimates of non-cancer effects from acute and chronic inhalation exposures at the high-end do not support an unreasonable risk determination. Respirators with APF of 50 and gloves with PF of 20 are the maximum assumed personal protective equipment for workers at non-incorporative processing facilities, based on professional judgment regarding practices at non-incorporative processing facilities.
- Inhalation exposures were assessed based on exposure data from the 2002 EU Risk Assessment for 1,4-dioxane. The data sets used were limited and mostly lacked specific descriptions of worker tasks, exposure sources, and possible engineering controls. The values were reported to be full-shift values, which EPA assumed to be 8-hour time-weighted average (TWA) values.
- Dermal exposures were assessed using modeled data.
- Based on EPA's analysis, the data for worker and ONU inhalation exposure could not be distinguished; however, ONU inhalation exposures are assumed to be lower than inhalation exposures for workers directly handling the chemical substance. To account for this uncertainty, EPA considered the workers' central tendency estimate of inhalation exposures when determining ONU risk.

In summary, the risk estimates, the health effects of 1,4-dioxane, the exposures, and consideration of uncertainties support EPA's determination that there is an unreasonable risk of injury to health (workers and ONUs) from the non-incorporative processing of 1,4-dioxane.

5.2.1.6 Processing – Processing as a reactant – Polymerization catalyst

Section 6(b)(4)(A) unreasonable risk determination for the processing as a reactant of 1,4-dioxane: Presents an unreasonable risk of injury to health (workers and ONUs).

For workers, EPA found that there was an unreasonable risk of non-cancer effects (liver toxicity and olfactory epithelium effects) from acute and chronic dermal exposures at the central tendency and high-end and cancer from chronic inhalation exposures at the high-end and dermal exposures at the central tendency and high-end, even when assuming use of PPE. For ONUs, EPA found that there was an unreasonable risk of non-cancer effects (liver toxicity and olfactory epithelium effects) from acute and chronic inhalation exposures and cancer from chronic inhalation exposures at the central tendency.

EPA's determination that the processing as a reactant of 1,4-dioxane presents an unreasonable risk is based on the comparison of the risk estimates for non-cancer effects and cancer to the benchmarks (Table 4-23.). As explained in Section 5.1., EPA also considered the health effects of 1,4-dioxane, the exposures from the condition of use, and the uncertainties in the analysis (Section 4.3), including uncertainties related to the exposures for ONUs:

- For workers, when assuming the use of gloves with PF of 20, the risk estimates for non-cancer effects from acute and chronic dermal exposures and cancer from chronic dermal

exposures at the central tendency and high-end support an unreasonable risk determination. Similarly, for workers, even when assuming the use of respirators with APF of 50, the risk estimates for cancer from chronic inhalation exposures at the high-end support an unreasonable risk determination.

- For workers, when assuming use of respirators with APF of 50, the risk estimates of non-cancer effects from acute and chronic inhalation exposures at the high-end do not support an unreasonable risk determination. Respirators with APF of 50 and gloves with PF of 20 are the maximum assumed personal protective equipment for workers at processing facilities that process 1,4-dioxane as a reactant, based on professional judgment regarding practices at processing facilities that processes 1,4-dioxane as a reactant.
- Inhalation exposures were assessed based on exposure data from the 2002 EU Risk Assessment for 1,4-dioxane. The data sets used were limited and mostly lacked specific descriptions of worker tasks, exposure sources, and possible engineering controls. The values were reported to be full-shift values, which EPA assumed to be 8-hour time-weighted average (TWA) values.
- Dermal exposures were assessed using modeled data.
- Based on EPA's analysis, the data for worker and ONU inhalation exposure could not be distinguished; however, ONU inhalation exposures are assumed to be lower than inhalation exposures for workers directly handling the chemical substance. To account for this uncertainty, EPA considered the workers' central tendency estimate of inhalation exposures when determining ONU risk.

In summary, the risk estimates, the health effects of 1,4-dioxane, the exposures, and consideration of uncertainties support EPA's determination that there is an unreasonable risk of injury to health (workers and ONUs) from the processing as a reactant of 1,4-dioxane.

5.2.1.7 Distribution in Commerce

Section 6(b)(4)(A) unreasonable risk determination for distribution in commerce of 1,4-dioxane:
Does not present an unreasonable risk of injury to health (workers and ONUs).

For the purposes of the unreasonable risk determination, distribution in commerce of 1,4-dioxane is the transportation associated with the moving of 1,4-dioxane in commerce. EPA is assuming that workers and ONUs will not be handling 1,4-dioxane because the loading and unloading activities are associated with other conditions of use and EPA assumes transportation of 1,4-dioxane is in compliance with existing regulations for the transportation of hazardous materials ([49 CFR 172](#)). Emissions are therefore minimal during transportation, so there is limited exposure (with the exception of spills and leaks, which are outside the scope of the risk evaluation). Based on the limited emissions from the transportation of chemicals, EPA determines there is no unreasonable risk of injury to health (workers and ONUs) from the distribution in commerce of 1,4-dioxane.

5.2.1.8 Industrial Use – Intermediate Use – Agricultural chemical intermediate; Plasticizer intermediate; Catalysts and reagents for anhydrous acid reactions, brominations and sulfonations

Section 6(b)(4)(A) unreasonable risk determination for industrial use of 1,4-dioxane as an intermediate: Presents an unreasonable risk of injury to health (workers and ONUs).

For workers, EPA found that there was an unreasonable risk of non-cancer effects (liver toxicity and olfactory epithelium effects) from acute and chronic dermal exposures at the central tendency and high-end and cancer from chronic inhalation exposures at the high-end and dermal exposures at the central tendency and high-end, even when assuming use of PPE. For ONUs, EPA found that there was an unreasonable risk of non-cancer effects (liver toxicity and olfactory epithelium effects) from acute and chronic inhalation exposures and cancer from chronic inhalation exposures at the central tendency.

EPA's determination that the industrial use of 1,4-dioxane as an intermediate presents an unreasonable risk is based on the comparison of the risk estimates for non-cancer effects and cancer to the benchmarks (Table 4-23.). As explained in Section 5.1., EPA also considered the health effects of 1,4-dioxane, the exposures from the condition of use, and the uncertainties in the analysis (Section 4.3), including uncertainties related to the exposures for ONUs:

- For workers, when assuming the use of gloves with PF of 20, the risk estimates for non-cancer effects from acute and chronic dermal exposures and cancer from chronic dermal exposures at the central tendency and high-end support an unreasonable risk determination. Similarly, for workers, even when assuming the use of respirators with APF of 50, the risk estimates for cancer from chronic inhalation exposures at the high-end support an unreasonable risk determination.
- For workers, when assuming use of respirators with APF of 50, the risk estimates of non-cancer effects from acute and chronic inhalation exposures at the high-end do not support an unreasonable risk determination. Respirators with APF of 50 and gloves with PF of 20 are the maximum assumed personal protective equipment for workers at industrial use facilities, based on professional judgment regarding practices at industrial use facilities.
- Inhalation exposures were assessed based on exposure data from the 2002 EU Risk Assessment for 1,4-dioxane. The data sets used were limited and mostly lacked specific descriptions of worker tasks, exposure sources, and possible engineering controls. The values were reported to be full-shift values, which EPA assumed to be 8-hour time-weighted average (TWA) values.
- Dermal exposures were assessed using modeled data.
- Based on EPA's analysis, the data for worker and ONU inhalation exposure could not be distinguished; however, ONU inhalation exposures are assumed to be lower than inhalation exposures for workers directly handling the chemical substance. To account for this uncertainty, EPA considered the workers' central tendency estimate of inhalation exposures when determining ONU risk.

In summary, the risk estimates, the health effects of 1,4-dioxane, the exposures, and consideration of uncertainties support EPA's determination that there is an unreasonable risk of injury to health (workers and ONUs) from the industrial use of 1,4-dioxane as an intermediate.

5.2.1.9 Industrial use – Processing aids, not otherwise listed – Wood pulping; Extraction of animal and vegetable oils; Wetting and dispersing agent in textile processing; Purification of process intermediates; Etching of fluoropolymers

Section 6(b)(4)(A) unreasonable risk determination for the industrial use of 1,4-dioxane as a processing aid: Presents an unreasonable risk of injury to health (workers and ONUs).

For workers, EPA found that there was an unreasonable risk of non-cancer effects (liver toxicity and olfactory epithelium effects) from acute and chronic dermal exposures at the central tendency and high-end and cancer from chronic inhalation exposures at the high-end and dermal exposures at the central tendency and high-end, even when assuming use of PPE. For ONUs, EPA found that there was an unreasonable risk of non-cancer effects (liver toxicity and olfactory epithelium effects) from acute and chronic inhalation exposures and cancer from chronic inhalation exposures at the central tendency.

EPA's determination that the industrial use of 1,4-dioxane as a processing aid presents an unreasonable risk is based on the comparison of the risk estimates for non-cancer effects and cancer to the benchmarks (Table 4-23.). As explained in Section 5.1., EPA also considered the health effects of 1,4-dioxane, the exposures from the condition of use, and the uncertainties in the analysis (Section 4.3), including uncertainties related to the exposures for ONUs:

- For workers, when assuming the use of gloves with PF of 20, the risk estimates for non-cancer effects from acute and chronic dermal exposures and cancer from chronic dermal exposures at the central tendency and high-end support an unreasonable risk determination. Similarly, for workers, even when assuming the use of respirators with APF of 50, the risk estimates for cancer from chronic inhalation exposures at the high-end support an unreasonable risk determination.
- For workers, when assuming use of respirators with APF of 50, the risk estimates of non-cancer effects from acute and chronic inhalation exposures at the high-end do not support an unreasonable risk determination. Respirators with APF of 50 and gloves with PF of 20 are the maximum assumed personal protective equipment for workers at industrial use facilities, based on professional judgment regarding practices at industrial use facilities.
- Inhalation exposures were assessed based on exposure data from the 2002 EU Risk Assessment for 1,4-dioxane. The data sets used were limited and mostly lacked specific descriptions of worker tasks, exposure sources, and possible engineering controls. The values were reported to be full-shift values, which EPA assumed to be 8-hour time-weighted average (TWA) values.
- Dermal exposures were assessed using modeled data.
- Based on EPA's analysis, the data for worker and ONU inhalation exposure could not be distinguished; however, ONU inhalation exposures are assumed to be lower than inhalation exposures for workers directly handling the chemical substance. To account for this uncertainty, EPA considered the workers' central tendency estimate of inhalation exposures when determining ONU risk.

In summary, the risk estimates, the health effects of 1,4-dioxane, the exposures, and consideration of uncertainties support EPA's determination that there is an unreasonable risk of injury to health (workers and ONUs) from the industrial use of 1,4-dioxane as a processing aid.

5.2.1.10 Industrial use – Functional fluids, open system – Metalworking fluid; Cutting and tapping fluid; Polyalkylene glycol fluid

Section 6(b)(4)(A) unreasonable risk determination for the industrial use of 1,4-dioxane as a functional fluid in an open system: Does not present an unreasonable risk of injury to health (workers and ONUs).

For workers, EPA found that there was no unreasonable risk of non-cancer effects (liver toxicity and olfactory epithelium effects) from acute or chronic inhalation or dermal exposures or cancer from chronic inhalation exposures at the central tendency or high-end, even when PPE is not used. In addition, for workers, EPA found that there was no unreasonable risk of cancer from chronic dermal exposures at the central tendency and high-end, when assuming use of PPE. For ONUs, EPA found that there was no unreasonable risk of non-cancer effects or cancer from chronic inhalation exposures at the central tendency and high-end.

EPA's determination that the industrial use of 1,4-dioxane as a functional fluid in an open system does not present an unreasonable risk is based on the comparison of the risk estimates for non-cancer effects and cancer to the benchmarks (Table 4-23.). As explained in Section 5.1., EPA also considered the health effects of 1,4-dioxane, the exposures from the condition of use, and the uncertainties in the analysis (Section 4.3):

- For workers, when assuming use of gloves with PF of 20, the risk estimates for cancer from chronic dermal exposures at the central tendency and the high-end do not support an unreasonable risk determination. Respirators with APF of 50 and gloves with PF of 20 are the maximum assumed personal protective equipment for workers at industrial facilities using functional fluids, based on professional judgment regarding practices at industrial facilities using functional fluids.
- Inhalation exposures were assessed using modeled data along with personal breathing zone (PBZ) samples from a 1997 NIOSH Health Hazard Evaluation (HHE) report on a facility that manufactured axles for trucks and recreational vehicles.
- Dermal exposures were assessed using modeled data.
- ONU inhalation exposures were assessed by combining area measurements from the 1997 NIOSH HHE report into a single sample set with five datapoints.

In summary, the risk estimates, the health effects of 1,4-dioxane, the exposures, and consideration of uncertainties support EPA's determination that there is no unreasonable risk of injury to health (workers and ONUs) from the industrial use of 1,4-dioxane as a functional fluid in an open system.

5.2.1.11 Industrial/commercial use – Laboratory chemicals – Chemical reagent, reference material; Spectroscopic and photometric measurement, liquid scintillation counting medium; Stable reaction medium, cryoscopic solvent for molecular mass determinations; Preparation of histological sections for microscopic examination

Section 6(b)(4)(A) unreasonable risk determination for the industrial use of 1,4-dioxane as a laboratory chemical: Presents an unreasonable risk of injury to health (workers); does not present an unreasonable risk of injury to health (ONUs)

For workers, EPA found that there was an unreasonable risk of non-cancer effects (liver toxicity and olfactory epithelium effects) from acute and chronic dermal exposures and cancer from chronic dermal exposures at the central tendency and high-end, even when assuming the use of PPE. For ONUs, EPA found that there was no unreasonable risk of non-cancer effects or cancer from acute or chronic inhalation exposures at the central tendency.

EPA's determination that the industrial/commercial use of 1,4-dioxane as a laboratory chemical presents an unreasonable risk is based on the comparison of the risk estimates for non-cancer effects and cancer to the benchmarks (Table 4-23.). As explained in Section 5.1., EPA also considered the health effects of 1,4-dioxane, the exposures from the condition of use, and the uncertainties in the analysis (Section 4.3), including uncertainties related to the exposures for ONUs:

- For workers, when assuming the use of gloves with PF of 20, the risk estimates for non-cancer effects from acute and chronic dermal exposures and cancer from chronic dermal exposures at the central tendency and high-end support an unreasonable risk determination.
- For workers, when assuming use of respirators with APF of 50, the risk estimates of non-cancer effects from acute and chronic inhalation exposures and cancer effects from chronic exposures at the high-end do not support an unreasonable risk determination. Respirators with APF of 50 and gloves with PF of 20 are the maximum assumed personal protective equipment for workers at industrial/commercial facilities using laboratory chemicals, based on professional judgment regarding practices at industrial/commercial facilities using laboratory chemicals.
- Inhalation exposures were assessed based on exposure data from the 2002 EU Risk Assessment for 1,4-dioxane. The data sets used were limited and mostly lacked specific descriptions of worker tasks, exposure sources, and possible engineering controls. Most of the datasets were only presented in ranges with key statistics, so EPA was unable to directly calculate final values from the raw data and relied on the statistics provided in the report.
- Dermal exposures were assessed using modeled data.
- Based on EPA's analysis, the data for worker and ONU inhalation exposure could not be distinguished; however, ONU inhalation exposures are assumed to be lower than inhalation exposures for workers directly handling the chemical substance. To account for this uncertainty, EPA considered the workers' central tendency estimate of inhalation exposures when determining ONU risk.

In summary, the risk estimates, the health effects of 1,4-dioxane, the exposures, and consideration of uncertainties support EPA's determination that there is an unreasonable risk of injury to health (workers) from the industrial/commercial use of 1,4-dioxane as a laboratory chemical.

5.2.1.12 Industrial/commercial use – Adhesives and sealants – Film cement

Section 6(b)(4)(A) unreasonable risk determination for the industrial/commercial use of 1,4-dioxane as an adhesive or sealant: **Presents an unreasonable risk of injury to health (workers)**; does not present an unreasonable risk of injury to health (ONUs)

For workers, EPA found that there was an unreasonable risk of non-cancer effects (liver toxicity and olfactory epithelium effects) from acute and chronic dermal exposures and cancer from chronic dermal exposures at the central tendency and high-end, even when assuming the use of PPE. For ONUs, EPA found that there was no unreasonable risk of non-cancer effects or cancer from chronic inhalation exposures at the high end or central tendency.

EPA's determination that the industrial/commercial use of 1,4-dioxane as an adhesive or sealant presents an unreasonable risk is based on the comparison of the risk estimates for non-cancer effects and cancer to the benchmarks (Table 4-23.). As explained in Section 5.1., EPA also considered the health effects of 1,4-dioxane, the exposures from the condition of use, and the uncertainties in the analysis (Section 4.3):

- For workers, when assuming the use of gloves with PF of 20, the risk estimates for non-cancer effects from acute and chronic dermal exposures and cancer from chronic dermal exposures at the central tendency and high end support an unreasonable risk determination.
- For workers, when assuming use of respirators with APF of 10, the risk estimates of non-cancer effects from acute and chronic inhalation exposures do not support an unreasonable risk determination. Similarly, for workers, when assuming use of respirators with APF of 50, the risk estimates for cancer from chronic inhalation exposures do not support an unreasonable risk determination. Respirators with APF of 50 and gloves with PF of 20 are the maximum assumed personal protective equipment for workers at industrial/commercial facilities using film cement, based on professional judgment regarding practices at industrial/commercial facilities using film cement.
- Inhalation exposures were assessed using personal breathing zone (PBZ) and area samples from a 1982 NIOSH Health Hazard Evaluation (HHE) report.
- Dermal exposures were assessed using modeled data.
- To assess ONU exposure, EPA calculated an upper bound for the NIOSH HHE samples and used it to calculate an 8-hour time-weighted average (TWA) value. The 8-hour TWA was used to calculate acute and chronic inhalation exposures for ONUs.

In summary, the risk estimates, the health effects of 1,4-dioxane, the exposures, and consideration of uncertainties support EPA's determination that there is an unreasonable risk of injury to health (workers) from the industrial/commercial use of 1,4-dioxane as an adhesive or sealant.

5.2.1.13 Industrial/commercial use – Other uses – Spray polyurethane foam

Section 6(b)(4)(A) unreasonable risk determination for the industrial/commercial use of 1,4-dioxane in spray polyurethane foam: Does not present an unreasonable risk of injury to health (workers and ONUs).

For workers, EPA found that there was no unreasonable risk of non-cancer effects (liver toxicity and olfactory epithelium effects) from acute or chronic inhalation or dermal exposures or cancer from chronic inhalation exposures at the central tendency or high-end, even when PPE is not used. In addition, for workers, EPA found that there was no unreasonable risk of cancer from chronic dermal exposures at the central tendency and high-end when assuming use of PPE. For ONUs, EPA found that there was no unreasonable risk of non-cancer effects or cancer from chronic inhalation exposures at the central tendency and high-end.

EPA's determination that the industrial use of 1,4-dioxane as a spray polyurethane foam does not present an unreasonable risk is based on the comparison of the risk estimates for non-cancer effects and cancer to the benchmarks (Table 4-23.). As explained in Section 5.1., EPA also considered the health effects of 1,4-dioxane, the exposures from the condition of use, and the uncertainties in the analysis (Section 4.3):

- For workers, when assuming use of gloves with PF of 20, the risk estimates for cancer from chronic dermal exposures at the central tendency and high-end do not support an unreasonable risk determination. Respirators with APF of 10 and gloves with PF of 20 are the maximum assumed personal protective equipment for workers applying spray polyurethane foam, based on professional judgment regarding practices for workers applying spray polyurethane foam.
- Worker and ONU inhalation exposures were assessed using modeled and surrogate data.
- Dermal exposures were assessed using modeled data.

In summary, the risk estimates, the health effects of 1,4-dioxane, the exposures, and consideration of uncertainties support EPA's determination that there is no unreasonable risk of injury to health (workers and ONUs) from the industrial use of 1,4-dioxane in spray polyurethane foam.

5.2.1.14 Industrial/commercial use – Other uses – Printing and printing compositions

Section 6(b)(4)(A) unreasonable risk determination for the industrial/commercial use of 1,4-dioxane in printing and printing compositions: **Presents an unreasonable risk of injury to health (workers);** does not present an unreasonable risk of injury to health (ONUs)

For workers, EPA found that there was an unreasonable risk of non-cancer effects (liver toxicity and olfactory epithelium effects) from acute and chronic dermal exposures and cancer from chronic dermal exposures at the central tendency and high-end, even when assuming the use of

PPE. For ONUs, EPA found that there was no unreasonable risk of non-cancer effects or cancer from chronic inhalation exposures at the central tendency.

EPA's determination that the industrial/commercial use of 1,4-dioxane in printing and printing compositions presents an unreasonable risk is based on the comparison of the risk estimates for non-cancer effects and cancer to the benchmarks (Table 4-23.). As explained in Section 5.1., EPA also considered the health effects of 1,4-dioxane, the exposures from the condition of use, and the uncertainties in the analysis (Section 4.3), including uncertainties related to the exposures for ONUs:

- For workers, when assuming the use of gloves with PF of 20, the risk estimates for non-cancer effects from acute and chronic dermal exposures and cancer from chronic dermal exposures at the central tendency and high-end support an unreasonable risk determination. Gloves with PF of 20 are the maximum assumed personal protective equipment for workers at industrial/commercial facilities doing printing and using printing compositions, based on professional judgment regarding practices at industrial/commercial facilities doing printing and using printing compositions.
- For workers, the risk estimates of non-cancer effects from acute and chronic inhalation exposures and cancer from chronic inhalation exposures at the central tendency and high-end do not support an unreasonable risk determination, even without assuming the use of PPE.
- Inhalation exposures were assessed using a single data point from a published literature review and hazard assessment for material jetting that measured exposures to a number of chemicals including 1,4-dioxane.
- Dermal exposures were assessed using modeled data.
- Based on EPA's analysis, the data for worker and ONU inhalation exposure could not be distinguished; however, ONU inhalation exposures are assumed to be lower than inhalation exposures for workers directly handling the chemical substance. To account for this uncertainty, EPA considered the workers' central tendency estimate of inhalation exposures when determining ONU risk. However, as previously noted, the risk estimates for workers of non-cancer effects from acute and chronic inhalation exposures and cancer from chronic inhalation exposures at the high-end also do not support an unreasonable risk determination, even without the use of PPE.

In summary, the risk estimates, the health effects of 1,4-dioxane, the exposures, and consideration of uncertainties support EPA's determination that there is an unreasonable risk of injury to health (workers) from the industrial/commercial use of 1,4-dioxane in printing and printing compositions.

5.2.1.15 Industrial/commercial use – Other uses – Dry film lubricant

Section 6(b)(4)(A) unreasonable risk determination for the industrial/commercial use of 1,4-dioxane in dry film lubricants: **Presents an unreasonable risk of injury to health (workers);** does not present an unreasonable risk of injury to health (ONUs)

For workers, EPA found that there was an unreasonable risk of non-cancer effects (liver toxicity and olfactory epithelium effects) from acute and chronic dermal exposures and cancer from chronic dermal exposures at the central tendency and high-end, even when assuming the use of PPE. For ONUs, EPA found that there was no unreasonable risk of non-cancer effects or cancer from chronic inhalation exposures at the central tendency.

EPA's determination that the industrial/commercial use of 1,4-dioxane in dry film lubricants presents an unreasonable risk is based on the comparison of the risk estimates for non-cancer effects and cancer to the benchmarks (Table 4-23.). As explained in Section 5.1., EPA also considered the health effects of 1,4-dioxane, the exposures from the condition of use, and the uncertainties in the analysis (Section 4.3), including uncertainties related to the exposures for ONUs:

- For workers, when assuming the use of gloves with PF of 20, the risk estimates for non-cancer effects from acute and chronic dermal exposures and cancer from chronic dermal exposures at the central tendency and high-end support an unreasonable risk determination.
- For workers, when assuming use of respirators with APF of 10, the risk estimates of non-cancer effects from acute inhalation exposure and cancer effects from chronic exposures at the high end do not support an unreasonable risk determination. Respirators with APF of 10 and gloves with PF of 20 are the maximum assumed personal protective equipment for workers at industrial/commercial facilities using 1,4-dioxane in dry film lubricants, based on process and work activity descriptions at industrial/commercial facilities using 1,4-dioxane in dry film lubricants.
- Inhalation exposures were assessed using personal breathing zone (PBZ) monitoring sample data provided by the U.S. Department of Defense, Kansas City National Security Campus. Information was not available as to whether other facilities within the National Nuclear Security Administration (NNSA) use 1,4-dioxane like the KCNSC.
- Dermal exposures were assessed using modeled data.
- Based on EPA's analysis, the data for worker and ONU inhalation exposure could not be distinguished; however, ONU inhalation exposures are assumed to be lower than inhalation exposures for workers directly handling the chemical substance. To account for this uncertainty, EPA considered the workers' central tendency estimate of inhalation exposures when determining ONU risk.

In summary, the risk estimates, the health effects of 1,4-dioxane, the exposures, and consideration of uncertainties support EPA's determination that there is an unreasonable risk of injury to health (workers) from the industrial/commercial use of 1,4-dioxane in dry film lubricants.

5.2.1.16 Consumer use – Arts, crafts and hobby materials – Textile dye

Section 6(b)(4)(A) unreasonable risk determination for the consumer use of 1,4-dioxane in textile dye: Does not present an unreasonable risk of injury to health (consumers and bystanders).

For consumers, EPA found that there was no unreasonable risk of non-cancer effects (liver toxicity) from acute inhalation or dermal exposures at the high-intensity use. For bystanders, EPA found that there was no unreasonable risk of non-cancer effects (liver toxicity) from acute inhalation exposures at the high intensity use.

EPA's determination that the consumer use of 1,4-dioxane in textile dye does not present an unreasonable risk is based on the comparison of the risk estimates for non-cancer effects to the benchmarks (Table 4-24.). As explained in Section 5.1., EPA also considered the health effects of 1,4-dioxane, the exposures from the condition of use, and the uncertainties in the analysis (Section 4.3):

- Chronic exposures were not evaluated for this condition of use because daily use intervals are not reasonably expected to occur.
- Inhalation exposures to consumers and bystanders were evaluated with the Consumer Exposure Model Version 2.1 (CEM 2.1). The magnitude of inhalation exposures to consumers and bystanders depends on several factors, including the concentration of 1,4-dioxane in products used, use patterns (including frequency, duration, amount of product used, room of use, and local ventilation), and application method.
- Dermal exposures to consumers were evaluated with the CEM (Fraction Absorbed). Dermal exposures to consumers result from dermal contact not involving impeded evaporation while using the product. The magnitude of dermal exposures depends on several factors, including skin surface area, film thickness, concentration of 1,4-dioxane in product used, dermal exposure duration, and estimated fractional absorption.

In summary, the risk estimates, the health effects of 1,4-dioxane, the exposures, and consideration of uncertainties support EPA's determination that there is no unreasonable risk of injury to health (consumers and bystanders) from the consumer use of 1,4-dioxane in textile dye.

5.2.1.17 Consumer use – Automotive care products – Antifreeze

Section 6(b)(4)(A) unreasonable risk determination for the consumer use of 1,4-dioxane in antifreeze: Does not present an unreasonable risk of injury to health (consumers and bystanders).

For consumers, EPA found that there was no unreasonable risk of non-cancer effects (liver toxicity) from acute inhalation or dermal exposures at the high-intensity use. For bystanders, EPA found that there was no unreasonable risk of non-cancer effects (liver toxicity) from acute inhalation exposures at the high intensity use.

EPA's determination that the consumer use of 1,4-dioxane in antifreeze does not present an unreasonable risk is based on the comparison of the risk estimates for non-cancer effects to the benchmarks (Table 4-24.). As explained in Section 5.1., EPA also considered the health effects of 1,4-dioxane, the exposures from the condition of use, and the uncertainties in the analysis (Section 4.3):

- Chronic exposures were not evaluated for this condition of use because daily use intervals are not reasonably expected to occur.
- Inhalation exposures to consumers and bystanders were evaluated with the Consumer Exposure Model Version 2.1 (CEM 2.1). The magnitude of inhalation exposures to consumers and bystanders depends on several factors, including the concentration of 1,4-dioxane in products used and use patterns (including frequency, duration, amount of product used, and local ventilation).
- Dermal exposures to consumers were evaluated with the CEM (Fraction Absorbed). Dermal exposures to consumers result from dermal contact not involving impeded evaporation while using the product. The magnitude of dermal exposures depends on several factors, including skin surface area, film thickness, concentration of 1,4-dioxane in product used, dermal exposure duration, and estimated fractional absorption.

In summary, the risk estimates, the health effects of 1,4-dioxane, the exposures, and consideration of uncertainties support EPA's determination that there is no unreasonable risk of injury to health (consumers and bystanders) from the consumer use of 1,4-dioxane in antifreeze.

5.2.1.18 Consumer use – Cleaning and furniture care products – Surface cleaner

Section 6(b)(4)(A) unreasonable risk determination for the consumer use of 1,4-dioxane in general purpose cleaners: Does not present an unreasonable risk of injury to health (consumers and bystanders).

For consumers, EPA found that there was no unreasonable risk of non-cancer effects (liver toxicity) from acute inhalation or dermal exposures or of cancer from chronic inhalation or dermal exposures at the high intensity use. For bystanders, EPA found that there was no unreasonable risk of non-cancer effects (liver toxicity) from acute inhalation exposures at the high intensity use.

EPA's determination that the consumer use of 1,4-dioxane in surface cleaner does not present an unreasonable risk is based on the comparison of the risk estimates for non-cancer effects and cancer to the benchmarks (Table 4-24.). As explained in Section 5.1., EPA also considered the health effects of 1,4-dioxane, the exposures from the condition of use, and the uncertainties in the analysis (Section 4.3):

- Inhalation exposures to consumers and bystanders were evaluated with the Consumer Exposure Model Version 2.1 (CEM 2.1). The magnitude of inhalation exposures to consumers and bystanders depends on several factors, including the concentration of 1,4-dioxane in products used and use patterns (including frequency, duration, amount of product used, and local ventilation).
- Dermal exposures to consumers were evaluated with the CEM (Fraction Absorbed). Dermal exposures to consumers result from dermal contact not involving impeded evaporation while using the product. The magnitude of dermal exposures depends on several factors, including skin surface area, film thickness, concentration of 1,4-dioxane in product used, dermal exposure duration, and estimated fractional absorption.

In summary, the risk estimates, the health effects of 1,4-dioxane, the exposures, and consideration of uncertainties support EPA's determination that there is no unreasonable risk of injury to health (consumers and bystanders) from the consumer use of 1,4-dioxane in surface cleaner.

5.2.1.19 Consumer use – Laundry and dishwashing products – Dish soap

Section 6(b)(4)(A) unreasonable risk determination for the consumer use of 1,4-dioxane in dish soap: Does not present an unreasonable risk of injury to health (consumers and bystanders).

For consumers, EPA found that there was no unreasonable risk of non-cancer effects (liver toxicity) from acute inhalation or dermal exposures or of cancer from chronic inhalation or dermal exposures at the high intensity use. For bystanders, EPA found that there was no unreasonable risk of non-cancer effects (liver toxicity) from acute inhalation exposures at the high intensity use.

EPA's determination that the consumer use of 1,4-dioxane in dish soap does not present an unreasonable risk is based on the comparison of the risk estimates for non-cancer effects and cancer to the benchmarks (Table 4-24.). As explained in Section 5.1., EPA also considered the health effects of 1,4-dioxane, the exposures from the condition of use, and the uncertainties in the analysis (Section 4.3):

- Inhalation exposures to consumers and bystanders were evaluated with the Consumer Exposure Model Version 2.1 (CEM 2.1). The magnitude of inhalation exposures to consumers and bystanders depends on several factors, including the concentration of 1,4-dioxane in products used and use patterns (including frequency, duration, amount of product used, and local ventilation).
- Dermal exposures to consumers were evaluated with the CEM (Fraction Absorbed). Dermal exposures to consumers result from dermal contact not involving impeded evaporation while using the product. The magnitude of dermal exposures depends on several factors, including skin surface area, film thickness, concentration of 1,4-dioxane in product used, dermal exposure duration, and estimated fractional absorption.

In summary, the risk estimates, the health effects of 1,4-dioxane, the exposures, and consideration of uncertainties support EPA's determination that there is no unreasonable risk of injury to health (consumers and bystanders) from the consumer use of 1,4-dioxane in dish soap.

5.2.1.20 Consumer use – Laundry and dishwashing products – Dishwasher detergent

Section 6(b)(4)(A) unreasonable risk determination for the consumer use of 1,4-dioxane in dishwasher detergent: Does not present an unreasonable risk of injury to health (consumers and bystanders).

For consumers, EPA found that there was no unreasonable risk of non-cancer effects (liver toxicity) from acute inhalation or dermal exposures or of cancer from chronic inhalation or dermal exposures at the high intensity use. For bystanders, EPA found that there was no unreasonable risk of non-cancer effects (liver toxicity) from acute inhalation exposures at the high intensity use.

EPA's determination that the consumer use of 1,4-dioxane in dishwasher detergent does not present an unreasonable risk is based on the comparison of the risk estimates for non-cancer effects and cancer to the benchmarks (Table 4-24.). As explained in Section 5.1., EPA also considered the health effects of 1,4-dioxane, the exposures from the condition of use, and the uncertainties in the analysis (Section 4.3):

- Inhalation exposures to consumers and bystanders were evaluated with the Consumer Exposure Model Version 2.1 (CEM 2.1). The magnitude of inhalation exposures to consumers and bystanders depends on several factors, including the concentration of 1,4-dioxane in products used and use patterns (including frequency, duration, amount of product used, and local ventilation).
- Dermal exposures to consumers were evaluated with the CEM (Fraction Absorbed). Dermal exposures to consumers result from dermal contact not involving impeded evaporation while using the product. The magnitude of dermal exposures depends on several factors, including skin surface area, film thickness, concentration of 1,4-dioxane in product used, dermal exposure duration, and estimated fractional absorption.

In summary, the risk estimates, the health effects of 1,4-dioxane, the exposures, and consideration of uncertainties support EPA's determination that there is no unreasonable risk of injury to health (consumers and bystanders) from the consumer use of 1,4-dioxane in dishwasher detergent.

5.2.1.21 Consumer use – Laundry and dishwashing products – Laundry detergent

Section 6(b)(4)(A) unreasonable risk determination for the consumer use of 1,4-dioxane in laundry detergent: Does not present an unreasonable risk of injury to health (consumers and bystanders).

For consumers, EPA found that there was no unreasonable risk of non-cancer effects (liver toxicity) from acute inhalation or dermal exposures or of cancer from chronic inhalation or dermal exposures at the high intensity use. For bystanders, EPA found that there was no unreasonable risk of non-cancer effects (liver toxicity) from acute inhalation exposures at the high intensity use.

EPA's determination that the consumer use of 1,4-dioxane in laundry detergent does not present an unreasonable risk is based on the comparison of the risk estimates for non-cancer effects and cancer to the benchmarks (Table 4-24.). As explained in Section 5.1., EPA also considered the health effects of 1,4-dioxane, the exposures from the condition of use, and the uncertainties in the analysis (Section 4.3):

- Inhalation exposures to consumers and bystanders were evaluated with the Consumer Exposure Model Version 2.1 (CEM 2.1). The magnitude of inhalation exposures to consumers and bystanders depends on several factors, including the concentration of 1,4-dioxane in products used and use patterns (including frequency, duration, amount of product used, and local ventilation).
- Dermal exposures to consumers were evaluated with the CEM (Fraction Absorbed). Dermal exposures to consumers result from dermal contact not involving impeded evaporation while using the product. The magnitude of dermal exposures depends on several factors, including skin surface area, film thickness, concentration of 1,4-dioxane in product used, dermal exposure duration, and estimated fractional absorption.

In summary, the risk estimates, the health effects of 1,4-dioxane, the exposures, and consideration of uncertainties support EPA's determination that there is no unreasonable risk of injury to health (consumers and bystanders) from the consumer use of 1,4-dioxane in laundry detergent.

5.2.1.22 Consumer use – Paints and coatings – Paint and floor lacquer

Section 6(b)(4)(A) unreasonable risk determination for the consumer use of 1,4-dioxane in paint and floor lacquer: Does not present an unreasonable risk of injury to health (consumers and bystanders).

For consumers, EPA found that there was no unreasonable risk of non-cancer effects (liver toxicity) from acute inhalation or dermal exposures at the high-intensity use. For bystanders, EPA found that there was no unreasonable risk of non-cancer effects (liver toxicity) from acute inhalation exposures at the high intensity use.

EPA's determination that the consumer use of 1,4-dioxane in paint and floor lacquer does not present an unreasonable risk is based on the comparison of the risk estimates for non-cancer effects to the benchmarks (Table 4-24.). As explained in Section 5.1., EPA also considered the health effects of 1,4-dioxane, the exposures from the condition of use, and the uncertainties in the analysis (Section 4.3):

- Chronic exposures were not evaluated for this condition of use because daily use intervals are not reasonably expected to occur.
- Inhalation exposures to consumers and bystanders were evaluated with the Consumer Exposure Model Version 2.1 (CEM 2.1). The magnitude of inhalation exposures to consumers and bystanders depends on several factors, including the concentration of 1,4-dioxane in products used and use patterns (including frequency, duration, amount of product used, and local ventilation).
- Dermal exposures to consumers were evaluated with the CEM (Fraction Absorbed). Dermal exposures to consumers result from dermal contact not involving impeded evaporation while using the product. The magnitude of dermal exposures depends on several factors, including skin surface area, film thickness, concentration of 1,4-dioxane in product used, dermal exposure duration, and estimated fractional absorption.

In summary, the risk estimates, the health effects of 1,4-dioxane, the exposures, and consideration of uncertainties support EPA's determination that there is no unreasonable risk of injury to health (consumers and bystanders) from the consumer use of 1,4-dioxane in paint and floor lacquer.

5.2.1.23 Consumer use – Other uses – Spray Polyurethane Foam

Section 6(b)(4)(A) unreasonable risk determination for the consumer use of 1,4-dioxane in spray polyurethane foam: Does not present an unreasonable risk of injury to health (consumers and bystanders).

For consumers, EPA found that there was no unreasonable risk of non-cancer effects (liver toxicity) from acute inhalation and dermal exposures at the high-intensity use. For bystanders, EPA found that there was no unreasonable risk of non-cancer effects (liver toxicity) from acute inhalation exposures at the high intensity use.

EPA's determination that the consumer use of 1,4-dioxane in spray polyurethane foam does not present an unreasonable risk is based on the comparison of the risk estimates for non-cancer effects to the benchmarks (Table 4-24.). As explained in Section 5.1., EPA also considered the health effects of 1,4-dioxane, the exposures from the condition of use, and the uncertainties in the analysis (Section 4.3):

- Chronic exposures were not evaluated for this condition of use because daily use intervals are not reasonably expected to occur.
- Inhalation exposures to consumers and bystanders were evaluated with the Consumer Exposure Model Version 2.1 (CEM 2.1). The magnitude of inhalation exposures to consumers and bystanders depends on several factors, including the concentration of 1,4-dioxane in products used and use patterns (including frequency, duration, amount of product used, and local ventilation).
- Dermal exposures to consumers were evaluated with the CEM (Fraction Absorbed). Dermal exposures to consumers result from dermal contact not involving impeded evaporation while using the product. The magnitude of dermal exposures depends on several factors, including skin surface area, film thickness, concentration of 1,4-dioxane in product used, dermal exposure duration, and estimated fractional absorption.

In summary, the risk estimates, the health effects of 1,4-dioxane, the exposures, and consideration of uncertainties support EPA's determination that there is no unreasonable risk of injury to health (consumers and bystanders) from the consumer use of 1,4-dioxane in spray polyurethane foam.

5.2.1.24 Disposal – Disposal – Wastewater; Underground injection; Landfill; Incineration

Section 6(b)(4)(A) unreasonable risk determination for the disposal of 1,4-dioxane: **Presents an unreasonable risk of injury to health (workers and ONUs).**

For workers, EPA found that there was an unreasonable risk of non-cancer effects (liver toxicity and olfactory epithelium effects) from acute and chronic dermal exposures and cancer from chronic dermal exposures, even when assuming use of PPE. For ONUs, EPA found that there was an unreasonable risk of non-cancer effects and cancer from chronic inhalation exposures at the central tendency.

EPA's determination that the disposal of 1,4-dioxane presents an unreasonable risk is based on the comparison of the risk estimates for non-cancer effects and cancer to the benchmarks (Table 4-23.). As explained in Section 5.1., EPA also considered the health effects of 1,4-dioxane, the exposures from the condition of use, and the uncertainties in the analysis (Section 4.3), including uncertainties related to the exposures for ONUs:

- For workers, when assuming the use of gloves with PF of 20, the risk estimates for non-cancer effects from acute and chronic dermal exposures and cancer from chronic dermal exposures at the central tendency and high-end support an unreasonable risk determination.
- For workers, when assuming use of respirators with APF of 50, the risk estimates of non-cancer effects from acute and chronic inhalation exposures do not support an unreasonable risk determination. Similarly, for workers, when assuming use of respirators with APF of 50, the risk estimates for cancer from chronic inhalation exposures do not support an unreasonable risk determination. Respirators with APF of 50 and gloves with PF of 20 are the maximum assumed personal protective equipment for workers at disposal facilities, based on professional judgment regarding practices at disposal facilities.
- Inhalation and dermal exposures were assessed using modeled data.
- Based on EPA's analysis, the data for worker and ONU inhalation exposure could not be distinguished; however, ONU inhalation exposures are assumed to be lower than inhalation exposures for workers directly handling the chemical substance. To account for this uncertainty, EPA considered the workers' central tendency estimate of inhalation exposures when determining ONU risk.

In summary, the risk estimates, the health effects of 1,4-dioxane, the exposures, and consideration of uncertainties support EPA's determination that there is an unreasonable risk of injury to health (workers and ONUs) from the disposal of 1,4-dioxane.

5.2.2 Environment

6(b)(4)(A) unreasonable risk determination for all conditions of use of 1,4-dioxane: Does not present an unreasonable risk of injury **to the environment** (aquatic, sediment dwelling, and terrestrial organisms).

For all conditions of use, EPA found that there were no exceedances of benchmarks to aquatic organisms from exposures to 1,4-dioxane. The RQ values for acute and chronic risks are 0.2 and 0.397, respectively, based on the best available science.

The high volatility, high water solubility and low Log K_{oc} of 1,4-dioxane suggest that 1,4-dioxane will only be present at low concentrations in sediment and land-applied biosolids.

In summary, the risk estimates, the environmental effects of 1,4-dioxane, the exposures, physical chemical properties of 1,4-dioxane and consideration of uncertainties support a determination that there is no unreasonable risk for the environment from all conditions of use of 1,4-dioxane.

5.3 Changes to the Unreasonable Risk Determination from Draft Risk Evaluation to Final Risk Evaluation

In this final risk evaluation, EPA made changes to the unreasonable risk determination for 1,4-dioxane following the publication of the draft risk evaluation, as a result of the analysis following peer review and public comments. In particular, in November 2020, EPA issued a Draft Supplemental Analysis to the Draft Risk Evaluation of 1,4-Dioxane that covered eight consumer conditions of use not included in the original draft risk evaluation, as well as general population exposures from recreational swimming in ambient water. The consumer conditions of use presented in the supplemental analysis are use of 1,4-dioxane in textile dye, antifreeze, surface cleaner, dish soap, dishwasher detergent, laundry detergent, paint and floor lacquer, and spray polyurethane foam. As a result of the supplemental analysis, this final risk evaluation includes risk determinations for the general population in Section 5.1.1 and for the eight consumer conditions of use at Sections 5.2.1.15 – 5.2.1.23.

In addition, while use of 1,4-dioxane as a process solvent and as an intermediate in the manufacture of pharmaceuticals was included in the problem formulation and draft risk evaluation, upon further analysis of the details of these processes, EPA has determined that these uses fall outside TSCA's definition of "chemical substance." Under TSCA § 3(2)(B)(vi), the definition of "chemical substance" does not include any food, food additive, drug, cosmetic, or device (as such terms are defined in section 201 of the Federal Food, Drug, and Cosmetic Act) when manufactured, processed, or distributed in commerce for use as a food, food additive, drug, cosmetic, or device. EPA has concluded that 1,4-dioxane use as a process solvent and an intermediate during pharmaceutical manufacturing falls outside TSCA's definition of a chemical substance when used for these purposes. As a result, the use of 1,4-dioxane as a process solvent and an intermediate during pharmaceutical manufacturing are not included in the scope of this risk evaluation.

Finally, EPA is correcting two minor errors that appeared in the risk determination table in the draft risk evaluation. The "Etching of fluoropolymers" condition of use was inadvertently omitted from the "Industrial use: Processing aids, not otherwise listed" subcategory. Also, "Hydraulic fluid" should not have appeared under the "Industrial use: Functional fluids (open system)" subcategory. Hydraulic fluid is a closed system functional fluid and, as noted in the risk determination table in the draft risk evaluation, EPA determined that functional fluid use in closed systems was not a condition of use for 1,4-dioxane.

5.4 Unreasonable Risk Determination Conclusion

5.4.1 No Unreasonable Risk Determinations

TSCA Section 6(b)(4) requires EPA to conduct risk evaluations to determine whether chemical substances present unreasonable risk under their conditions of use. In conducting risk evaluations, “EPA will determine whether the chemical substance presents an unreasonable risk of injury to health or the environment under each condition of use within the scope of the risk evaluation...” 40 CFR 702.47. Pursuant to TSCA Section 6(i)(1), a determination of “no unreasonable risk” shall be issued by order and considered to be final agency action. Under EPA’s implementing regulations, “[a] determination by EPA that the chemical substance, under one or more of the conditions of use within the scope of the risk evaluation, does not present an unreasonable risk of injury to health or the environment will be issued by order and considered to be a final Agency action, effective on the date of issuance of the order.” 40 CFR 702.49(d).

EPA has determined that the following conditions of use of 1,4-dioxane do not present an unreasonable risk of injury to health or the environment:

- Distribution in commerce (Section 5.1.1, Section 5.2.1.7, Section 5.2.2, Section 4, Section 3)
- Industrial/commercial use: Functional fluids, open system (Section 5.1.1, Section 5.2.1.10, Section 5.2.2, Section 4, Section 3, and Section 2.4.1.1.5)
- Industrial/commercial use: Other uses: Spray polyurethane foam (Section 5.1.1, Section 5.2.1.13, Section 5.2.2, Section 4, Section 3, and Section 2.4.1.1.9)
- Consumer use: Arts, crafts, and hobby materials – Textile dye (Section 5.1.1, Section 5.2.1.16, Section 5.2.2, Section 4, Section 3, and Section 2.4.3.4.7)
- Consumer use: Automotive care products – Antifreeze (Section 5.1.1, Section 5.2.1.17, Section 5.2.2, Section 4, Section 3, and Section 2.4.3.4.2)
- Consumer use: Cleaning and furniture care products – Surface cleaner (Section 5.1.1, Section 5.2.1.18, Section 5.2.2, Section 4, Section 3, and Section 2.4.3.4.1)
- Consumer use: Laundry and dishwashing products – Dish soap (Section 5.1.1, Section 5.2.1.19, Section 5.2.2, Section 4, Section 3, and Section 2.4.3.4.3)
- Consumer use: Laundry and dishwashing products – Dishwasher detergent (Section 5.1.1, Section 5.2.1.20, Section 5.2.2, Section 4, Section 3, and Section 2.4.3.4.4)
- Consumer use: Laundry and dishwashing products – Laundry detergent (Section 5.1.1, Section 5.2.1.21, Section 5.2.2, Section 4, Section 3, and Section 2.4.3.4.5)
- Consumer use: Paints and coatings – Paint and floor lacquer (Section 5.1.1, Section 5.2.1.22, Section 5.2.2, Section 4, Section 3, and Section 2.4.3.4.6)
- Consumer use: Other uses – Spray polyurethane foam (Section 5.1.1, Section 5.2.1.23, Section 5.2.2, Section 4, Section 3, and Section 2.4.3.4.8)

This subsection of the final risk evaluation therefore constitutes the order required under TSCA Section 6(i)(1), and the “no unreasonable risk” determinations in this subsection are considered to be final agency action effective on the date of issuance of this order. All assumptions that went into reaching the determinations of no unreasonable risk for these conditions of use, including any considerations excluded for these conditions of use, are incorporated into this order.

The support for each determination of no unreasonable risk is set forth in Section 5.2 of the final risk evaluation, “Detailed Unreasonable Risk Determinations by Condition of Use.” This subsection also constitutes the statement of basis and purpose required by TSCA Section 26(f).

5.4.2 Unreasonable Risk Determinations

EPA has determined that the following conditions of use of 1,4-dioxane present an unreasonable risk of injury:

- Manufacture: Domestic manufacture
- Manufacture: Import/repackaging (bottle and drums)
- Processing: Repackaging (bottle and drums)
- Processing: Recycling
- Processing: Non-incorporative
- Processing: Reactant
- Industrial use: Intermediate
- Industrial use: Processing aid
- Industrial use: Laboratory chemicals
- Industrial/commercial use: Adhesives or sealants
- Industrial/commercial use: Printing and printing compositions
- Industrial/commercial use: Dry film lubricant
- Disposal

EPA will initiate TSCA Section 6(a) risk management actions on these conditions of use as required under TSCA Section 6(c)(1). Pursuant to TSCA Section 6(i)(2), the “unreasonable risk” determinations for these conditions of use are not considered final agency action.

6 REFERENCES

- Almeida, RN; Costa, P; Pereira, J; Cassel, E; Rodrigues, AE. (2019). Evaporation and Permeation of Fragrance Applied to the Skin. *Industrial & Engineering Chemistry* 58: 9644-9650. <http://dx.doi.org/10.1021/acs.iecr.9b01004>
- An, YJ; Kwak, J; Nam, SH; Jung, MS. (2014). Development and implementation of surface water quality standards for protection of human health in Korea. *Environ Sci Pollut Res Int* 21: 77-85. <http://dx.doi.org/10.1007/s11356-013-1626-9> ; <https://link.springer.com/content/pdf/10.1007%2Fs11356-013-1626-9.pdf>
- Argus, MF; Arcos, JC; Hoch-Ligeti, C. (1965). Studies on the carcinogenic activity of protein-denaturing agents: Hepatocarcinogenicity of dioxane. *J Natl Cancer Inst* 35: 949-958.
- Argus, MF; Sohal, RS; Bryant, GM; Hoch-Ligeti, C; Arcos, JC. (1973). Dose-response and ultrastructural alterations in dioxane carcinogenesis. Influence of methylcholanthrene on acute toxicity. *Eur J Cancer* 9: 237-243. [http://dx.doi.org/10.1016/0014-2964\(73\)90088-1](http://dx.doi.org/10.1016/0014-2964(73)90088-1)
- ATSDR. (2012). Toxicological profile for 1,4 dioxane [ATSDR Tox Profile]. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service. <http://www.atsdr.cdc.gov/toxprofiles/tp.asp?id=955&tid=199>
- Baciocchi, R; Berardi, S; Verginelli, I. (2010). Human health risk assessment: Models for predicting the effective exposure duration of on-site receptors exposed to contaminated groundwater. *J Hazard Mater* 181: 226-233.
- Bailer, AJ; Piegorsch, WW. (1997). *Statistics for environmental biology and toxicology.* London, England: Chapman & Hall/CRC Press. <http://www.crcpress.com/product/isbn/9780412047312>
- Baldwin, PE; Maynard, AD. (1998). A Survey of Wind Speed in Indoor Workplaces. *Ann Occup Hyg* 42: 303-313.
- Bannasch, P; Krech, R; Zerban, H. (1980). Morphogenese und Mikromorphologie epithelialer Nierentumoren bei Nitrosomorpholin-vergifteten Ratten: IV tubulaere Laesionen und basophile Tumoren [Morphogenesis and micromorphology of epithelial tumors induced in the rat kidney by nitrosomorpholine: IV tubular lesions and basophilic tumors]. *Cancer Res* 98: 243-265.
- Bannasch, P; Mayer, D; Krech, R. (1979). Neoplastic And Preneoplastic Lesions In Rats After Oral-Administration Of A Single Dose Of N-Nitrosomorpholine. *J Cancer Res Clin Oncol* 94: 233-248. <http://dx.doi.org/10.1007/BF00419283>
- Bannasch, P; Moore, MA; Klimek, F; Zerban, H. (1982). Biological markers of preneoplastic foci and neoplastic nodules in rodent liver. *Toxicol Pathol* 10: 19-34. <http://dx.doi.org/10.1177/019262338201000204>
- BASF. (2016). Analytical Reports and Data Summaries from Worker Monitoring at the US Facility for 1,4-Dioxane Production.
- BASF. (2017). Information in response to the "Preliminary information on manufacturing, processing, distribution, use, and disposal: 1,4-dioxane" document. <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0723-0012>
- BASF. (2018a). BASF Additional Information re: "Problem Formulation of the Risk Evaluation for 1,4-Dioxane". (EPA-HQ-OPPT-2016-0723). <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0723-0069>.
- BASF. (2018b). Safety Data Sheet: 1,4-Dioxane. https://worldaccount.basf.com/wa/NAFTA~en_US/Catalog/ChemicalsNAFTA/doc4/BA

- [SF/PRD/30036718/.pdf?asset_type=msds/pdf&language=EN&validArea=US&urn=urn:dokumentum:ProductBase_EU:09007af8800a8763.pdf](#)
- [Bell, N; Vaughan, NP; Morris, L; Griffin, P.](#) (2012). An assessment of workplace programmes designed to control inhalation risks using respiratory protective equipment. *Ann Occup Hyg* 56: 350-361.
- [BLS.](#) (2014). Employee Tenure News Release.
- [BLS.](#) (2015). Hours and Employment by Industry Tables - August 6, 2015 [Website]. <http://www.bls.gov/lpc/tables.htm>
- [BLS.](#) (2016). May 2016 Occupational Employment and Wage Estimates: National Industry-Specific Estimates [Website]. <http://www.bls.gov/oes/tables.htm>
- [Braun, WH; Young, JD.](#) (1977). Identification of beta-hydroxyethoxyacetic acid as the major urinary metabolite of 1,4-dioxane in the rat. *Toxicol Appl Pharmacol* 39: 33-38. [http://dx.doi.org/10.1016/0041-008X\(77\)90174-0](http://dx.doi.org/10.1016/0041-008X(77)90174-0)
- [Bringman, G; Kuhn, R.](#) (1977). Limiting values of the harmful action of water endangering substances on bacteria (*Pseudomonas putida*) and green algae (*Scenedesmus quadricauda*) in the cell multiplication inhibition test. *Z f Wasser- und Abwasser-Forschung* 10: 87-98.
- [Bringmann, G; Kuehn, R.](#) (1982). Results of Toxic Action of Water Pollutants on *Daphnia magna* Straus Tested by an Improved Standardized Procedure. 15: 1-6(GER) (ENG ABS) (OECDG Data File).
- [Bringmann, G; Kuhn, R.](#) (1977). The effects of water pollutants on *Daphnia magna*. *Wasser und Abwasser in Forschung und Praxis* 10: 161-166.
- [Bringmann, G; Kuhn, R.](#) (1978). Grenzwerte der Schadwirkung wassergefährdender Stoffe gegen Blaualgen (*Microcystis aeruginosa*) und Grünalgen (*Scenedesmus quadricauda*) im Zellvermehrungshemmtest [Limiting values for the noxious effects of water pollutant material to blue algae (*Microcystis aeruginosa*) and green algae (*Scenedesmus quadricauda*) in cell propagation inhibition tests]. *Vom Wasser* 50: 45-60.
- [Bronaugh, RL.](#) (1982). Percutaneous absorption of cosmetic ingredients. In P Frost; SN Horwitz (Eds.), *Principles of cosmetics for the dermatologist* (pp. 277-284). St. Louis, MO: C.V. Mosby.
- [Brooke, L.](#) (1987). Report of the flow-through and static acute test comparisons with fathead minnows and acute tests with an amphipod and a cladoceran. Superior, WI: Center for Lake Superior Environmental Studies, University of Wisconsin.
- [Bruno, TJ; PDN, S.](#) (2006). *CRC Handbook of Fundamental Spectroscopic Correlation Charts*. Boca Raton, FL: CRC Press. <http://www.hbcnpnetbase.com/>
- [Buffler, PA; Wood, SM; Suarez, L; Kilian, DJ.](#) (1978). Mortality follow-up of workers exposed to 1,4-dioxane. *J Occup Environ Med* 20: 255-259.
- [Burton, NC; Driscoll, RJ.](#) (1997). Health hazard evaluation report no. HETA-95-0293-2655, Dana Corporation, Spicer Axle Division, Fort Wayne, Indiana. (HETA-95-0293-2655). Cincinnati, OH: National Institute for Occupational Safety and Health.
- [CalRecycle.](#) (2018). Beyond 2000: California's Continuing Need for Landfills. Available online at <https://www.calrecycle.ca.gov/SWFacilities/Landfills/NeedFor>
- [Cherrie, JW; Semple, S; Brouwer, D.](#) (2004). Gloves and Dermal Exposure to Chemicals: Proposals for Evaluating Workplace Effectiveness. *Ann Occup Hyg* 48: 607-615. <http://dx.doi.org/10.1093/annhyg/meh060>

- [Chittenden, JT; Brooks, JD; Riviere, JE.](#) (2014). Development of a Mixed-Effect Pharmacokinetic Model for Vehicle Modulated In Vitro Transdermal Flux of Topically Applied Penetrants. *J Pharm Sci* 103: 1002-1012.
<http://dx.doi.org/https://doi.org/10.1002/jps.23862>Get
- [Chittenden, JT; Riviere, JE.](#) (2015). Quantification of vehicle mixture effects on in vitro transdermal chemical flux using a random process diffusion model. *J Control Release* 217: 74-81. <http://dx.doi.org/https://doi.org/10.1016/j.jconrel.2015.08.023>
- [Cowan, DM; Benson, SM; Cheng, TJ; Hecht, S; Boulos, NM; Henshaw, J.](#) (2017). Evaluation of reported fatality data associated with workers using respiratory protection in the United States (1990-2012). *Arch Environ Occup Health* 72: 235-246.
- [Dancik, Y; Bigliardi, PL; Bigliardi-Qi, Me.](#) (2015). What happens in the skin? Integrating skin permeation kinetics into studies of developmental and reproductive toxicity following topical exposure. *Reprod Toxicol* 58: 252-281.
<http://dx.doi.org/10.1016/j.reprotox.2015.10.001>
- [Dawson, GW; Jennings, AL; Drozdowski, D; Rider, E.](#) (1977). The acute toxicity of 47 industrial chemicals to fresh and saltwater fishes. *J Hazard Mater* 1: 303-318.
[http://dx.doi.org/10.1016/0304-3894\(75\)80003-3](http://dx.doi.org/10.1016/0304-3894(75)80003-3)
- [DoD.](#) (2018). Update: DoD Exposure Data for EPA Risk Evaluation - EPA request for additional information. Available online
- [DOE.](#) (2018a). [FW: 1,4-Dioxane]. Stites, M.
- [DOE.](#) (2018b). [RE: Discussion Follow-up]. Stites, M.
- [Dourson, M; Higginbotham, J; Crum, J; Burleigh-Flayer, H; Nance, P; Forsberg, N; Lafranconi, M; Reichard, J.](#) (2017). Update: Mode of action (MOA) for liver tumors induced by oral exposure to 1,4-dioxane. *Regul Toxicol Pharmacol* 88: 45-55.
<http://dx.doi.org/10.1016/j.yrtph.2017.02.025>
- [Dourson, M; Reichard, J; Nance, P; Burleigh-Flayer, H; Parker, A; Vincent, M; McConnell, EE.](#) (2014). Mode of action analysis for liver tumors from oral 1,4-dioxane exposures and evidence-based dose response assessment. *Regul Toxicol Pharmacol* 68: 387-401.
<http://dx.doi.org/10.1016/j.yrtph.2014.01.011>
- [Dow Chemical.](#) (1989a). 1,4-Dioxane: Embryo-larval toxicity test with the Fathead minnow, *Pimephales promelas Rafinesque*. (OTS: OTS0000719; 8EHQ Num: FYI-OTS-1089-0719; DCN: NA). Dow Chem Co.
<https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/OTS0000719.xhtml>
- [Dow Chemical.](#) (1989b). Differentiation of the mechanisms of oncogenicity of 1,4-dioxane and 1,3-hexachlorobutadiene in the rat. (OTS: OTS0000719; 8EHQ Num: FYI-OTS-1089-0719; DCN: NA; TSCATS RefID: 404730). Midland, MI.
- [Dow Chemical.](#) (1989c). Assessment of health and environmental effects of 1,4-dioxane and publications concerning 1,4-dioxane. (8EHQ-1088-0761). Office of Toxic Substances :: OTS.
- [Dow Chemical.](#) (1989d). The evaluation of 1,3-hexachlorobutadiene and 1,4-dioxane in the rat hepatocyte unscheduled DNA synthesis assay. (OTS: OTS0000719; 8EHQ Num: FYI-OTS-1089-0719; DCN: NA; TSCATS RefID: 404730). Dow Chem Co.
- [Drew, RT; Patel, JM; Lin, FN.](#) (1978). Changes in serum enzymes in rats after inhalation of organic solvents singly and in combination. *Toxicol Appl Pharmacol* 45: 809-819.
[http://dx.doi.org/10.1016/0041-008X\(78\)90172-2](http://dx.doi.org/10.1016/0041-008X(78)90172-2)

- [EC](#). (2004). Recommendation from the Scientific Committee on Occupational Exposure Limits for 1,4-dioxane. Employment, Social Affairs and Inclusion.
- [ECETOC](#). (2006). Guidance for Setting Occupational Exposure Limits: Emphasis on Data-Poor Substances. (101). Brussels, Belgium: European Centre for Ecotoxicology and Toxicology of Chemicals.
- [ECHA](#). (1996). 1,4- dioxane- Exp. Key Biodegradation in water: screening test.001. <https://echa.europa.eu/registration-dossier/-/registered-dossier/15842/5/3/2>
- [ECHA](#). (2010). Guidance on information requirements and chemical safety assessment Chapter R.8: Characterization of dose-response for human health.
- [ECHA](#). (2008). Chapter R.8: Characterisation of dose [concentration]-response for human health. In Echa (Ed.). Helsinki, Finland. http://wko.at/up/enet/chemie/TL_ChapterR8.pdf
- [ECJRC](#). (2002). European Union risk assessment report: 1,4-dioxane. (EUR 19833 EN). Luxembourg: Office for Official Publications of the European Communities. <https://echa.europa.eu/documents/10162/a4e83a6a-c421-4243-a8df-3e84893082aa>
- [Elcombe, CR; Peffer, RC; Wolf, DC; Bailey, J; Bars, R; Bell, D; Cattley, RC; Ferguson, SS; Geter, D; Goetz, A; Goodman, JI; Hester, S; Jacobs, A; Omiecinski, CJ; Schoeny, R; Xie, W; Lake, BG](#). (2014). Mode of action and human relevance analysis for nuclear receptor-mediated liver toxicity: A case study with phenobarbital as a model constitutive androstane receptor (CAR) activator [Review]. *Crit Rev Toxicol* 44: 64-82. <http://dx.doi.org/10.3109/10408444.2013.835786>
- [Eleftheriadou, D; Luetete, S; and Kneuer, C](#). (2019). In silico prediction of dermal absorption of pesticides – an evaluation of selected models against results from in vitro testing. *SAR QSAR Environ Res* 30: 561-585. <http://dx.doi.org/10.1080/1062936X.2019.1644533>.
- [Ernstgard, L; Iregren, A; Sjogren, B; Johanson, G](#). (2006). Acute effects of exposure to vapours of dioxane in humans. *Hum Exp Toxicol* 25: 723-729. <http://dx.doi.org/10.1177/0960327106073805>
- [Esmen, N; Corn, M; Hammad, Y; Whittier, D; Kotsko, N](#). (1979). Summary of measurements of employee exposure to airborne dust and fiber in sixteen facilities producing man-made mineral fibers. *Am Ind Hyg Assoc J* 40: 108-117.
- [ETC](#). (2018). High Temperature Incineration. Available online at <http://etc.org/advanced-technologies/high-temperature-incineration.aspx>.
- [Fisher, J; Mahle, D; Bankston, L; Greene, R; Gearhart, J](#). (1997). Lactational transfer of volatile chemicals in breast milk. *Am Ind Hyg Assoc J* 58: 425-431. <http://dx.doi.org/10.1080/15428119791012667>
- [Frasch, FH](#). (2012). Dermal Absorption of Finite doses of Volatile Compounds. *J Pharm Sci* 101: 2616-2619. <http://dx.doi.org/10.1080/15287394>
- [Frasch, HF; Bunge, AL](#). (2015). The transient dermal exposure II: post-exposure absorption and evaporation of volatile compounds. *J Pharm Sci* 104: 1499-1507. <http://dx.doi.org/10.1002/jps.24334>
- [Frasch, HF; Dotson, GS; Barbero, AM](#). (2011). In vitro human epidermal penetration of 1-bromopropane. *J Toxicol Environ Health A* 74: 1249-1260. <http://dx.doi.org/10.1080/15287394.2011.595666>
- [GAF](#). (2014). Safety Data Sheet: OlyBond Part B (Amber/Red). https://sweets.construction.com/swts_content_files/1772/714412.pdf

- Gajjar, RM; Kasting, GB. (2014). Absorption of ethanol, acetone, benzene and 1,2-dichloroethane through human skin in vitro: a test of diffusion model predictions. *Toxicol Appl Pharmacol* 281: 109-117. <http://dx.doi.org/10.1016/j.taap.2014.09.013>
- Galloway, SM; Armstrong, MJ; Reuben, C; Colman, S; Brown, B; Cannon, C; Bloom, AD; Nakamura, F; Ahmed, M; Duk, S; Rimpou, J; Margolin, BH; Resnick, MA; Anderson, B; Zeiger, E. (1987). Chromosome aberrations and sister chromatid exchanges in Chinese hamster ovary cells: evaluations of 108 chemicals [Review]. *Environ Mol Mutagen* 10: 1-175. <http://dx.doi.org/10.1002/em.2850100502>
- Garcia, E; Hurley, S; Nelson, DO; Hertz, A; Reynolds, P. (2015). Hazardous air pollutants and breast cancer risk in California teachers: a cohort study. *Environ Health* 14: 14. <http://dx.doi.org/10.1186/1476-069X-14-14>
- Garrod, AN; Phillips, AM; Pemberton, JA. (2001). Potential exposure of hands inside protective gloves—a summary of data from non-agricultural pesticide surveys. *Ann Occup Hyg* 45: 55-60. [http://dx.doi.org/10.1016/S0003-4878\(00\)00013-2](http://dx.doi.org/10.1016/S0003-4878(00)00013-2)
- Geiger, DL; Brooke, LT; Call, DJ. (1990). Acute toxicities of organic chemicals to fathead minnows (*Pimephales promelas*): Volume V. Superior, WI: University of Wisconsin-Superior, Center for Lake Superior Environmental Studies.
- Gi, M; Fujioka, M; Kakehashi, A; Okuno, T; Masumura, K; Nohmi, T; Matsumoto, M; Omori, M; Wanibuchi, H; Fukushima, S. (2018). In vivo positive mutagenicity of 1,4-dioxane and quantitative analysis of its mutagenicity and carcinogenicity in rats. *Arch Toxicol* 92: 3207-3221. <http://dx.doi.org/10.1007/s00204-018-2282-0>
- Giavini, E; Vismara, C; Broccia, ML. (1985). Teratogenesis study of dioxane in rats. *Toxicol Lett* 26: 85-88. [http://dx.doi.org/10.1016/0378-4274\(85\)90189-4](http://dx.doi.org/10.1016/0378-4274(85)90189-4)
- Göen, T; von Helden, F; Eckert, E; Knecht, U; Drexler, H; Walter, D. (2016). Metabolism and toxicokinetics of 1,4-dioxane in humans after inhalational exposure at rest and under physical stress. *Arch Toxicol* 90: 1315-1324. <http://dx.doi.org/10.1007/s00204-015-1567-9>
- Goldberg, ME; Johnson, HE; Pozzani, UC; Smyth, HF, Jr. (1964). Effect of repeated inhalation of vapors of industrial solvents on animal behavior: I. Evaluation of nine solvent vapors on pole-climb performance in rats. *Am Ind Hyg Assoc J* 25: 369-375. <http://dx.doi.org/10.1080/00028896409342606>
- Goldsworthy, TL; Monticello, TM; Morgan, KT; Bermudez, E; Wilson, DM; Jäckh, R; BE, B. (1991). Examination of potential mechanisms of carcinogenicity of 1,4-dioxane in rat nasal epithelial cells and hepatocytes. *Arch Toxicol* 65: 1-9. <http://dx.doi.org/10.1007/BF01973495>
- Government of Canada. (2010). The Challenge: 1,4-Dioxane.
- Grasso, P; Crampton, RF. (1972). The value of the mouse in carcinogenicity testing [Review]. *Food Cosmet Toxicol* 10: 418-426.
- Hansch, C; Leo, A; Hoekman, D. (1995). Exploring QSAR: Hydrophobic, electronic, and steric constants. In C Hansch; A Leo; DH Hoekman (Eds.), *Exploring QSAR: Hydrophobic, Electronic, and Steric Constants*. Washington, DC: American Chemical Society.
- Hawkins, NC; Jaycock, MA; Lynch, J. (1992). A rationale and framework for establishing the quality of human exposure assessments. *AIHA J* 53: 34-41.
- Haworth, S; Lawlor, T; Mortelmans, K; Speck, W; Zeiger, E. (1983). Salmonella mutagenicity test results for 250 chemicals. *Environ Mutagen* 5: 3-142. <http://dx.doi.org/10.1002/em.2860050703>

- [Haynes, WM; Lide, DR; Bruno, TJ.](#) (2014). CRC handbook of chemistry and physics. In WM Haynes; DR Lide; TJ Bruno (Eds.), (95th ed.). Boca Raton, FL: CRC Press.
- [He, Y; Kilsby, S; Tuck, CJ; Wildman, RD; Christie, SDR; Edmondson, S; Yang, H.](#) (2013). Processing Biodegradable Polycaprolactone through 3D Printing. 24th International SFF Symposium - An Additive Manufacturing Conference.
- [He, Y; Wildman, RD; Tuck, CJ; Christie, SD; Edmondson, S.](#) (2016). An Investigation of the Behavior of Solvent based Polycaprolactone ink for Material Jetting. Sci Rep 6: 20852. <http://dx.doi.org/10.1038/srep20852>
- [Health Canada.](#) (2010). Screening assessment for the challenge: 1,4-Dioxane. Environment Canada, Health Canada. http://www.ec.gc.ca/ese-ees/789BC96E-F970-44A7-B306-3E32419255A6/batch7_123-91-1_en.pdf
- [Hellmér, L; Bolcsfoldi, G.](#) (1992). An evaluation of the E. coli K-12 uvrB/recA DNA repair host-mediated assay: I. In vitro sensitivity of the bacteria to 61 compounds. Mutat Res 272: 145-160. [http://dx.doi.org/10.1016/0165-1161\(92\)90043-L](http://dx.doi.org/10.1016/0165-1161(92)90043-L)
- [Heritage.](#) (2018). Incineration. Available online at <https://www.heritage-enviro.com/services/incineration/>
- [Hertlein, F.](#) (1980). Monitoring Airborne Contaminants In Chemical Laboratories (pp. 215-230). (NIOSH/00154119). Hertlein, F.
- [HomeAdvisor.](#) (2018). How Much Do Asphalt Shingles & Roofs Cost To Install Or Replace? Available online at <https://www.homeadvisor.com/cost/roofing/asphalt-shingles-install-replace/>
- [Huber, J.](#) (2018). Roofing: A Guide to the Options. Available online at <https://www.houselogic.com/organize-maintain/home-maintenance-tips/roofing-guide-options/>
- [IARC.](#) (1999). IARC monographs on the evaluation of carcinogenic risks to humans: Re-evaluation of some organic chemicals, hydrazine and hydrogen peroxide [IARC Monograph]. Lyon, France: World Health Organization.
- [ICCR.](#) (2017). Considerations on acceptable trace level of 1,4-dioxane in cosmetic products, final report. Report of the ICCR Working Group. http://www.iccrnet.org/files/2414/8717/1555/ICCR_14-Dioxane_Final_2017.pdf
- [Insitut fur Arbeitsschutz der](#) (IFA) Deutschen Gesetzlichen Unfallversicherung. (2017). GESTIS international limit values 1,4-dioxane, tech. grade. http://limitvalue.ifa.dguv.de/WebForm_ueliste2.aspx
- [Ito, N; Imaida, K; Asamoto, M; Shirai, T.](#) (2000). Early detection of carcinogenic substances and modifiers in rats [Review]. Mutat Res 462: 209-217. [http://dx.doi.org/10.1016/s1383-5742\(00\)00038-7](http://dx.doi.org/10.1016/s1383-5742(00)00038-7)
- [Itoh, S; Hattori, C.](#) (2019). In vivo genotoxicity of 1,4-dioxane evaluated by liver and bone marrow micronucleus tests and Pig-a assay in rats. Mutat Res Genet Toxicol Environ Mutagen 837: 8-14. <http://dx.doi.org/10.1016/j.mrgentox.2018.09.004>
- [JBRC.](#) (1998). Two-year studies of 1,4-dioxane in F344 rats and BDF1 mice (drinking water). Kanagawa, Japan.
- [Johnson, R; Tietge, J; Stokes, G; Lothenbach, D.](#) (1993). The medaka carcinogenesis model (pp. 147-172). Duluth, MN: U.S. Environmental Protection Agency.
- [Johnstone, RT.](#) (1959). Death due to dioxane? AMA Arch Ind Health 20: 445-447.
- [Kano, H; Umeda, Y; Kasai, T; Sasaki, T; Matsumoto, M; Yamazaki, K; Nagano, K; Arito, H; Fukushima, S.](#) (2009). Carcinogenicity studies of 1,4-dioxane administered in drinking-

- water to rats and mice for 2 years. *Food Chem Toxicol* 47: 2776-2784.
<http://dx.doi.org/10.1016/j.fct.2009.08.012>
- Kano, H; Umeda, Y; Saito, M; Senoh, H; Ohbayashi, H; Aiso, S; Yamazaki, K; Nagano, K; Fukushima, S. (2008). Thirteen-week oral toxicity of 1,4-dioxane in rats and mice. *J Toxicol Sci* 33: 141-153. <http://dx.doi.org/10.2131/jts.33.141>
- Kasai, T. (2008). [Email to Dr. Reeder L Sams regarding 1,4-Dioxane toxicity studies (Kasai et al, 2009)] [Personal Communication].
- Kasai, T; Kano, H; Umeda, Y; Sasaki, T; Ikawa, N; Nishizawa, T; Nagano, K; Arito, H; Nagashima, H; Fukushima, S. (2009). Two-year inhalation study of carcinogenicity and chronic toxicity of 1,4-dioxane in male rats. *Inhal Toxicol* 21: 889-897.
<http://dx.doi.org/10.1080/08958370802629610>
- Kasai, T; Saito, M; Senoh, H; Umeda, Y; Aiso, S; Ohbayashi, H; Nishizawa, T; Nagano, K; Fukushima, S. (2008). Thirteen-week inhalation toxicity of 1,4-dioxane in rats. *Inhal Toxicol* 20: 961-971. <http://dx.doi.org/10.1080/08958370802105397>
- Kasting, BG; Miller, MA. (2006). Kinetics of finite dose absorption through skin 2: Volatile compounds. *J Pharm Sci* 95: 268-280. <http://dx.doi.org/10.1002/jps.20497>
- KCNSC. (2018). Nuclear Security Mission. Available online at <https://kcncsc.doe.gov/missions>
- Kelley, SL; Aitchison, EW; Deshpande, M; Schnoor, JL; Alvarez, PJJ. (2001). Biodegradation of 1,4-dioxane in planted and unplanted soil: Effect of bioaugmentation with *Amycolata* sp CB1190. *Water Res* 35: 3791-3800. [http://dx.doi.org/10.1016/S0043-1354\(01\)00129-4](http://dx.doi.org/10.1016/S0043-1354(01)00129-4)
- Khudoley, VV; Mizgireuv, I; Pliss, GB. (1987). The study of mutagenic activity of carcinogens and other chemical agents with *Salmonella typhimurium* assays: Testing of 126 compounds. *Arch Geschwulstforsch* 57: 453-462.
- Kissel, JC; Bunge, AL; Frasc, HF; Kasting, GB. (2018). Dermal Exposure and Absorption of Chemicals. In CA McQueen (Ed.), (3rd ed., pp. 112-127). Oxford, UK: Elsevier Ltd.
<http://dx.doi.org/10.1016/B978-0-08-046884-6.00105-6>
- Kitchin, KT; Brown, JL. (1990). Is 1,4-dioxane a genotoxic carcinogen? *Cancer Lett* 53: 67-71.
[http://dx.doi.org/10.1016/0304-3835\(90\)90012-M](http://dx.doi.org/10.1016/0304-3835(90)90012-M)
- Kitto, JBStSC. (1992). Steam: Its Generation and Use. In JBSSC Kitto (Ed.), (40th ed.). Barberton, Ohio: The Babcock & Wilcox Company.
- Kociba, RJ; Mccollister, SB; Park, C; Torkelson, TR; Gehring, PJ. (1974). 1,4-dioxane. I. Results of a 2-year ingestion study in rats. *Toxicol Appl Pharmacol* 30: 275-286.
[http://dx.doi.org/10.1016/0041-008X\(74\)90099-4](http://dx.doi.org/10.1016/0041-008X(74)90099-4)
- Kociba, RJ; Torkelson, TR; Young, JD; Gehring, PJ. (1975). 1,4-Dioxane: Correlation of the results of chronic ingestion and inhalation studies with its dose-dependent fate in rats. In Proceedings of the 6th Annual Conference on Environmental Toxicology. Wright-Patterson Air Force Base, OH: Wright-Patterson Air Force Base, Air Force Systems Command, Aerospace Medical Division, Aerospace Medical Research Laboratory.
<https://ntrl.ntis.gov/NTRL/dashboard/searchResults.xhtml?searchQuery=ADA024899>
- Kodak. (2011). Material Safety Data Sheet: KODAK PROFESSIONAL Film Cement. Retrieved from https://www.freestylephoto.biz/pdf/msds/kodak/Kodak_Film_Cement.pdf.
- Krewski, D; Crump, KS; Farmer, J; Gaylor, DW; Howe, R; Portier, C; Salsburg, D; Sielken, RL; Van Ryzin, J. (1983). A comparison of statistical methods for low dose extrapolation utilizing time-to-tumour data. *Fundam Appl Toxicol* 3: 140-160.
[http://dx.doi.org/10.1016/S0272-0590\(83\)80075-X](http://dx.doi.org/10.1016/S0272-0590(83)80075-X)

- Kurl, RN; Poellinger, L; Lund, J; Gustafsson, JA. (1981). Effects of dioxane on RNA synthesis in the rat liver. *Arch Toxicol* 49: 29-33. <http://dx.doi.org/10.1007/BF00352068>
- Kwan, KK; Dutka, BJ; Rao, SS; Liu, D. (1990). Mutatox test: A new test for monitoring environmental genotoxic agents. *Environ Pollut* 65: 323-332. [http://dx.doi.org/10.1016/0269-7491\(90\)90124-U](http://dx.doi.org/10.1016/0269-7491(90)90124-U)
- Larranaga Md, LeRJLeRA. (2016). Hawley's condensed chemical dictionary. In LRJLRA Larranaga Md (Ed.), (16th ed.). Hoboken, NJ: John Wiley & Sons, Inc.
- Leblanc, M; Allen, JG; Herrick, RF; Stewart, JH. (2018). Comparison of the near field/far field model and the advanced reach tool (ART) model V1.5: exposure estimates to benzene during parts washing with mineral spirits. *Int J Hyg Environ Health* 221: 231-238. <http://dx.doi.org/10.1016/j.ijheh.2017.10.016>
- Leung, HW; Paustenbach, DJ. (1990). Cancer risk assessment for dioxane based upon a physiologically-based pharmacokinetic approach. *Toxicol Lett* 51: 147-162.
- Lewis, RJ, Sr. (2000). Sax's dangerous properties of industrial materials. In Sax's Dangerous Properties of Industrial Materials (10 ed.). New York, NY: John Wiley & Sons, Inc.
- Lewis, RJ, Sr. (2012). Sax's dangerous properties of industrial materials (12th ed.). Hoboken, NJ: John Wiley & Sons. <http://dx.doi.org/10.1002/0471701343>
- Lipscomb, J; Teuschler, L; Swartout, J; Striley, C; Snawder, J. (2003). Variance of Microsomal Protein and Cytochrome P450 2E1 and 3A Forms in Adult Human Liver. *Toxicol Mech Meth* 13: 45-51. <http://dx.doi.org/10.1080/15376510309821>
- Lundberg, I; Ekdahl, M; Kronevi, T; Lidums, V; Lundberg, S. (1986). Relative hepatotoxicity of some industrial solvents after intraperitoneal injection or inhalation exposure in rats. *Environ Res* 40: 411-420. [http://dx.doi.org/10.1016/S0013-9351\(86\)80116-5](http://dx.doi.org/10.1016/S0013-9351(86)80116-5)
- Lundberg, I; Hogberg, J; Kronevi, T; Holmberg, B. (1987). Three industrial solvents investigated for tumor promoting activity in the rat liver. *Cancer Lett* 36: 29-33. [http://dx.doi.org/10.1016/0304-3835\(87\)90099-1](http://dx.doi.org/10.1016/0304-3835(87)90099-1)
- Makino, R; Kawasaki, H; Kishimoto, A; Gamo, M; Nakanishi, J. (2006). Estimating health risk from exposure to 1,4-dioxane in Japan. *Environ Sci* 13: 43-58.
- Mallongi, A; Bustan, MN; Juliana, N; Herawati. (2018). Risks Assessment due to the Exposure of Copper and Nitrogen Dioxide in the Goldsmith in Malimongan Makassar.
- Marquart, H; Franken, R; Goede, H; Fransman, W; Schinkel, J. (2017). Validation of the dermal exposure model in ECETOC TRA. 61: 854-871. <http://dx.doi.org/10.1093/annweh/wxx059>
- Marzulli, FN; Anjo, DM; Maibach, HI. (1981). In vivo skin penetration studies of 2,4-toluenediamine, 2,4-diaminoanisole, 2-nitro-p-phenylenediamine, p-dioxane and N-nitrosodiethanolamine in cosmetics. *Food Cosmet Toxicol* 19: 743-747. [http://dx.doi.org/10.1016/0015-6264\(81\)90530-7](http://dx.doi.org/10.1016/0015-6264(81)90530-7)
- Mattie, DR; Bucher, TW; Carter, AL; Stoffregen, DE; Reboulet, JE. (2012). Acute Inhalation Toxicity Study of 1, 4-Dioxane in Rats (*Rattus norvegicus*). *GRA and I*: 29.
- McConnell, EE; Solleveld, HA; Swenberg, JA; Boorman, GA. (1986). Guidelines for combining neoplasms for evaluation of rodent carcinogenesis studies. *J Natl Cancer Inst* 76: 283-289. <http://dx.doi.org/10.1093/jnci/76.2.283>
- McConnell, G. (2013). Report on the review of liver slides from the National Cancer Institute's bioassay of 1,4-dioxane for possible carcinogenicity conducted in 1978. McConnell, G.
- McFee, AF; Abbott, MG; Gulati, DK; Shelby, MD. (1994). Results of mouse bone marrow micronucleus studies on 1,4-dioxane. *Mutat Res* 322: 145-148.

Mcgregor, DB; Brown, AG; Howgate, S; McBride, D; Riach, C; Caspary, WJ. (1991). Responses of the L5178Y mouse lymphoma cell forward mutation assay. V: 27 coded chemicals. *Environ Mol Mutagen* 17: 196-219. <http://dx.doi.org/10.1002/em.2850170309>

Medinsky, MA; Bond, JA. (2001). Sites and mechanisms for uptake of gases and vapors in the respiratory tract [Review]. *Toxicology* 160: 165-172. [http://dx.doi.org/10.1016/S0300-483X\(00\)00448-0](http://dx.doi.org/10.1016/S0300-483X(00)00448-0)

Mendeloff, J; D'Alessandro, M; Liu, H; Steiner, E; Kopsic, J; Burns, R. (2013). Using OSHA inspection data to analyze respirator protection program compliance. (Monthly Labor Review). U.S. Bureau of Labor Statistics. <https://doi.org/10.21916/mlr.2013.37>.

Mikheev, MI; Gorlinskaya Ye, P; Solovyova, TV. (1990). The body distribution and biological action of xenobiotics. *J Hyg Epidemiol Microbiol Immunol* 34: 329-336.

Mirkova, ET. (1994). Activity of the rodent carcinogen 1,4-dioxane in the mouse bone marrow micronucleus assay. *Mutat Res* 322: 142-144.

Mitragotri, S; Anissimov, Y; Bunge, A; Frasc, F; Guy, R; Kasting, G; Lane, M; Roberts, M. (2011). Mathematical Models of Skin Permeability: An Overview. *Int J Pharm* 418: 115-129. <http://dx.doi.org/10.1016/j.ijpharm.2011.02.023>

Miyagawa, M; Shirotori, T; Tsuchitani, M; Yoshikawa, K. (1999). Repeat-assessment of 1,4-dioxane in a rat-hepatocyte replicative DNA synthesis (RDS) test: Evidence for stimulus of hepatocyte proliferation. *Exp Toxicol Pathol* 51: 555-558.

Morita, T. (1994). No clastogenicity of 1,4 dioxane as examined in the mouse peripheral blood micronucleus test. *Mammalian Mutagenicity Study Group Communications* 2: 7-8.

Morita, T; Hayashi, M. (1998). 1,4-Dioxane is not mutagenic in five in vitro assays and mouse peripheral blood micronucleus assay, but is in mouse liver micronucleus assay. *Environ Mol Mutagen* 32: 269-280. [http://dx.doi.org/10.1002/\(SICI\)1098-2280\(1998\)32:3<269::AID-EM10>3.0.CO;2-8](http://dx.doi.org/10.1002/(SICI)1098-2280(1998)32:3<269::AID-EM10>3.0.CO;2-8)

Munoz, ER; Barnett, BM. (2002). The rodent carcinogens 1,4-dioxane and thiourea induce meiotic non-disjunction in *Drosophila melanogaster* females. *Mutat Res* 517: 231-238. [http://dx.doi.org/10.1016/S1383-5718\(02\)00083-9](http://dx.doi.org/10.1016/S1383-5718(02)00083-9)

Nannelli, A; De Rubertis, A; Longo, V; Gervasi, PG. (2005). Effects of dioxane on cytochrome P450 enzymes in liver, kidney, lung and nasal mucosa of rat. *Arch Toxicol* 79: 74-82. <http://dx.doi.org/10.1007/s00204-004-0590-z>

NCI. (1978). Bioassay of 1,4-dioxane for possible carcinogenicity. (78-1330 NCICGTR-80). Bethesda, MD. http://ntp.niehs.nih.gov/ntp/htdocs/LT_rpts/tr080.pdf

Nestmann, ER; Otson, R; Kowbel, DJ; Bothwell, PD; Harrington, TR. (1984). Mutagenicity in a modified Salmonella assay of fabric-protecting products containing 1,1,1-trichloroethane. *Environ Mol Mutagen* 6: 71-80. <http://dx.doi.org/10.1002/em.2860060109>

NICNAS. (1998). 1, 4-Dioxane. Priority existing chemical assessment report No. 7. Canberra, ACT: National Occupational Health and Safety Commission, Commonwealth of Australia. <https://www.nicnas.gov.au/chemical-information/pec-assessments>

NIOSH. (1994). Dioxane: Method 1602, issue 2. In NIOSH manual of analytical methods (NMAM) (Fourth Edition ed.). Washington, DC: National Institute for Occupational Safety and Health. <https://www.cdc.gov/niosh/docs/2003-154/pdfs/1602.pdf>

NIOSH. (2003). Respirator Usage in Private Sector Firms. Washington D.C.: United States Department of Labor, Bureau of Labor Statistics and National Institute for Occupational Safety and Health. <https://www.cdc.gov/niosh/docs/respsurv/>

- NIOSH. (2004). NIOSH pocket guide to chemical hazards: Dioxane. Cincinnati, OH.
<http://www.cdc.gov/niosh/npg/npgd0237.html>
- NIOSH. (2005). NIOSH pocket guide to chemical hazards (NPG)--index of chemical abstract numbers (CAS No): Dioxane. Cincinnati, OH.
<http://www.cdc.gov/niosh/npg/npgd0237.html>
- NITE. (2015). Chemical Risk Information Platform (CHRIP). Japan.
http://www.safe.nite.go.jp/english/sougou/view/ComprehensiveInfoDisplay_en.faces
- Nitsche, JM; Kasting, GB. (2013). A microscopic multiphase diffusion model of viable epidermis permeability. *Biophys J* 104: 2307-2320.
<http://dx.doi.org/10.1016/j.bpj.2013.03.056>
- NRC. (1994). Science and judgment in risk assessment. Washington, DC: The National Academies Press. <http://dx.doi.org/10.17226/2125>
- NRC. (1996). Use of reclaimed water and sludge in food crop production. Washington, D.C.: The National Academies Press. <http://dx.doi.org/10.17226/5175>
- NTP. (2011). 1,4-dioxane (pp. 176-178). Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service, National Toxicology Program.
<http://ntp.niehs.nih.gov/ntp/roc/twelfth/roc12.pdf>
- NTP. (2016). 14th Report on carcinogens. Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service.
<https://ntp.niehs.nih.gov/pubhealth/roc/index-1.html>
- O'Neil, MJ. (2013). The Merck index: An encyclopedia of chemicals, drugs, and biologicals. In MJ O'Neil (Ed.), (15th ed.). Cambridge, UK: Royal Society of Chemistry.
- O'Neil, MJ; Heckelman, PE; Koch, CB. (2006). The Merck index: An encyclopedia of chemicals, drugs, and biologicals (14th ed.). Whitehouse Station, NJ: Merck & Co.
- O'Neil, MJ; Smith, A; Heckelman, PE; Obenchain, JR; Gallipeau, JR; D'Arecca, MA. (2001). Dioxane. In MJ O'Neil; A Smith; PE Heckelman; JR Obenchain; JR Gallipeau; MA D'Arecca (Eds.), *The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals* (13th ed., pp. 3332). Whitehouse Station, NJ: Merck & Co., Inc.
- Obst, JR; Kirk, TK. (1988). Isolation of lignin. *Methods Enzymol* 161: 3-12.
[http://dx.doi.org/10.1016/0076-6879\(88\)61003-2](http://dx.doi.org/10.1016/0076-6879(88)61003-2)
- OECD. (1999). SIDS initial assessment profile: 1,4 Dioxane [OECD SIDS]. Paris, France.
<http://webnet.oecd.org/Hpv/UI/handler.axd?id=59ef0859-2583-4a94-ab54-00fcab06d81c>
- OECD. (2011). Emission scenario document on the use of metalworking fluids. (JT03304938). Organization for Economic Cooperation and Development.
- OEHHA. (2012). Air toxics hot spots program risk assessment guidelines: Technical support document for exposure assessment and stochastic analysis.
<https://oehha.ca.gov/media/downloads/crn/combedsmall.pdf>
- Ohmori, T; Rice, JM; Williams, GM. (1981). Histochemical characteristics of spontaneous and chemically induced hepatocellular neoplasms in mice and the development of neoplasms with gamma-glutamyl transpeptidase activity during phenobarbital exposure. *Histochem J* 13: 85-99. <http://dx.doi.org/10.1007/BF01005842>
- Okawa, MT; Coye, MJ. (1982). Health Hazard Evaluation Report, No. HETA-80-144-1109, Film Processing Industry, Hollywood, California. (NIOSH/00127502). Okawa, MT; Coye, MJ.

- OMG Roofing Products. (2018). Product Data Specifications: OMG Olybond500 Insulation Adhesive. Available online at <https://www.omgroofing.com/specifications-details.html?language=en>
- OSHA. (2005). OSHA permissible exposure limit and general information: dioxane. Washington, D.C.
- Park, JH; Hussam, A; Couasnon, P; Fritz, D; Carr, PW. (1987). Experimental reexamination of selected partition coefficients from Rohrschneider's data set. *Anal Chem* 59: 1970-1976. <http://dx.doi.org/10.1021/ac00142a016>
- Patil, PG; Kamble, SH; Shah, TS; Iyer, KR. (2015). Effect of water miscible organic solvents on p-nitrophenol hydroxylase (CYP2E1) activity in rat liver microsomes. *Indian J Pharmaceut Sci* 77: 283-289.
- Portier, CJ; Bailer, AJ. (1989). Testing for increased carcinogenicity using a survival-adjusted quantal response test. *Fundam Appl Toxicol* 12: 731-737.
- Portier, CJ; Hedges, JC; Hoel, DG. (1986). Age-specific models of mortality and tumor onset for historical control animals in the National Toxicology Program's carcinogenicity experiments. *Cancer Res* 46: 4372-4378.
- Reitz, RH; McCroskey, PS; Park, CN; Andersen, ME; Gargas, ML. (1990). Development of a physiologically based pharmacokinetic model for risk assessment with 1,4-dioxane. *Toxicol Appl Pharmacol* 105: 37-54. [http://dx.doi.org/10.1016/0041-008X\(90\)90357-Z](http://dx.doi.org/10.1016/0041-008X(90)90357-Z)
- Rimatori, V; Fronduto, M; et al. (1994). Monitoring and evaluation of occupational exposure of laboratory workers. *10*: 481-484.
- Roy, SK; Thilagar, AK; Eastmond, DA. (2005). Chromosome breakage is primarily responsible for the micronuclei induced by 1,4-dioxane in the bone marrow and liver of young CD-1 mice. *Mutat Res* 586: 28-37. <http://dx.doi.org/10.1016/j.mrgentox.2005.05.007>
- Ruggiero, F; Netti, PA; Torino, E. (2015). Experimental Investigation and Thermodynamic Assessment of Phase Equilibria in the PLLA/Dioxane/Water Ternary System for Applications in the Biomedical Field. *Langmuir* 31: 13003-13010. <http://dx.doi.org/10.1021/acs.langmuir.5b02460>
- Ryan, T; Hubbard, D. (2016). 3-D Printing Hazards: Literature Review & Preliminary Hazard Assessment. In *Professional Safety*. Ryan, T; Hubbard, D. <https://www.onepetro.org/journal-paper/ASSE-16-06-56>
- Sander, R. (2017). Henry's Law Constants in NIST chemistry WebBook: NIST standard reference database number 69. Available online at <http://webbook.nist.gov/>
- Sapphire Group. (2007). Voluntary Children's Chemical Evaluation Program [VCCEP]. Tiers 1, 2, and 3 Pilot Submission For 1,4-Dioxane. Cleveland, OH: Sponsored by Ferro Corporation, Inc. <http://www.tera.org/Peer/VCCEP/p-Dioxane/p-Dioxane%20Submission.pdf>
- Sample, S. (2004). Dermal exposure to chemicals in the workplace: just how important is skin absorption? *Occup Environ Med* 61: 376-382. <http://dx.doi.org/10.1136/oem.2003.010645>
- Shah, TS; Kamble, SH; Patil, PG; Iyer, KR. (2015). Effect of Water-miscible Organic Solvents on CYP450-mediated Metoprolol and Imipramine Metabolism in Rat Liver Microsomes. *Indian J Pharmaceut Sci* 77: 382-390.
- Sheu, CW; Moreland, FM; Lee, JK; Dunkel, VC. (1988). In vitro BALB/3T3 cell transformation assay of nonoxynol-9 and 1,4-dioxane. *Environ Mol Mutagen* 11: 41-48. <http://dx.doi.org/10.1002/em.2850110106>

- [Sina, JF; Bean, CL; Dysart, GR; Taylor, VI; Bradley, MO.](#) (1983). Evaluation of the alkaline elution/rat hepatocyte assay as a predictor of carcinogenic/mutagenic potential. *Mutat Res Environ Mutagen Relat Subj* 113: 357-391. [http://dx.doi.org/10.1016/0165-1161\(83\)90228-5](http://dx.doi.org/10.1016/0165-1161(83)90228-5)
- [Stott, WT; Quast, JF; Watanabe, PG.](#) (1981). Differentiation of the mechanisms of oncogenicity of 1,4-dioxane and 1,3-hexachlorobutadiene in the rat. *Toxicol Appl Pharmacol* 60: 287-300. [http://dx.doi.org/10.1016/0041-008X\(91\)90232-4](http://dx.doi.org/10.1016/0041-008X(91)90232-4)
- [Sugibayashi, K.](#) (2017). *Skin Permeation and Disposition of Therapeutic and Cosmeceutical Compounds*. Springer. <https://link.springer.com/book/10.1007/978-4-431-56526-0>
- [Sun, M; Lopez-Velandia, C; Knappe, DR.](#) (2016). Determination of 1,4-Dioxane in the Cape Fear River Watershed by Heated Purge-and-Trap Preconcentration and Gas Chromatography-Mass Spectrometry. *Environ Sci Technol* 50: 2246-2254. <http://dx.doi.org/10.1021/acs.est.5b05875>
- [Suter, G.](#) (2016). *Weight of evidence in ecological assessment*. (EPA100R16001). Washington, DC: U.S. Environmental Protection Agency. https://cfpub.epa.gov/si/si_public_record_report.cfm?dirEntryId=335523
- [Sweeney, LM; Thrall, KD; Poet, TS; Corley, RA; Weber, TJ; Locey, BJ; Clarkson, J; Sager, S; Gargas, ML.](#) (2008). Physiologically based pharmacokinetic modeling of 1,4-dioxane in rats, mice, and humans. *Toxicol Sci* 101: 32-50. <http://dx.doi.org/10.1093/toxsci/kfm251>
- [Take, M; Ohnishi, M; Yamamoto, S; Matsumoto, M; Nagano, K; Fukushima, S.](#) (2012). Distribution of 1,4-dioxane by combined inhalation plus oral exposure routes in rats. *Int J Environ Anal Chem* 92: 1715-1728. <http://dx.doi.org/10.1080/03067319.2011.581370>
- [Tedia.](#) (2014). SAFETY DATA SHEET: 1,4-Dioxane. Available online at <http://reports.tedia.com/msds/M0085.pdf>
- [Thiess, AM; Tress, E; Fleig, I.](#) (1976). [Industrial-medical investigation results in the case of workers exposed to dioxane]. *Arbeitsmed Sozialmed Praventivmed* 11: 35-46.
- [Tickner, J; Friar, J; Creely, KS; Cherrie, JW; Pryde, DE; Kingston, J.](#) (2005). The Development of the EASE Model. *Ann Occup Hyg* 49: 105-110.
- [Tielemans, E; Schneider, T; Goede, H; Tischer, M; Warren, N; Kromhout, H; Van Tongeren, M; Van Hemmen, J; Cherrie, JW.](#) (2008). Conceptual model for assessment of inhalation exposure: Defining modifying factors. *Ann Occup Hyg* 52: 577-586. <http://dx.doi.org/10.1093/annhyg/men059>
- [Tinwell, H; Ashby, J.](#) (1994). Activity of 1,4-dioxane in mouse bone marrow micronucleus assays. *Mutat Res* 322: 148-150.
- [Tomer, A; Kane, J.](#) (2015). *The great port mismatch*. U.S. goods trade and international transportation. The Global Cities Initiative. A joint project of Brookings and JPMorgan Chase. <https://www.brookings.edu/wp-content/uploads/2015/06/brgkssrvygcifreightnetworks.pdf>
- [ToxNet Hazardous Substances Data Bank.](#) (2017). HSDB: 1,4-Dioxane. Bethesda, MD: National Institute of Health, U.S. National Library of Medicine. Retrieved from <https://toxnet.nlm.nih.gov/newtoxnet/hsdb.htm>
- [U.S. Census Bureau.](#) (2012). *Code Lists and Crosswalks - Census 2012 Detailed Industry Code List*.
- [U.S. Census Bureau.](#) (2015). *Statistics of U.S. Businesses (SUSB)*. <https://www.census.gov/data/tables/2015/econ/susb/2015-susb-annual.html>
- [U.S. Census Bureau.](#) (2016a). *Survey of Income and Program Participation - Data*.

- [U.S. Census Bureau](#). (2016b). Survey of Income and Program Participation - SIPP Introduction and History.
- [U.S. EPA](#). (1974). Process design manual for sludge treatment and disposal [EPA Report]. (EPA 625/1-74-006). Washington, D.C.: Office of Technology Transfer.
<https://nepis.epa.gov/Exe/ZyPDF.cgi/20007TN9.PDF?Dockey=20007TN9.PDF>
- [U.S. EPA](#). (1978). OAQPS guideline series: Control of volatile organic emissions from manufacture of synthesized pharmaceutical products. (EPA-450/2-78-029). Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards. https://www3.epa.gov/airquality/ctg_act/197812_voc_epa450_2-78-029_pharmaceutical_products.pdf
- [U.S. EPA](#). (1980). USEPA status report: 1,4-Dioxane contaminated ethoxysulfate products with cover letter dated 041580 (sanitized). (8EHQ-0979-0326S). US EPA.
- [U.S. EPA](#). (1991). Chemical engineering branch manual for the preparation of engineering assessments. Volume I. Ceb Engineering Manual. Washington, DC: Office of Pollution Prevention and Toxics, US Environmental Protection Agency.
- [U.S. EPA](#). (1992). The toxics release inventory. Hazardous Waste and Hazardous Materials 1.
- [U.S. EPA](#). (1994a). Guidelines for Statistical Analysis of Occupational Exposure Data: Final. United States Environmental Protection Agency :: U.S. EPA.
- [U.S. EPA](#). (1994b). Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry [EPA Report]. (EPA/600/8-90/066F). Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Research and Development, Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office.
<https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=71993&CFID=51174829&CFTOKEN=25006317>
- [U.S. EPA](#). (1998). Guidelines for ecological risk assessment [EPA Report]. (EPA/630/R-95/002F). Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum. <https://www.epa.gov/risk/guidelines-ecological-risk-assessment>
- [U.S. EPA](#). (2001). Risk assessment guidance for superfund (RAGS: Volume III - part A, Process for conducting probabilistic risk assessment [EPA Report]. (EPA 540-R-02-002). Washington, DC: U.S. Environmental Protection Agency, Office of Emergency and Remedial Response. <http://www.epa.gov/oswer/riskassessment/rags3adt/index.htm>
- [U.S. EPA](#). (2002). A review of the reference dose and reference concentration processes (pp. 1-192). (EPA/630/P-02/002F). Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum. <http://www.epa.gov/osa/review-reference-dose-and-reference-concentration-processes>
- [U.S. EPA](#). (2005a). Guidelines for carcinogen risk assessment [EPA Report] (pp. 1-166). (EPA/630/P-03/001F). Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum. <http://www2.epa.gov/osa/guidelines-carcinogen-risk-assessment>
- [U.S. EPA](#). (2005b). Interim acute exposure guideline levels (AEGs) 1,4-dioxane. Washington, DC: NAS/COT Subcommittee for AEGs. <https://www.epa.gov/aegl/14-dioxane-results-aegl-program>
- [U.S. EPA](#). (2006a). Approaches for the application of physiologically based pharmacokinetic (PBPK) models and supporting data in risk assessment (Final Report) [EPA Report] (pp. 1-123). (EPA/600/R-05/043F). Washington, DC: U.S. Environmental Protection Agency,

- Office of Research and Development, National Center for Environmental Assessment.
<http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=157668>
- U.S. EPA. (2006b). Treatment Technologies for 1,4-Dioxane: Fundamentals and Field Applications. (EPA-542-R-06-009). Environmental Protection Agency, Office of Solid Waste and Emergency Response. http://costperformance.org/remediation/pdf/EPA-Treatment_of_1,4-Dioxane.pdf
- U.S. EPA. (2009). Toxicological review of 1,4-dioxane (CAS No. 123-91-1) in support of summary information on the Intergrated Risk Information System (IRIS) [External Review Draft] [EPA Report] (pp. 1-276). (EPA/635/R-09/005). Washington, DC. <http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=199330>
- U.S. EPA. (2010). Toxicological review of 1,4-Dioxane (CAS No. 123-91-1) in support of summary information on the Integrated Risk Information System (IRIS) [EPA Report]. (EPA635R09005F). Washington, DC. <https://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=P100FHIM.txt>
- U.S. EPA. (2011a). Exposure factors handbook: 2011 edition (final) [EPA Report]. (EPA/600/R-090/052F). Washington, DC: U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment. <http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=236252>
- U.S. EPA. (2011b). Recommended use of body weight 3/4 as the default method in derivation of the oral reference dose (pp. 1-50). (EPA/100/R11/0001). Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum, Office of the Science Advisor. <https://www.epa.gov/risk/recommended-use-body-weight-34-default-method-derivation-oral-reference-dose>
- U.S. EPA. (2012a). 2012 Edition of the drinking water standards and health advisories [EPA Report]. (EPA/822/S-12/001). Washington, DC: U.S. Environmental Protection Agency, Office of Water. https://rais.ornl.gov/documents/2012_drinking_water.pdf
- U.S. EPA. (2012b). Benchmark dose technical guidance. (EPA/100/R-12/001). Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum. <https://www.epa.gov/risk/benchmark-dose-technical-guidance>
- U.S. EPA. (2012c). Estimation Programs Interface Suite™ for Microsoft® Windows, v 4.11 [Computer Program]. Washington, DC. Retrieved from <https://www.epa.gov/tsca-screening-tools/epi-suitetm-estimation-program-interface>
- U.S. EPA. (2012d). Sustainable futures P2 framework manual [EPA Report]. (EPA-748-B12-001). Washington DC. <http://www.epa.gov/sustainable-futures/sustainable-futures-p2-framework-manual>
- U.S. EPA. (2013a). 1,4-Dioxane PBPK model code in support of IRIS assessment.
- U.S. EPA. (2013b). ChemSTEER User Guide - Chemical Screening Tool for Exposures and Environmental Releases. Environmental Protection Agency. https://www.epa.gov/sites/production/files/2015-05/documents/user_guide.pdf
- U.S. EPA. (2013c). Interpretive assistance document for assessment of discrete organic chemicals. Sustainable futures summary assessment [EPA Report]. Washington, DC. http://www.epa.gov/sites/production/files/2015-05/documents/05-iaad_discretres_june2013.pdf
- U.S. EPA. (2013d). Toxicological review of 1,4-Dioxane (with inhalation update) (CAS No. 123-91-1) in support of summary information on the Integrated Risk Information System (IRIS) [EPA Report]. (EPA-635/R-11/003-F). Washington, DC.

- U.S. EPA. (2014a). ChemView. Environmental Protection Agency.
<https://chemview.epa.gov/chemview>
- U.S. EPA. (2014b). Choosing number of stages of multistage model for cancer modeling: SOP for contractor and IRIS analysts.
- U.S. EPA. (2014c). Exposure and Fate Assessment Screening Tool Version 2014 (E-FAST 2014). <https://www.epa.gov/tsc-screening-tools/e-fast-exposure-and-fate-assessment-screening-tool-version-2014>
- U.S. EPA. (2014d). Framework for human health risk assessment to inform decision making. Final [EPA Report]. (EPA/100/R-14/001). Washington, DC: U.S. Environmental Protection, Risk Assessment Forum. <https://www.epa.gov/risk/framework-human-health-risk-assessment-inform-decision-making>
- U.S. EPA. (2014e). Human Health Evaluation Manual, Supplemental Guidance: Update of Standard Default Exposure Factors. OSWER Directive 9200.1-120. (PB91-921314). Washington, D.C.: U.S. EPA.
- U.S. EPA. (2014f). Technical Fact Sheet - 1,4-Dioxane. (EPA 505-F-14-011). Environmental Protection Agency. http://www2.epa.gov/sites/production/files/2014-03/documents/ffrro_factsheet_contaminant_14-dioxane_january2014_final.pdf
- U.S. EPA. (2014g). Technology news & trends (Issue 66 ed.). (EPA 542-N-12-002). Cincinnati, OH: U.S. Environmental Protection Agency, Solid Waste and Emergency Response. <https://nepis.epa.gov/Exe/ZyPDF.cgi/P100OPAG.PDF?Dockey=P100OPAG.PDF>
- U.S. EPA. (2015). TSCA work plan chemical problem formulation and initial assessment. 1,4-Dioxane. (740-R1-5003). Washington, DC: Environmental Protection Agency, Office of Chemical Safety and Pollution Prevention. <http://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=P100MDC1.TXT>
- U.S. EPA. (2016c). Public database 2016 chemical data reporting (May 2017 release). Washington, DC: US Environmental Protection Agency, Office of Pollution Prevention and Toxics. Retrieved from <https://www.epa.gov/chemical-data-reporting>
- U.S. EPA. (2017a). 1,4-dioxane (CASRN: 123-91-1) bibliography: Supplemental file for the TSCA Scope Document [EPA Report]. https://www.epa.gov/sites/production/files/2017-06/documents/14dioxane_comp_bib.pdf
- U.S. EPA. (2017b). Information on the various spray polyurethane foam products. U.S. Environmental Protection Agency, Design for the Environment. https://www.epa.gov/sites/production/files/2015-08/documents/spf_product_types.pdf
- U.S. EPA. (2017c). Preliminary Information on Manufacturing, Processing, Distribution, Use, and Disposal: 1,4-Dioxane. Available online at <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0723-0003>
- U.S. EPA. (2017d). Scope of the risk evaluation for 1,4-dioxane. CASRN: 123-91-1 [EPA Report]. (EPA-740-R1-7003). https://www.epa.gov/sites/production/files/2017-06/documents/dioxane_scope_06-22-2017.pdf
- U.S. EPA. (2017f). Toxics Release Inventory (TRI), reporting year 2015. Retrieved from <https://www.epa.gov/toxics-release-inventory-tri-program/tri-data-and-tools>
- U.S. EPA. (2018a). Application of Spray Polyurethane Foam Insulation - Generic Scenario for Estimating Occupational Exposures and Environmental Releases-Methodology Review Draft, Revised. Available online
- U.S. EPA. (2018b). Application of systematic review in TSCA risk evaluations. (740-P1-8001). Washington, DC: U.S. Environmental Protection Agency, Office of Chemical Safety and

- Pollution Prevention. https://www.epa.gov/sites/production/files/2018-06/documents/final_application_of_sr_in_tzca_05-31-18.pdf
- U.S. EPA. (2018c). Problem formulation of the risk evaluation for 1,4-dioxane. (EPA-740-R1-7012). Washington, DC: Office of Chemical Safety and Pollution Prevention, United States Environmental Protection Agency.
https://www.epa.gov/sites/production/files/2018-06/documents/14-dioxane_problem_formulation_5-31-18.pdf
- U.S. EPA. (2018d). Problem formulation of the risk evaluation for methylene chloride (dichloromethane, DCM). (EPA-740-R1-7016). Washington, DC: Office of Chemical Safety and Pollution Prevention, United States Environmental Protection Agency.
https://www.epa.gov/sites/production/files/2018-06/documents/mecl_problem_formulation_05-31-18.pdf
- U.S. EPA. (2018e). Strategy for assessing data quality in TSCA risk evaluations. Washington DC: U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics.
- U.S. EPA. (2018f). An umbrella Quality Assurance Project Plan (QAPP) for PBPK models [EPA Report]. (ORD QAPP ID No: B-0030740-QP-1-1). Research Triangle Park, NC.
- U.S. EPA. (2019a). Draft Risk Evaluation for 1,4-Dioxane, Systematic Review Supplemental File: Data Quality Evaluation of Environmental Fate and Transport Studies.
- U.S. EPA. (2019b). Risk Evaluation for Methylene Chloride, Systematic Review Supplemental File: Data Quality Evaluation of Environmental Hazard Studies. Docket # EPA-HQ-OPPT-2016-0742. Washington, DC.
- Uno, Y; Takasawa, H; Miyagawa, M; Inoue, Y; Murata, T; Yoshikawa, K. (1994). An in vivo-in vitro replicative DNA synthesis (RDS) test using rat hepatocytes as an early prediction assay for nongenotoxic hepatocarcinogens screening of 22 known positives and 25 noncarcinogens. *Mutat Res* 320: 189-205. [http://dx.doi.org/10.1016/0165-1218\(94\)90046-9](http://dx.doi.org/10.1016/0165-1218(94)90046-9)
- USCG. (1999). Chemical Hazards Response Information System (CHRIS) Hazardous Chemical Data. (Commandant Instruction 16465.12C). Washington, DC: Department of Transportation.
http://www.suttercountyfire.org/YSHMRT/CHRIS%20MANUAL%20CIM_16465_12C.pdf
- Versar. (2011). External Peer Review of EPA's MS-COMBO Multi-tumor Model and Test Report. (Contract No. EP-C-07-025, Task Order 97).
- Walker, AI; Thorpe, E; Stevenson, DE. (1973). The toxicology of dieldrin (HEOD). I. Long-term oral toxicity studies in mice. *Food Cosmet Toxicol* 11: 415-432.
- Washburn, S; Arsnow, D; Harris, R. (1998). Risk Analysis - Quantifying uncertainty in human health risk assessment using probabilistic techniques. Southampton: WIT Transactions on Ecology and the Environment.
- Method for Producing Polyester Polyols Having Low Amounts of Dioxane Waste, (2013).
- Almeida, RN; Costa, P; Pereira, J; Cassel, E; Rodrigues, AE. (2019). Evaporation and Permeation of Fragrance Applied to the Skin. *Industrial & Engineering Chemistry* 58: 9644-9650. <http://dx.doi.org/10.1021/acs.iecr.9b01004>.
- An, YJ; Kwak, J; Nam, SH; Jung, MS. (2014). Development and implementation of surface water quality standards for protection of human health in Korea. *Environ Sci Pollut Res Int* 21: 77-85. <http://dx.doi.org/10.1007/s11356-013-1626-9> ;
<https://link.springer.com/content/pdf/10.1007%2Fs11356-013-1626-9.pdf>.

- [Argus, MF; Arcos, JC; Hoch-Ligeti, C.](#) (1965). Studies on the carcinogenic activity of protein-denaturing agents: Hepatocarcinogenicity of dioxane. *J Natl Cancer Inst* 35: 949-958.
- [Argus, MF; Sohal, RS; Bryant, GM; Hoch-Ligeti, C; Arcos, JC.](#) (1973). Dose-response and ultrastructural alterations in dioxane carcinogenesis. Influence of methylcholanthrene on acute toxicity. *Eur J Cancer* 9: 237-243. [http://dx.doi.org/10.1016/0014-2964\(73\)90088-1](http://dx.doi.org/10.1016/0014-2964(73)90088-1).
- [ATSDR.](#) (2012). Toxicological profile for 1,4 dioxane [ATSDR Tox Profile]. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service. <http://www.atsdr.cdc.gov/toxprofiles/tp.asp?id=955&tid=199>.
- [Baciocchi, R; Berardi, S; Verginelli, I.](#) (2010). Human health risk assessment: Models for predicting the effective exposure duration of on-site receptors exposed to contaminated groundwater. *J Hazard Mater* 181: 226-233.
- [Baldwin, PE; Maynard, AD.](#) (1998). A Survey of Wind Speed in Indoor Workplaces. *Ann Occup Hyg* 42: 303-313.
- [Bannasch, P; Krech, R; Zerban, H.](#) (1980). Morphogenese und Mikromorphologie epithelialer Nierentumoren bei Nitrosomorpholin-vergifteten Ratten: IV tubulaere Laesionen und basophile Tumoren [Morphogenesis and micromorphology of epithelial tumors induced in the rat kidney by nitrosomorpholine: IV tubular lesions and basophilic tumors]. *Cancer Res* 98: 243-265.
- [Bannasch, P; Mayer, D; Krech, R.](#) (1979). NEOPLASTIC AND PRENEOPLASTIC LESIONS IN RATS AFTER ORAL-ADMINISTRATION OF A SINGLE DOSE OF N-NITROSOMORPHOLINE. *J Cancer Res Clin Oncol* 94: 233-248. <http://dx.doi.org/10.1007/BF00419283>.
- [Bannasch, P; Moore, MA; Klimek, F; Zerban, H.](#) (1982). Biological markers of preneoplastic foci and neoplastic nodules in rodent liver. *Toxicol Pathol* 10: 19-34. <http://dx.doi.org/10.1177/019262338201000204>.
- [BASF.](#) (2016). Analytical Reports and Data Summaries from Worker Monitoring at the US Facility for 1,4-Dioxane Production.
- [BASF.](#) (2017). Information in response to the "Preliminary information on manufacturing, processing, distribution, use, and disposal: 1,4-dioxane" document. <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0723-0012>.
- [BASF.](#) (2018a). BASF Additional Information re: "Problem Formulation of the Risk Evaluation for 1,4-Dioxane". (EPA-HQ-OPPT-2016-0723). <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0723-0069>.
- [BASF.](#) (2018b). Safety Data Sheet: 1,4-Dioxane. https://worldaccount.basf.com/wa/NAFTA~en_US/Catalog/ChemicalsNAFTA/doc4/BASF/PRD/30036718/.pdf?asset_type=msds/pdf&language=EN&validArea=US&urn=urn:documentum:ProductBase_EU:09007af8800a8763.pdf.
- [BLS.](#) (2014). Employee Tenure News Release.
- [BLS.](#) (2015). Hours and Employment by Industry Tables - August 6, 2015 [Website]. <http://www.bls.gov/lpc/tables.htm>.
- [BLS.](#) (2016). May 2016 Occupational Employment and Wage Estimates: National Industry-Specific Estimates [Website]. <http://www.bls.gov/oes/tables.htm>.
- [Braun, WH; Young, JD.](#) (1977). Identification of beta-hydroxyethoxyacetic acid as the major urinary metabolite of 1,4-dioxane in the rat. *Toxicol Appl Pharmacol* 39: 33-38. [http://dx.doi.org/10.1016/0041-008X\(77\)90174-0](http://dx.doi.org/10.1016/0041-008X(77)90174-0).

- [Bringman, G; Kuhn, R.](#) (1977). Limiting values of the harmful action of water endangering substances on bacteria (*Pseudomonas putida*) and green algae (*Scenedesmus quadricauda*) in the cell multiplication inhibition test. *Z f Wasser- und Abwasser-Forschung* 10: 87-98.
- [Bringmann, G; Kuehn, R.](#) (1982). Results of Toxic Action of Water Pollutants on *Daphnia magna* Straus Tested by an Improved Standardized Procedure. 15: 1-6(GER) (ENG ABS) (OECDG Data File).
- [Bringmann, G; Kuhn, R.](#) (1977). The effects of water pollutants on *Daphnia magna*. *Wasser und Abwasser in Forschung und Praxis* 10: 161-166.
- [Bringmann, G; Kuhn, R.](#) (1978). Grenzwerte der Schadwirkung wassergefährdender Stoffe gegen Blaualgen (*Microcystis aeruginosa*) und Grünalgen (*Scenedesmus quadricauda*) im Zellvermehrungshemmtest [Limiting values for the noxious effects of water pollutant material to blue algae (*Microcystis aeruginosa*) and green algae (*Scenedesmus quadricauda*) in cell propagation inhibition tests]. *Vom Wasser* 50: 45-60.
- [Bronaugh, RL.](#) (1982). Percutaneous absorption of cosmetic ingredients. In P Frost; SN Horwitz (Eds.), *Principles of cosmetics for the dermatologist* (pp. 277-284). St. Louis, MO: C.V. Mosby.
- [Brooke, L.](#) (1987). Report of the flow-through and static acute test comparisons with fathead minnows and acute tests with an amphipod and a cladoceran. Superior, WI: Center for Lake Superior Environmental Studies, University of Wisconsin.
- [Bruno, TJ; PDN, S.](#) (2006). *CRC Handbook of Fundamental Spectroscopic Correlation Charts*. Boca Raton, FL: CRC Press. <http://www.hbcnetbase.com/>.
- [Buffler, PA; Wood, SM; Suarez, L; Kilian, DJ.](#) (1978). Mortality follow-up of workers exposed to 1,4-dioxane. *J Occup Environ Med* 20: 255-259.
- [Burton, NC; Driscoll, RJ.](#) (1997). Health hazard evaluation report no. HETA-95-0293-2655, Dana Corporation, Spicer Axle Division, Fort Wayne, Indiana. (HETA-95-0293-2655). Cincinnati, OH: National Institute for Occupational Safety and Health.
- [CalRecycle.](#) (2018). Beyond 2000: California's Continuing Need for Landfills. Available online at <https://www.calrecycle.ca.gov/SWFacilities/Landfills/NeedFor> (accessed
- [Cherrie, JW; Semple, S; Brouwer, D.](#) (2004). Gloves and Dermal Exposure to Chemicals: Proposals for Evaluating Workplace Effectiveness. *Ann Occup Hyg* 48: 607-615. <http://dx.doi.org/10.1093/annhyg/meh060>.
- [Chittenden, JT; Brooks, JD; Riviere, JE.](#) (2014). Development of a Mixed-Effect Pharmacokinetic Model for Vehicle Modulated In Vitro Transdermal Flux of Topically Applied Penetrants. *J Pharm Sci* 103: 1002-1012. <http://dx.doi.org/https://doi.org/10.1002/jps.23862Get>.
- [Chittenden, JT; Riviere, JE.](#) (2015). Quantification of vehicle mixture effects on in vitro transdermal chemical flux using a random process diffusion model. *J Control Release* 217: 74-81. <http://dx.doi.org/https://doi.org/10.1016/j.jconrel.2015.08.023>.
- [Corn, M; Esmen, NA.](#) (1979). Workplace exposure zones for classification of employee exposures to physical and chemical agents. *Am Ind Hyg Assoc J* 40: 47-57. <http://dx.doi.org/10.1080/15298667991429318>.
- [Cowan, DM; Benson, SM; Cheng, TJ; Hecht, S; Boulos, NM; Henshaw, J.](#) (2017). Evaluation of reported fatality data associated with workers using respiratory protection in the United States (1990-2012). *Arch Environ Occup Health* 72: 235-246.

- [Dancik, Y; Bigliardi, PL; Bigliardi-Qi, Me.](#) (2015). What happens in the skin? Integrating skin permeation kinetics into studies of developmental and reproductive toxicity following topical exposure. *Reprod Toxicol* 58: 252-281.
<http://dx.doi.org/10.1016/j.reprotox.2015.10.001>.
- [Dawson, GW; Jennings, AL; Drozdowski, D; Rider, E.](#) (1977). The acute toxicity of 47 industrial chemicals to fresh and saltwater fishes. *J Hazard Mater* 1: 303-318.
[http://dx.doi.org/10.1016/0304-3894\(75\)80003-3](http://dx.doi.org/10.1016/0304-3894(75)80003-3).
- [Dennerlein, K; Schneider, D; Göen, T; Schaller, KH; Drexler, H; Korinth, G.](#) (2013). Studies on percutaneous penetration of chemicals - Impact of storage conditions for excised human skin. *Toxicol In Vitro* 27: 708-713. <http://dx.doi.org/10.1016/j.tiv.2012.11.016>.
- [DoD.](#) (2018). Update: DoD Exposure Data for EPA Risk Evaluation - EPA request for additional information. Available online at (accessed
- [DOE.](#) (2018a). [FW: 1,4-Dioxane]. Stites, M.
- [DOE.](#) (2018b). [RE: Discussion Follow-up]. Stites, M.
- [Dourson, M; Higginbotham, J; Crum, J; Burleigh-Flayer, H; Nance, P; Forsberg, N; Lafranconi, M; Reichard, J.](#) (2017). Update: Mode of action (MOA) for liver tumors induced by oral exposure to 1,4-dioxane. *Regul Toxicol Pharmacol* 88: 45-55.
<http://dx.doi.org/10.1016/j.yrtph.2017.02.025>.
- [Dourson, M; Reichard, J; Nance, P; Burleigh-Flayer, H; Parker, A; Vincent, M; McConnell, EE.](#) (2014). Mode of action analysis for liver tumors from oral 1,4-dioxane exposures and evidence-based dose response assessment. *Regul Toxicol Pharmacol* 68: 387-401.
<http://dx.doi.org/10.1016/j.yrtph.2014.01.011>.
- [Dow Chemical.](#) (1989a). 1,4-Dioxane: Embryo-larval toxicity test with the Fathead minnow, *Pimephales promelas Rafinesque*. (OTS: OTS0000719; 8EHQ Num: FYI-OTS-1089-0719; DCN: NA). Dow Chem Co.
<https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/OTS0000719.xhtml>.
- [Dow Chemical.](#) (1989b). Assessment of health and environmental effects of 1,4-dioxane and publications concerning 1,4-dioxane. (8EHQ-1088-0761). Office of Toxic Substances :: OTS.
- [Dow Chemical.](#) (1989c). Differentiation of the mechanisms of oncogenicity of 1,4-dioxane and 1,3-hexachlorobutadiene in the rat. (OTS: OTS0000719; 8EHQ Num: FYI-OTS-1089-0719; DCN: NA; TSCATS RefID: 404730). Midland, MI.
- [Dow Chemical.](#) (1989d). The evaluation of 1,3-hexachlorobutadiene and 1,4-dioxane in the rat hepatocyte unscheduled DNA synthesis assay. (OTS: OTS0000719; 8EHQ Num: FYI-OTS-1089-0719; DCN: NA; TSCATS RefID: 404730). Dow Chem Co.
- [Drew, RT; Patel, JM; Lin, FN.](#) (1978). Changes in serum enzymes in rats after inhalation of organic solvents singly and in combination. *Toxicol Appl Pharmacol* 45: 809-819.
[http://dx.doi.org/10.1016/0041-008X\(78\)90172-2](http://dx.doi.org/10.1016/0041-008X(78)90172-2).
- [EC.](#) (2004). Recommendation from the Scientific Committee on Occupational Exposure Limits for 1,4-dioxane. Employment, Social Affairs and Inclusion.
- [ECETOC.](#) (2006). Guidance for Setting Occupational Exposure Limits: Emphasis on Data-Poor Substances. (101). Brussels, Belgium: European Centre for Ecotoxicology and Toxicology of Chemicals.
- [ECHA.](#) (1996). 1,4- dioxane- Exp. Key Biodegradation in water: screening test.001.
<https://echa.europa.eu/registration-dossier/-/registered-dossier/15842/5/3/2>.

- [ECHA](#). (2010). Guidance on information requirements and chemical safety assessment Chapter R.8: Characterization of dose-response for human health.
- [ECHA](#). (2008). Chapter R.8: Characterisation of dose [concentration]-response for human health. In Echa (Ed.). Helsinki, Finland. http://wko.at/up/enet/chemie/TL_ChapterR8.pdf.
- [ECJRC](#). (2002). European Union risk assessment report: 1,4-dioxane. (EUR 19833 EN). Luxembourg: Office for Official Publications of the European Communities. <https://echa.europa.eu/documents/10162/a4e83a6a-c421-4243-a8df-3e84893082aa>.
- [Elcombe, CR; Peffer, RC; Wolf, DC; Bailey, J; Bars, R; Bell, D; Cattley, RC; Ferguson, SS; Geter, D; Goetz, A; Goodman, JI; Hester, S; Jacobs, A; Omiecinski, CJ; Schoeny, R; Xie, W; Lake, BG](#). (2014). Mode of action and human relevance analysis for nuclear receptor-mediated liver toxicity: A case study with phenobarbital as a model constitutive androstane receptor (CAR) activator [Review]. *Crit Rev Toxicol* 44: 64-82. <http://dx.doi.org/10.3109/10408444.2013.835786>.
- [Eleftheriadou, D; Luetete, S; and Kneuer, C](#). (2019). In silico prediction of dermal absorption of pesticides – an evaluation of selected models against results from in vitro testing. *SAR QSAR Environ Res* 30: 561-585. <http://dx.doi.org/10.1080/1062936X.2019.1644533>.
- [EPA, D](#). (2018a). Survey and risk assessment of chemical substances in chemical products used for "do-it-yourself" projects in the home. (167).
- [EPA, D](#). (2019a). Danish surveys on chemicals in consumer products. Ministry of Environment and Food of Denmark. <https://eng.mst.dk/chemicals/chemicals-in-products/consumers-consumer-products/danish-surveys-on-consumer-products/>.
- [EPA, US](#). (2010). Multi-chamber concentration and exposure model (MCCEM) version 1.2 [Website]. <https://www.epa.gov/tsca-screening-tools/multi-chamber-concentration-and-exposure-model-mccem-version-12>.
- [EPA, US](#). (2015). Evaluation of Swimmer Exposures Using the SWIMODEL Algorithms and Assumptions. https://www.epa.gov/sites/production/files/2016-11/documents/swimodel_final.pdf.
- [EPA, US](#). (2018b). Problem formulation of the risk evaluation for perchloroethylene (ethene, 1,1,2,2-tetrachloro). (EPA-740-R1-7017). Washington, DC: Office of Chemical Safety and Pollution Prevention, United States Environmental Protection Agency. https://www.epa.gov/sites/production/files/2018-06/documents/perc_problem_formulation_5-31-2018v3.pdf.
- [EPA, US](#). (2019b). Exposure factors Handbook 2019 Update. <https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=340635>.
- [EPA, US](#). (2019c). Multi-Chamber Concentration and Exposure Model (MCCEM) User Guide. U.S. EPA.
- [Ernstgard, L; Iregren, A; Sjogren, B; Johanson, G](#). (2006). Acute effects of exposure to vapours of dioxane in humans. *Hum Exp Toxicol* 25: 723-729. <http://dx.doi.org/10.1177/0960327106073805>.
- [ETC](#). (2018). High Temperature Incineration. Available online at <http://etc.org/advanced-technologies/high-temperature-incineration.aspx>. (accessed
- [FDA](#). (2007). 1,4-Dioxane- A manufacturing byproduct. Silver Spring, MD: Food and Drug Administration. <http://www.fda.gov/cosmetics/productsingredients/potentialcontaminants/ucm101566.htm>.

- [Fisher, J; Mahle, D; Bankston, L; Greene, R; Gearhart, J.](#) (1997). Lactational transfer of volatile chemicals in breast milk. *Am Ind Hyg Assoc J* 58: 425-431. <http://dx.doi.org/10.1080/15428119791012667>.
- [Frasch, FH.](#) (2012). Dermal Absorption of Finite doses of Volatile Compounds. *J Pharm Sci* 101: 2616-2619. <http://dx.doi.org/10.1080/15287394>.
- [Frasch, HF; Bunge, AL.](#) (2015). The transient dermal exposure II: post-exposure absorption and evaporation of volatile compounds. *J Pharm Sci* 104: 1499-1507. <http://dx.doi.org/10.1002/jps.24334>.
- [Frasch, HF; Dotson, GS; Barbero, AM.](#) (2011). In vitro human epidermal penetration of 1-bromopropane. *J Toxicol Environ Health A* 74: 1249-1260. <http://dx.doi.org/10.1080/15287394.2011.595666>.
- [Frasch, HF; Dotson, GS; Bunge, AL; Chen, C; Cherrie, JW; Kasting, GB; Kissel, JC; Sahmel, J; Semple, S; Wilkinson, S.](#) (2014). Analysis of finite dose dermal absorption data: Implications for dermal exposure assessment. *J Expo Sci Environ Epidemiol* 24: 65-73. <http://dx.doi.org/10.1038/jes.2013.23>.
- [GAF.](#) (2014). Safety Data Sheet: OlyBond Part B (Amber/Red). https://sweets.construction.com/swts_content_files/1772/714412.pdf.
- [Gajjar, RM; Kasting, GB.](#) (2014). Absorption of ethanol, acetone, benzene and 1,2-dichloroethane through human skin in vitro: a test of diffusion model predictions. *Toxicol Appl Pharmacol* 281: 109-117. <http://dx.doi.org/10.1016/j.taap.2014.09.013>.
- [Galloway, SM; Armstrong, MJ; Reuben, C; Colman, S; Brown, B; Cannon, C; Bloom, AD; Nakamura, F; Ahmed, M; Duk, S; Rimpo, J; Margolin, BH; Resnick, MA; Anderson, B; Zeiger, E.](#) (1987). Chromosome aberrations and sister chromatid exchanges in Chinese hamster ovary cells: evaluations of 108 chemicals [Review]. *Environ Mol Mutagen* 10: 1-175. <http://dx.doi.org/10.1002/em.2850100502>.
- [Garcia, E; Hurley, S; Nelson, DO; Hertz, A; Reynolds, P.](#) (2015). Hazardous air pollutants and breast cancer risk in California teachers: a cohort study. *Environ Health* 14: 14. <http://dx.doi.org/10.1186/1476-069X-14-14>.
- [Garrod, AN; Phillips, AM; Pemberton, JA.](#) (2001). Potential exposure of hands inside protective gloves—a summary of data from non-agricultural pesticide surveys. *Ann Occup Hyg* 45: 55-60. [http://dx.doi.org/10.1016/S0003-4878\(00\)00013-2](http://dx.doi.org/10.1016/S0003-4878(00)00013-2).
- [Geiger, DL; Brooke, LT; Call, DJ.](#) (1990). Acute toxicities of organic chemicals to fathead minnows (*Pimephales promelas*): Volume V. Superior, WI: University of Wisconsin-Superior, Center for Lake Superior Environmental Studies.
- [Gi, M; Fujioka, M; Kakehashi, A; Okuno, T; Masumura, K; Nohmi, T; Matsumoto, M; Omori, M; Wanibuchi, H; Fukushima, S.](#) (2018). In vivo positive mutagenicity of 1,4-dioxane and quantitative analysis of its mutagenicity and carcinogenicity in rats. *Arch Toxicol* 92: 3207-3221. <http://dx.doi.org/10.1007/s00204-018-2282-0>.
- [Giavini, E; Vismara, C; Broccia, ML.](#) (1985). Teratogenesis study of dioxane in rats. *Toxicol Lett* 26: 85-88. [http://dx.doi.org/10.1016/0378-4274\(85\)90189-4](http://dx.doi.org/10.1016/0378-4274(85)90189-4).
- [Göen, T; von Helden, F; Eckert, E; Knecht, U; Drexler, H; Walter, D.](#) (2016). Metabolism and toxicokinetics of 1,4-dioxane in humans after inhalational exposure at rest and under physical stress. *Arch Toxicol* 90: 1315-1324. <http://dx.doi.org/10.1007/s00204-015-1567-9>.
- [Goldberg, ME; Johnson, HE; Pozzani, UC; Smyth, HF, Jr.](#) (1964). Effect of repeated inhalation of vapors of industrial solvents on animal behavior: I. Evaluation of nine solvent vapors

- on pole-climb performance in rats. *Am Ind Hyg Assoc J* 25: 369-375.
<http://dx.doi.org/10.1080/00028896409342606>.
- [Goldsworthy, TL; Monticello, TM; Morgan, KT; Bermudez, E; Wilson, DM; Jäckh, R; BE, B.](#) (1991). Examination of potential mechanisms of carcinogenicity of 1,4-dioxane in rat nasal epithelial cells and hepatocytes. *Arch Toxicol* 65: 1-9.
<http://dx.doi.org/10.1007/BF01973495>.
- [Government of Canada.](#) (2010). The Challenge: 1,4-Dioxane.
- [Grasso, P; Crampton, RF.](#) (1972). The value of the mouse in carcinogenicity testing [Review]. *Food Cosmet Toxicol* 10: 418-426.
- [Hansch, C; Leo, A; Hoekman, D.](#) (1995). Exploring QSAR: Hydrophobic, electronic, and steric constants. In C Hansch; A Leo; DH Hoekman (Eds.), *Exploring QSAR: Hydrophobic, Electronic, and Steric Constants*. Washington, DC: American Chemical Society.
- [Hawkins, NC; Jaycock, MA; Lynch, J.](#) (1992). A rationale and framework for establishing the quality of human exposure assessments. *AIHA J* 53: 34-41.
- [Haworth, S; Lawlor, T; Mortelmans, K; Speck, W; Zeiger, E.](#) (1983). Salmonella mutagenicity test results for 250 chemicals. *Environ Mutagen* 5: 3-142.
<http://dx.doi.org/10.1002/em.2860050703>.
- [Haynes, WM; Lide, DR; Bruno, TJ.](#) (2014). CRC handbook of chemistry and physics. In WM Haynes; DR Lide; TJ Bruno (Eds.), (95th ed.). Boca Raton, FL: CRC Press.
- [He, Y; Kilsby, S; Tuck, CJ; Wildman, RD; Christie, SDR; Edmondson, S; Yang, H.](#) (2013). Processing Biodegradable Polycaprolactone through 3D Printing. 24th International SFF Symposium - An Additive Manufacturing Conference.
- [He, Y; Wildman, RD; Tuck, CJ; Christie, SD; Edmondson, S.](#) (2016). An Investigation of the Behavior of Solvent based Polycaprolactone ink for Material Jetting. *Sci Rep* 6: 20852.
<http://dx.doi.org/10.1038/srep20852>.
- [Health Canada.](#) (2010). Screening assessment for the challenge: 1,4-Dioxane. Environment Canada, Health Canada. http://www.ec.gc.ca/ese-ees/789BC96E-F970-44A7-B306-3E32419255A6/batch7_123-91-1_en.pdf.
- [Hellmér, L; Bolcsfoldi, G.](#) (1992). An evaluation of the E. coli K-12 uvrB/recA DNA repair host-mediated assay: I. In vitro sensitivity of the bacteria to 61 compounds. *Mutat Res* 272: 145-160. [http://dx.doi.org/10.1016/0165-1161\(92\)90043-L](http://dx.doi.org/10.1016/0165-1161(92)90043-L).
- [Heritage.](#) (2018). Incineration. Available online at <https://www.heritage-enviro.com/services/incineration/> (accessed
- [Hertlein, F.](#) (1980). Monitoring Airborne Contaminants In Chemical Laboratories (pp. 215-230). (NIOSH/00154119). Hertlein, F.
- [HomeAdvisor.](#) (2018). How Much Do Asphalt Shingles & Roofs Cost To Install Or Replace? Available online at <https://www.homeadvisor.com/cost/roofing/asphalt-shingles-install-replace/> (accessed
- [Huber, J.](#) (2018). Roofing: A Guide to the Options. Available online at <https://www.houselogic.com/organize-maintain/home-maintenance-tips/roofing-guide-options/> (accessed
- [IARC.](#) (1999). IARC monographs on the evaluation of carcinogenic risks to humans: Re-evaluation of some organic chemicals, hydrazine and hydrogen peroxide [IARC Monograph]. Lyon, France: World Health Organization.

- ICCR. (2017). Considerations on acceptable trace level of 1,4-dioxane in cosmetic products, final report. Report of the ICCR Working Group.
http://www.iccrnet.org/files/2414/8717/1555/ICCR_14-Dioxane_Final_2017.pdf.
- Institut für Arbeitsschutz der (IFA) Deutschen Gesetzlichen Unfallversicherung. (2017). GESTIS international limit values 1,4-dioxane, tech. grade.
http://limitvalue.ifa.dguv.de/WebForm_ueliste2.aspx.
- Isaacs, K. (2014). The consolidated human activity database - master version (CHAD-Master) technical memorandum. Washington, DC: U.S. Environmental Protection Agency, National Exposure Research Laboratory.
https://www.epa.gov/sites/production/files/2015-02/documents/chadmaster_091814_1.pdf.
- Ito, N; Imaida, K; Asamoto, M; Shirai, T. (2000). Early detection of carcinogenic substances and modifiers in rats [Review]. *Mutat Res* 462: 209-217. [http://dx.doi.org/10.1016/s1383-5742\(00\)00038-7](http://dx.doi.org/10.1016/s1383-5742(00)00038-7).
- Itoh, S; Hattori, C. (2019). In vivo genotoxicity of 1,4-dioxane evaluated by liver and bone marrow micronucleus tests and Pig-a assay in rats. *Mutat Res Genet Toxicol Environ Mutagen* 837: 8-14. <http://dx.doi.org/10.1016/j.mrgentox.2018.09.004>.
- JBRC. (1998). Two-year studies of 1,4-dioxane in F344 rats and BDF1 mice (drinking water). Kanagawa, Japan.
- Johnson, R; Tietge, J; Stokes, G; Lothenbach, D. (1993). The medaka carcinogenesis model (pp. 147-172). Duluth, MN: U.S. Environmental Protection Agency.
- Johnstone, RT. (1959). Death due to dioxane? *AMA Arch Ind Health* 20: 445-447.
- Kano, H; Umeda, Y; Kasai, T; Sasaki, T; Matsumoto, M; Yamazaki, K; Nagano, K; Arito, H; Fukushima, S. (2009). Carcinogenicity studies of 1,4-dioxane administered in drinking-water to rats and mice for 2 years. *Food Chem Toxicol* 47: 2776-2784.
<http://dx.doi.org/10.1016/j.fct.2009.08.012>.
- Kano, H; Umeda, Y; Saito, M; Senoh, H; Ohbayashi, H; Aiso, S; Yamazaki, K; Nagano, K; Fukushima, S. (2008). Thirteen-week oral toxicity of 1,4-dioxane in rats and mice. *J Toxicol Sci* 33: 141-153. <http://dx.doi.org/10.2131/jts.33.141>.
- Karlovich, B; Thompson, C; Lambach, J. (2011a). Polyurethanes Technical Conference 2010: Houston, Texas, USA, 11-13 October 2010
- A proposed methodology for development of building re-occupancy guidelines following installation of spray polyurethane foam insulation. Red Hook, NY: Curran.
- Karlovich, B; Thompson, C; Lambach, J. (2011b). A Proposed Methodology for Development of Building Re-Occupancy Guidelines Following Installation of Spray Polyurethane Foam Insulation - Revision. Pittsburgh, PA: Bayer Material Science.
<https://www.pharosproject.net/uploads/files/sources/1221/5be64ae6180cb64590e6b7db69d2666c1f5d702f.pdf>.
- Kasai, T. (2008). [Email to Dr. Reeder L Sams regarding 1,4-Dioxane toxicity studies (Kasai et al, 2009)] [Personal Communication].
- Kasai, T; Kano, H; Umeda, Y; Sasaki, T; Ikawa, N; Nishizawa, T; Nagano, K; Arito, H; Nagashima, H; Fukushima, S. (2009). Two-year inhalation study of carcinogenicity and chronic toxicity of 1,4-dioxane in male rats. *Inhal Toxicol* 21: 889-897.
<http://dx.doi.org/10.1080/08958370802629610>.

- [Kasai, T; Saito, M; Senoh, H; Umeda, Y; Aiso, S; Ohbayashi, H; Nishizawa, T; Nagano, K; Fukushima, S.](#) (2008). Thirteen-week inhalation toxicity of 1,4-dioxane in rats. *Inhal Toxicol* 20: 961-971. <http://dx.doi.org/10.1080/08958370802105397>.
- [Kasting, BG; Miller, MA.](#) (2006). Kinetics of finite dose absorption through skin 2: Volatile compounds. *J Pharm Sci* 95: 268-280. <http://dx.doi.org/10.1002/jps.20497>.
- [KCNSC.](#) (2018). Nuclear Security Mission. Available online at <https://kcns.coe.gov/missions> (accessed
- [Kelley, SL; Aitchison, EW; Deshpande, M; Schnoor, JL; Alvarez, PJJ.](#) (2001). Biodegradation of 1,4-dioxane in planted and unplanted soil: Effect of bioaugmentation with *Amycolata* sp CB1190. *Water Res* 35: 3791-3800. [http://dx.doi.org/10.1016/S0043-1354\(01\)00129-4](http://dx.doi.org/10.1016/S0043-1354(01)00129-4).
- [Khudoley, VV; Mizgireuv, I; Pliss, GB.](#) (1987). The study of mutagenic activity of carcinogens and other chemical agents with *Salmonella typhimurium* assays: Testing of 126 compounds. *Arch Geschwulstforsch* 57: 453-462.
- [Kissel, JC; Bunge, AL; Fransch, HF; Kasting, GB.](#) (2018). Dermal Exposure and Absorption of Chemicals. In CA McQueen (Ed.), (3rd ed., pp. 112-127). Oxford, UK: Elsevier Ltd. <http://dx.doi.org/10.1016/B978-0-08-046884-6.00105-6>.
- [Kitchin, KT; Brown, JL.](#) (1990). Is 1,4-dioxane a genotoxic carcinogen? *Cancer Lett* 53: 67-71. [http://dx.doi.org/10.1016/0304-3835\(90\)90012-M](http://dx.doi.org/10.1016/0304-3835(90)90012-M).
- [Kitto, JBStSC.](#) (1992). Steam: Its Generation and Use. In JBSSC Kitto (Ed.), (40th ed.). Barberton, Ohio: The Babcock & Wilcox Company.
- [Kociba, RJ; Mccollister, SB; Park, C; Torkelson, TR; Gehring, PJ.](#) (1974). 1,4-dioxane. I. Results of a 2-year ingestion study in rats. *Toxicol Appl Pharmacol* 30: 275-286. [http://dx.doi.org/10.1016/0041-008X\(74\)90099-4](http://dx.doi.org/10.1016/0041-008X(74)90099-4).
- [Kociba, RJ; Torkelson, TR; Young, JD; Gehring, PJ.](#) (1975). 1,4-Dioxane: Correlation of the results of chronic ingestion and inhalation studies with its dose-dependent fate in rats. In Proceedings of the 6th Annual Conference on Environmental Toxicology. Wright-Patterson Air Force Base, OH: Wright-Patterson Air Force Base, Air Force Systems Command, Aerospace Medical Division, Aerospace Medical Research Laboratory. <https://ntrl.ntis.gov/NTRL/dashboard/searchResults.xhtml?searchQuery=ADA024899>.
- [Kodak.](#) (2011). Material Safety Data Sheet: KODAK PROFESSIONAL Film Cement. Retrieved from https://www.freestylephoto.biz/pdf/msds/kodak/Kodak_Film_Cement.pdf.
- [Kurl, RN; Poellinger, L; Lund, J; Gustafsson, JA.](#) (1981). Effects of dioxane on RNA synthesis in the rat liver. *Arch Toxicol* 49: 29-33. <http://dx.doi.org/10.1007/BF00352068>.
- [Kwan, KK; Dutka, BJ; Rao, SS; Liu, D.](#) (1990). Mutatox test: A new test for monitoring environmental genotoxic agents. *Environ Pollut* 65: 323-332. [http://dx.doi.org/10.1016/0269-7491\(90\)90124-U](http://dx.doi.org/10.1016/0269-7491(90)90124-U).
- [Larranaga Md, LeRJLeRA.](#) (2016). Hawley's condensed chemical dictionary. In LRJLRA Larranaga Md (Ed.), (16th ed.). Hoboken, NJ: John Wiley & Sons, Inc.
- [Leblanc, M; Allen, JG; Herrick, RF; Stewart, JH.](#) (2018). Comparison of the near field/far field model and the advanced reach tool (ART) model V1.5: exposure estimates to benzene during parts washing with mineral spirits. *Int J Hyg Environ Health* 221: 231-238. <http://dx.doi.org/10.1016/j.ijheh.2017.10.016>.
- [Leung, HW; Paustenbach, DJ.](#) (1990). Cancer risk assessment for dioxane based upon a physiologically-based pharmacokinetic approach. *Toxicol Lett* 51: 147-162.
- [Lewis, RJ, Sr.](#) (2000). Sax's dangerous properties of industrial materials. In Sax's Dangerous Properties of Industrial Materials (10 ed.). New York, NY: John Wiley & Sons, Inc.

- [Lewis, RJ, Sr.](#) (2012). Sax's dangerous properties of industrial materials (12th ed.). Hoboken, NJ: John Wiley & Sons. <http://dx.doi.org/10.1002/0471701343>.
- [Lipscomb, J; Teuschler, L; Swartout, J; Striley, C; Snawder, J.](#) (2003). Variance of Microsomal Protein and Cytochrome P450 2E1 and 3A Forms in Adult Human Liver. *Toxicol Mech Meth* 13: 45-51. <http://dx.doi.org/10.1080/15376510309821>.
- [Lundberg, I; Ekdahl, M; Kronevi, T; Lidums, V; Lundberg, S.](#) (1986). Relative hepatotoxicity of some industrial solvents after intraperitoneal injection or inhalation exposure in rats. *Environ Res* 40: 411-420. [http://dx.doi.org/10.1016/S0013-9351\(86\)80116-5](http://dx.doi.org/10.1016/S0013-9351(86)80116-5).
- [Lundberg, I; Hogberg, J; Kronevi, T; Holmberg, B.](#) (1987). Three industrial solvents investigated for tumor promoting activity in the rat liver. *Cancer Lett* 36: 29-33. [http://dx.doi.org/10.1016/0304-3835\(87\)90099-1](http://dx.doi.org/10.1016/0304-3835(87)90099-1).
- [Mahdi, AJ.](#) (2014). Studies of the Physical and Chemical Properties of 1,4 Dioxane and their Relevance to Adsorption and Transdermal Absorption. Ph.D. Dissertation. Manhattan, Kansas: Kansas State University.
- [Makino, R; Kawasaki, H; Kishimoto, A; Gamo, M; Nakanishi, J.](#) (2006). Estimating health risk from exposure to 1,4-dioxane in Japan. *Environ Sci* 13: 43-58.
- [Mallongi, A; Bustan, MN; Juliana, N; Herawati.](#) (2018). Risks Assessment due to the Exposure of Copper and Nitrogen Dioxide in the Goldsmith in Malimongan Makassar.
- [Marlow, DDeJGaA.](#) (2014). Spray Polyurethane Foam Chemical Exposures during Spray Application-All About Kids, Crestwood, KY. (EPHB Report No. 005-163). National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention. <https://www.cdc.gov/niosh/surveyreports/pdfs/005-163.pdf?id=10.26613/NIOSHEPHB005163>.
- [Marquart, H; Franken, R; Goede, H; Fransman, W; Schinkel, J.](#) (2017). Validation of the dermal exposure model in ECETOC TRA. *61*: 854-871. <http://dx.doi.org/10.1093/annweh/wxx059>.
- [Marzulli, FN; Anjo, DM; Maibach, HI.](#) (1981). In vivo skin penetration studies of 2,4-toluenediamine, 2,4-diaminoanisole, 2-nitro-p-phenylenediamine, p-dioxane and N-nitrosodiethanolamine in cosmetics. *Food Cosmet Toxicol* 19: 743-747. [http://dx.doi.org/10.1016/0015-6264\(81\)90530-7](http://dx.doi.org/10.1016/0015-6264(81)90530-7).
- [Mattie, DR; Bucher, TW; Carter, AL; Stoffregen, DE; Reboulet, JE.](#) (2012). Acute Inhalation Toxicity Study of 1, 4-Dioxane in Rats (*Rattus norvegicus*). *GRA and I*: 29.
- [McConnell, EE; Solleveld, HA; Swenberg, JA; Boorman, GA.](#) (1986). Guidelines for combining neoplasms for evaluation of rodent carcinogenesis studies. *J Natl Cancer Inst* 76: 283-289. <http://dx.doi.org/10.1093/jnci/76.2.283>.
- [McConnell, G.](#) (2013). Report on the review of liver slides from the National Cancer Institute's bioassay of 1,4-dioxane for possible carcinogenicity conducted in 1978. McConnell, G.
- [McFee, AF; Abbott, MG; Gulati, DK; Shelby, MD.](#) (1994). Results of mouse bone marrow micronucleus studies on 1,4-dioxane. *Mutat Res* 322: 145-148.
- [Mcgregor, DB; Brown, AG; Howgate, S; McBride, D; Riach, C; Caspary, WJ.](#) (1991). Responses of the L5178Y mouse lymphoma cell forward mutation assay. *V*: 27 coded chemicals. *Environ Mol Mutagen* 17: 196-219. <http://dx.doi.org/10.1002/em.2850170309>.
- [Medinsky, MA; Bond, JA.](#) (2001). Sites and mechanisms for uptake of gases and vapors in the respiratory tract [Review]. *Toxicology* 160: 165-172. [http://dx.doi.org/10.1016/S0300-483X\(00\)00448-0](http://dx.doi.org/10.1016/S0300-483X(00)00448-0).

Mendeloff, J; D'Alessandro, M; Liu, H; Steiner, E; Kopsic, J; Burns, R. (2013). Using OSHA inspection data to analyze respirator protection program compliance. (Monthly Labor Review). U.S. Bureau of Labor Statistics. <https://doi.org/10.21916/mlr.2013.37>.

Mirkova, ET. (1994). Activity of the rodent carcinogen 1,4-dioxane in the mouse bone marrow micronucleus assay. *Mutat Res* 322: 142-144.

Mitragotri, S; Anissimov, Y; Bunge, A; Frasc, F; Guy, R; Kasting, G; Lane, M; Roberts, M. (2011). Mathematical Models of Skin Permeability: An Overview. *Int J Pharm* 418: 115-129. <http://dx.doi.org/10.1016/j.ijpharm.2011.02.023>.

Miyagawa, M; Shirotori, T; Tsuchitani, M; Yoshikawa, K. (1999). Repeat-assessment of 1,4-dioxane in a rat-hepatocyte replicative DNA synthesis (RDS) test: Evidence for stimulus of hepatocyte proliferation. *Exp Toxicol Pathol* 51: 555-558.

Morita, T. (1994). No clastogenicity of 1,4 dioxane as examined in the mouse peripheral blood micronucleus test. *Mammalian Mutagenicity Study Group Communications* 2: 7-8.

Morita, T; Hayashi, M. (1998). 1,4-Dioxane is not mutagenic in five in vitro assays and mouse peripheral blood micronucleus assay, but is in mouse liver micronucleus assay. *Environ Mol Mutagen* 32: 269-280. [http://dx.doi.org/10.1002/\(SICI\)1098-2280\(1998\)32:3<269::AID-EM10>3.0.CO;2-8](http://dx.doi.org/10.1002/(SICI)1098-2280(1998)32:3<269::AID-EM10>3.0.CO;2-8).

Munoz, ER; Barnett, BM. (2002). The rodent carcinogens 1,4-dioxane and thiourea induce meiotic non-disjunction in *Drosophila melanogaster* females. *Mutat Res* 517: 231-238. [http://dx.doi.org/10.1016/S1383-5718\(02\)00083-9](http://dx.doi.org/10.1016/S1383-5718(02)00083-9).

Naldzhiev, D; Mumovic, D; Strlic, M. (2019). An experimental study of spray foam insulation products-evidence of 1,2-dichloropropane and 1,4-dioxane emissions. *IOP Conference Series: Materials Science and Engineering* 609: 042053. <http://dx.doi.org/10.1088/1757-899X/609/4/042053>. https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=6322473

Nannelli, A; De Rubertis, A; Longo, V; Gervasi, PG. (2005). Effects of dioxane on cytochrome P450 enzymes in liver, kidney, lung and nasal mucosa of rat. *Arch Toxicol* 79: 74-82. <http://dx.doi.org/10.1007/s00204-004-0590-z>.

NCI. (1978). Bioassay of 1,4-dioxane for possible carcinogenicity. (78-1330 NCICGTR-80). Bethesda, MD. http://ntp.niehs.nih.gov/ntp/htdocs/LT_rpts/tr080.pdf.

Nekoomaram, J; Wieroniey, S. (2015). Comment submitted by Javaneh Nekoomaram, Counsel, Government Affairs and Stephen Wieroniey, Director, Occupational Health and Product Safety, American Coatings Association (ACA). <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2015-0078-0007>.

Nestmann, ER; Otson, R; Kowbel, DJ; Bothwell, PD; Harrington, TR. (1984). Mutagenicity in a modified Salmonella assay of fabric-protecting products containing 1,1,1-trichloroethane. *Environ Mol Mutagen* 6: 71-80. <http://dx.doi.org/10.1002/em.2860060109>.

NICNAS. (1998). 1, 4-Dioxane. Priority existing chemical assessment report No. 7. Canberra, ACT: National Occupational Health and Safety Commission, Commonwealth of Australia. <https://www.nicnas.gov.au/chemical-information/pec-assessments>.

NIOSH. (1994). Dioxane: Method 1602, issue 2. In *NIOSH manual of analytical methods (NMAM) (Fourth Edition ed.)*. Washington, DC: National Institute for Occupational Safety and Health. <https://www.cdc.gov/niosh/docs/2003-154/pdfs/1602.pdf>.

NIOSH. (2003). *Respirator Usage in Private Sector Firms*. Washington D.C.: United States Department of Labor, Bureau of Labor Statistics and National Institute for Occupational Safety and Health. <https://www.cdc.gov/niosh/docs/respsurv/>.

- NIOSH. (2004). NIOSH pocket guide to chemical hazards: Dioxane. Cincinnati, OH.
<http://www.cdc.gov/niosh/npg/npgd0237.html>.
- NIOSH. (2005). NIOSH pocket guide to chemical hazards (NPG)--index of chemical abstract numbers (CAS No): Dioxane. Cincinnati, OH.
<http://www.cdc.gov/niosh/npg/npgd0237.html>.
- NITE. (2015). Chemical Risk Information Platform (CHRIP). Japan.
http://www.safe.nite.go.jp/english/sougou/view/ComprehensiveInfoDisplay_en.faces.
- Nitsche, JM; Kasting, GB. (2013). A microscopic multiphase diffusion model of viable epidermis permeability. *Biophys J* 104: 2307-2320.
<http://dx.doi.org/10.1016/j.bpj.2013.03.056>.
- NRC. (1994). Science and judgment in risk assessment. Washington, DC: The National Academies Press. <http://dx.doi.org/10.17226/2125>.
- NRC. (1996). Use of reclaimed water and sludge in food crop production. Washington, D.C.: The National Academies Press. <http://dx.doi.org/10.17226/5175>.
- NTP. (2011). 1,4-dioxane (pp. 176-178). Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service, National Toxicology Program.
<http://ntp.niehs.nih.gov/ntp/roc/twelfth/roc12.pdf>.
- NTP. (2016). 14th Report on carcinogens. Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service.
<https://ntp.niehs.nih.gov/pubhealth/roc/index-1.html>.
- O'Neil, MJ. (2013). The Merck index: An encyclopedia of chemicals, drugs, and biologicals. In MJ O'Neil (Ed.), (15th ed.). Cambridge, UK: Royal Society of Chemistry.
- O'Neil, MJ; Heckelman, PE; Koch, CB. (2006). The Merck index: An encyclopedia of chemicals, drugs, and biologicals (14th ed.). Whitehouse Station, NJ: Merck & Co.
- O'Neil, MJ; Smith, A; Heckelman, PE; Obenchain, JR; Gallipeau, JR; D'Arecca, MA. (2001). Dioxane. In MJ O'Neil; A Smith; PE Heckelman; JR Obenchain; JR Gallipeau; MA D'Arecca (Eds.), *The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals* (13th ed., pp. 3332). Whitehouse Station, NJ: Merck & Co., Inc.
- Obst, JR; Kirk, TK. (1988). Isolation of lignin. *Methods Enzymol* 161: 3-12.
[http://dx.doi.org/10.1016/0076-6879\(88\)61003-2](http://dx.doi.org/10.1016/0076-6879(88)61003-2).
- OECD. (1999). SIDS initial assessment profile: 1,4 Dioxane [OECD SIDS]. Paris, France.
<http://webnet.oecd.org/Hpv/UI/handler.axd?id=59ef0859-2583-4a94-ab54-00fcab06d81c>.
- OECD. (2011). Emission scenario document on the use of metalworking fluids. (JT03304938). Organization for Economic Cooperation and Development.
- OEHHA. (2012). Air toxics hot spots program risk assessment guidelines: Technical support document for exposure assessment and stochastic analysis.
<https://oehha.ca.gov/media/downloads/crn/combedsmall.pdf>.
- Ohmori, T; Rice, JM; Williams, GM. (1981). Histochemical characteristics of spontaneous and chemically induced hepatocellular neoplasms in mice and the development of neoplasms with gamma-glutamyl transpeptidase activity during phenobarbital exposure. *Histochem J* 13: 85-99. <http://dx.doi.org/10.1007/BF01005842>.
- Okawa, MT; Coye, MJ. (1982). Health Hazard Evaluation Report, No. HETA-80-144-1109, Film Processing Industry, Hollywood, California. (NIOSH/00127502). Okawa, MT; Coye, MJ.

- OMG Roofing Products. (2018). Product Data Specifications: OMG Olybond500 Insulation Adhesive. Available online at <https://www.omgroofing.com/specifications-details.html?language=en> (accessed
- OSHA. (2005). OSHA permissible exposure limit and general information: dioxane. Washington, D.C.
- Park, JH; Hussam, A; Couasnon, P; Fritz, D; Carr, PW. (1987). Experimental reexamination of selected partition coefficients from Rohrschneider's data set. *Anal Chem* 59: 1970-1976. <http://dx.doi.org/10.1021/ac00142a016>.
- Patil, PG; Kamble, SH; Shah, TS; Iyer, KR. (2015). Effect of water miscible organic solvents on p-nitrophenol hydroxylase (CYP2E1) activity in rat liver microsomes. *Indian J Pharmaceut Sci* 77: 283-289.
- Poppendieck, D; Schlegel, M; Connor, A; Blickley, A. (2017). Flame retardant emissions from spray polyurethane foam insulation [Author's manuscript]. *J Occup Environ Hyg* 14: 681-693.
- Poppendieck, DGoMEms. (2017). Characterization of Emissions from Spray Polyurethane Foam: Final Report to U.S. Consumer Product Safety Commission. (NIST Technical Note 1921). National Institute of Standards and Technology. <https://doi.org/10.6028/NIST.TN.1921>.
- Potts Ro, GuRH. (1992). Predicting skin permeability. *Pharm Res* 9: 663-669.
- Reitz, RH; Mccroskey, PS; Park, CN; Andersen, ME; Gargas, ML. (1990). Development of a physiologically based pharmacokinetic model for risk assessment with 1,4-dioxane. *Toxicol Appl Pharmacol* 105: 37-54. [http://dx.doi.org/10.1016/0041-008X\(90\)90357-Z](http://dx.doi.org/10.1016/0041-008X(90)90357-Z).
- Rimatori, V; Fronduto, M; et al. (1994). Monitoring and evaluation of occupational exposure of laboratory workers. *10*: 481-484.
- Roy, SK; Thilagar, AK; Eastmond, DA. (2005). Chromosome breakage is primarily responsible for the micronuclei induced by 1,4-dioxane in the bone marrow and liver of young CD-1 mice. *Mutat Res* 586: 28-37. <http://dx.doi.org/10.1016/j.mrgentox.2005.05.007>.
- Ruggiero, F; Netti, PA; Torino, E. (2015). Experimental Investigation and Thermodynamic Assessment of Phase Equilibria in the PLLA/Dioxane/Water Ternary System for Applications in the Biomedical Field. *Langmuir* 31: 13003-13010. <http://dx.doi.org/10.1021/acs.langmuir.5b02460>.
- Ryan, T; Hubbard, D. (2016). 3-D Printing Hazards: Literature Review & Preliminary Hazard Assessment. In *Professional Safety*. Ryan, T; Hubbard, D. <https://www.onepetro.org/journal-paper/ASSE-16-06-56>.
- Sander, R. (2017). Henry's Law Constants in NIST chemistry WebBook: NIST standard reference database number 69. Available online at <http://webbook.nist.gov/> (accessed
- Sapphire Group. (2007). Voluntary Children's Chemical Evaluation Program [VCCEP]. Tiers 1, 2, and 3 Pilot Submission For 1,4-Dioxane. Cleveland, OH: Sponsored by Ferro Corporation, Inc. <http://www.tera.org/Peer/VCCEP/p-Dioxane/p-Dioxane%20Submission.pdf>.
- Semple, S. (2004). Dermal exposure to chemicals in the workplace: just how important is skin absorption? *Occup Environ Med* 61: 376-382. <http://dx.doi.org/10.1136/oem.2003.010645>.
- Shah, TS; Kamble, SH; Patil, PG; Iyer, KR. (2015). Effect of Water-miscible Organic Solvents on CYP450-mediated Metoprolol and Imipramine Metabolism in Rat Liver Microsomes. *Indian J Pharmaceut Sci* 77: 382-390.

- Sheu, CW; Moreland, FM; Lee, JK; Dunkel, VC. (1988). In vitro BALB/3T3 cell transformation assay of nonoxynol-9 and 1,4-dioxane. *Environ Mol Mutagen* 11: 41-48. <http://dx.doi.org/10.1002/em.2850110106>.
- Sina, JF; Bean, CL; Dysart, GR; Taylor, VI; Bradley, MO. (1983). Evaluation of the alkaline elution/rat hepatocyte assay as a predictor of carcinogenic/mutagenic potential. *Mutat Res Environ Mutagen Relat Subj* 113: 357-391. [http://dx.doi.org/10.1016/0165-1161\(83\)90228-5](http://dx.doi.org/10.1016/0165-1161(83)90228-5).
- Stott, WT; Quast, JF; Watanabe, PG. (1981). Differentiation of the mechanisms of oncogenicity of 1,4-dioxane and 1,3-hexachlorobutadiene in the rat. *Toxicol Appl Pharmacol* 60: 287-300. [http://dx.doi.org/10.1016/0041-008X\(91\)90232-4](http://dx.doi.org/10.1016/0041-008X(91)90232-4).
- Sugibayashi, K. (2017). *Skin Permeation and Disposition of Therapeutic and Cosmeceutical Compounds*. Springer. <https://link.springer.com/book/10.1007/978-4-431-56526-0>.
- Suter, G. (2016). *Weight of evidence in ecological assessment*. (EPA100R16001). Washington, DC: U.S. Environmental Protection Agency. https://cfpub.epa.gov/si/si_public_record_report.cfm?dirEntryId=335523.
- Sweeney, LM; Thrall, KD; Poet, TS; Corley, RA; Weber, TJ; Locey, BJ; Clarkson, J; Sager, S; Gargas, ML. (2008). Physiologically based pharmacokinetic modeling of 1,4-dioxane in rats, mice, and humans. *Toxicol Sci* 101: 32-50. <http://dx.doi.org/10.1093/toxsci/kfm251>.
- Take, M; Ohnishi, M; Yamamoto, S; Matsumoto, M; Nagano, K; Fukushima, S. (2012). Distribution of 1,4-dioxane by combined inhalation plus oral exposure routes in rats. *Int J Environ Anal Chem* 92: 1715-1728. <http://dx.doi.org/10.1080/03067319.2011.581370>.
- Tedia. (2014). SAFETY DATA SHEET: 1,4-Dioxane. Available online at <http://reports.tedia.com/msds/M0085.pdf> (accessed
- Thiess, AM; Tress, E; Fleig, I. (1976). [Industrial-medical investigation results in the case of workers exposed to dioxane]. *Arbeitsmed Sozialmed Praventivmed* 11: 35-46.
- Tickner, J; Friar, J; Creely, KS; Cherrie, JW; Pryde, DE; Kingston, J. (2005). The Development of the EASE Model. *Ann Occup Hyg* 49: 105-110.
- Tielemans, E; Schneider, T; Goede, H; Tischer, M; Warren, N; Kromhout, H; Van Tongeren, M; Van Hemmen, J; Cherrie, JW. (2008). Conceptual model for assessment of inhalation exposure: Defining modifying factors. *Ann Occup Hyg* 52: 577-586. <http://dx.doi.org/10.1093/annhyg/men059>.
- Tinwell, H; Ashby, J. (1994). Activity of 1,4-dioxane in mouse bone marrow micronucleus assays. *Mutat Res* 322: 148-150.
- Tomer, A; Kane, J. (2015). *The great port mismatch*. U.S. goods trade and international transportation. The Global Cities Initiative. A joint project of Brookings and JPMorgan Chase. <https://www.brookings.edu/wp-content/uploads/2015/06/brgkssrvygcifreightnetworks.pdf>.
- ToxNet Hazardous Substances Data Bank. (2017). HSDB: 1,4-Dioxane. Bethesda, MD: National Institute of Health, U.S. National Library of Medicine. Retrieved from <https://toxnet.nlm.nih.gov/newtoxnet/hsdb.htm>
- U.S. Census Bureau. (2012). *Code Lists and Crosswalks - Census 2012 Detailed Industry Code List*.
- U.S. Census Bureau. (2015). *Statistics of U.S. Businesses (SUSB)*. <https://www.census.gov/data/tables/2015/econ/susb/2015-susb-annual.html>.
- U.S. Census Bureau. (2016a). *Survey of Income and Program Participation - Data*.

- [U.S. Census Bureau](#). (2016b). Survey of Income and Program Participation - SIPP Introduction and History.
- [U.S. EPA](#). (1974). Process design manual for sludge treatment and disposal [EPA Report]. (EPA 625/1-74-006). Washington, D.C.: Office of Technology Transfer.
<https://nepis.epa.gov/Exe/ZyPDF.cgi/20007TN9.PDF?Dockey=20007TN9.PDF>.
- [U.S. EPA](#). (1978). OAQPS guideline series: Control of volatile organic emissions from manufacture of synthesized pharmaceutical products. (EPA-450/2-78-029). Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards. https://www3.epa.gov/airquality/ctg_act/197812_voc_epa450_2-78-029_pharmaceutical_products.pdf.
- [U.S. EPA](#). (1980). USEPA status report: 1,4-Dioxane contaminated ethoxysulfate products with cover letter dated 041580 (sanitized). (8EHQ-0979-0326S). US EPA.
- [U.S. EPA](#). (1991). Chemical engineering branch manual for the preparation of engineering assessments. Volume I. Ceb Engineering Manual. Washington, DC: Office of Pollution Prevention and Toxics, US Environmental Protection Agency.
- [U.S. EPA](#). (1992). The toxics release inventory. Hazardous Waste and Hazardous Materials 1.
- [U.S. EPA](#). (1994a). Guidelines for Statistical Analysis of Occupational Exposure Data: Final. United States Environmental Protection Agency :: U.S. EPA.
- [U.S. EPA](#). (1994b). Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry [EPA Report]. (EPA/600/8-90/066F). Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Research and Development, Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office.
<https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=71993&CFID=51174829&CFTOKEN=25006317>.
- [U.S. EPA](#). (1998). Guidelines for ecological risk assessment [EPA Report]. (EPA/630/R-95/002F). Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum. <https://www.epa.gov/risk/guidelines-ecological-risk-assessment>.
- [U.S. EPA](#). (2001). Risk assessment guidance for superfund (RAGS: Volume III - part A, Process for conducting probabilistic risk assessment [EPA Report]. (EPA 540-R-02-002). Washington, DC: U.S. Environmental Protection Agency, Office of Emergency and Remedial REsponse. <http://www.epa.gov/oswer/riskassessment/rags3adt/index.htm>.
- [U.S. EPA](#). (2002). A review of the reference dose and reference concentration processes (pp. 1-192). (EPA/630/P-02/002F). Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum. <http://www.epa.gov/osa/review-reference-dose-and-reference-concentration-processes>.
- [U.S. EPA](#). (2005a). Guidelines for carcinogen risk assessment [EPA Report] (pp. 1-166). (EPA/630/P-03/001F). Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum. <http://www2.epa.gov/osa/guidelines-carcinogen-risk-assessment>.
- [U.S. EPA](#). (2005b). Interim acute exposure guideline levels (AEGs) 1,4-dioxane. Washington, DC: NAS/COT Subcommittee for AEGs. <https://www.epa.gov/aegl/14-dioxane-results-aegl-program>.
- [U.S. EPA](#). (2006a). Approaches for the application of physiologically based pharmacokinetic (PBPK) models and supporting data in risk assessment (Final Report) [EPA Report] (pp. 1-123). (EPA/600/R-05/043F). Washington, DC: U.S. Environmental Protection Agency,

- Office of Research and Development, National Center for Environmental Assessment. <http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=157668>.
- U.S. EPA. (2006b). Treatment Technologies for 1,4-Dioxane: Fundamentals and Field Applications. (EPA-542-R-06-009). Environmental Protection Agency, Office of Solid Waste and Emergency Response. http://costperformance.org/remediation/pdf/EPA-Treatment_of_1,4-Dioxane.pdf.
- U.S. EPA. (2009). Toxicological review of 1,4-dioxane (CAS No. 123-91-1) in support of summary information on the Intergrated Risk Information System (IRIS) [External Review Draft] [EPA Report] (pp. 1-276). (EPA/635/R-09/005). Washington, DC. <http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=199330>.
- U.S. EPA. (2010). Toxicological review of 1,4-Dioxane (CAS No. 123-91-1) in support of summary information on the Integrated Risk Information System (IRIS) [EPA Report]. (EPA635R09005F). Washington, DC. <https://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=P100FHIM.txt>.
- U.S. EPA. (2011a). Exposure factors handbook: 2011 edition (final) [EPA Report]. (EPA/600/R-090/052F). Washington, DC: U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment. <http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=236252>.
- U.S. EPA. (2011b). Recommended use of body weight 3/4 as the default method in derivation of the oral reference dose (pp. 1-50). (EPA/100/R11/0001). Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum, Office of the Science Advisor. <https://www.epa.gov/risk/recommended-use-body-weight-34-default-method-derivation-oral-reference-dose>.
- U.S. EPA. (2012a). 2012 Edition of the drinking water standards and health advisories [EPA Report]. (EPA/822/S-12/001). Washington, DC: U.S. Environmental Protection Agency, Office of Water. https://rais.ornl.gov/documents/2012_drinking_water.pdf.
- U.S. EPA. (2012b). Benchmark dose technical guidance. (EPA/100/R-12/001). Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum. <https://www.epa.gov/risk/benchmark-dose-technical-guidance>.
- U.S. EPA. (2012c). Estimation Programs Interface Suite™ for Microsoft® Windows, v 4.11 [Computer Program]. Washington, DC. Retrieved from <https://www.epa.gov/tsca-screening-tools/epi-suitetm-estimation-program-interface>
- U.S. EPA. (2012d). Sustainable futures P2 framework manual [EPA Report]. (EPA-748-B12-001). Washington DC. <http://www.epa.gov/sustainable-futures/sustainable-futures-p2-framework-manual>.
- U.S. EPA. (2013a). 1,4-Dioxane PBPK model code in support of IRIS assessment.
- U.S. EPA. (2013b). ChemSTEER User Guide - Chemical Screening Tool for Exposures and Environmental Releases. Environmental Protection Agency. https://www.epa.gov/sites/production/files/2015-05/documents/user_guide.pdf.
- U.S. EPA. (2013c). Interpretive assistance document for assessment of discrete organic chemicals. Sustainable futures summary assessment [EPA Report]. Washington, DC. <http://www.epa.gov/sites/production/files/2015-05/documents/05-ia-discretet-june2013.pdf>.
- U.S. EPA. (2013d). Toxicological review of 1,4-Dioxane (with inhalation update) (CAS No. 123-91-1) in support of summary information on the Integrated Risk Information System (IRIS) [EPA Report]. (EPA-635/R-11/003-F). Washington, DC.

- U.S. EPA. (2014a). ChemView. Environmental Protection Agency.
<https://chemview.epa.gov/chemview>.
- U.S. EPA. (2014b). Choosing number of stages of multistage model for cancer modeling: SOP for contractor and IRIS analysts.
- U.S. EPA. (2014c). Exposure and Fate Assessment Screening Tool Version 2014 (E-FAST 2014). <https://www.epa.gov/tsca-screening-tools/e-fast-exposure-and-fate-assessment-screening-tool-version-2014>.
- U.S. EPA. (2014d). Framework for human health risk assessment to inform decision making. Final [EPA Report]. (EPA/100/R-14/001). Washington, DC: U.S. Environmental Protection, Risk Assessment Forum. <https://www.epa.gov/risk/framework-human-health-risk-assessment-inform-decision-making>.
- U.S. EPA. (2014e). Human Health Evaluation Manual, Supplemental Guidance: Update of Standard Default Exposure Factors. OSWER Directive 9200.1-120. (PB91-921314). Washington, D.C.: U.S. EPA.
- U.S. EPA. (2014f). Technical Fact Sheet - 1,4-Dioxane. (EPA 505-F-14-011). Environmental Protection Agency. http://www2.epa.gov/sites/production/files/2014-03/documents/ffrro_factsheet_contaminant_14-dioxane_january2014_final.pdf.
- U.S. EPA. (2014g). Technology news & trends (Issue 66 ed.). (EPA 542-N-12-002). Cincinnati, OH: U.S. Environmental Protection Agency, Solid Waste and Emergency Response. <https://nepis.epa.gov/Exe/ZyPDF.cgi/P100OPAG.PDF?Dockey=P100OPAG.PDF>.
- U.S. EPA. (2015). TSCA work plan chemical problem formulation and initial assessment. 1,4-Dioxane. (740-R1-5003). Washington, DC: Environmental Protection Agency, Office of Chemical Safety and Pollution Prevention. <http://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=P100MDC1.TXT>. https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=5176443
- U.S. EPA. (2016c). Public database 2016 chemical data reporting (May 2017 release). Washington, DC: US Environmental Protection Agency, Office of Pollution Prevention and Toxics. Retrieved from <https://www.epa.gov/chemical-data-reporting>
- U.S. EPA. (2017a). 1,4-dioxane (CASRN: 123-91-1) bibliography: Supplemental file for the TSCA Scope Document [EPA Report]. https://www.epa.gov/sites/production/files/2017-06/documents/14dioxane_comp_bib.pdf.
- U.S. EPA. (2017b). Consumer Exposure Model (CEM) version 2.0: User guide. U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics. https://www.epa.gov/sites/production/files/2017-06/documents/cem_2.0_user_guide.pdf.
- U.S. EPA. (2017c). Information on the various spray polyurethane foam products. U.S. Environmental Protection Agency, Design for the Environment. https://www.epa.gov/sites/production/files/2015-08/documents/spf_product_types.pdf.
- U.S. EPA. (2017d). Preliminary Information on Manufacturing, Processing, Distribution, Use, and Disposal: 1,4-Dioxane. Available online at <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0723-0003> (accessed
- U.S. EPA. (2017e). Scope of the risk evaluation for 1,4-dioxane. CASRN: 123-91-1 [EPA Report]. (EPA-740-R1-7003). https://www.epa.gov/sites/production/files/2017-06/documents/dioxane_scope_06-22-2017.pdf. https://hero.epa.gov/hero/index.cfm?action=search.view&reference_id=5041148
- U.S. EPA. (2017g). Toxics Release Inventory (TRI), reporting year 2015. Retrieved from <https://www.epa.gov/toxics-release-inventory-tri-program/tri-data-and-tools>

- [U.S. EPA](#). (2018a). Application of Spray Polyurethane Foam Insulation - Generic Scenario for Estimating Occupational Exposures and Environmental Releases-Methodology Review Draft, Revised. Available online at (accessed
- [U.S. EPA](#). (2018b). Application of systematic review in TSCA risk evaluations. (740-P1-8001). Washington, DC: U.S. Environmental Protection Agency, Office of Chemical Safety and Pollution Prevention. https://www.epa.gov/sites/production/files/2018-06/documents/final_application_of_sr_in_tsc_a_05-31-18.pdf.
- [U.S. EPA](#). (2018c). Problem formulation of the risk evaluation for 1,4-dioxane. (EPA-740-R1-7012). Washington, DC: Office of Chemical Safety and Pollution Prevention, United States Environmental Protection Agency. https://www.epa.gov/sites/production/files/2018-06/documents/14-dioxane_problem_formulation_5-31-18.pdf.
- [U.S. EPA](#). (2018d). Problem formulation of the risk evaluation for methylene chloride (dichloromethane, DCM). (EPA-740-R1-7016). Washington, DC: Office of Chemical Safety and Pollution Prevention, United States Environmental Protection Agency. https://www.epa.gov/sites/production/files/2018-06/documents/mecl_problem_formulation_05-31-18.pdf.
- [U.S. EPA](#). (2018e). Strategy for assessing data quality in TSCA risk evaluations. Washington DC: U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics.
- [U.S. EPA](#). (2018f). An umbrella Quality Assurance Project Plan (QAPP) for PBPK models [EPA Report]. (ORD QAPP ID No: B-0030740-QP-1-1). Research Triangle Park, NC.
- [U.S. EPA](#). (2019a). Consumer Exposure Model (CEM) 2.1 User Guide. (EPA Contract # EP-W-12-010). Washington, DC.
- [U.S. EPA](#). (2019b). Consumer Exposure Model (CEM) 2.1 User Guide - Appendices. (EPA Contract # EP-W-12-010). Washington, DC.
- [U.S. EPA](#). (2019c). Draft Risk Evaluation for 1,4-Dioxane, Systematic Review Supplemental File: Data Quality Evaluation of Environmental Fate and Transport Studies.
- [U.S. EPA](#). (2019d). Risk Evaluation for Methylene Chloride, Systematic Review Supplemental File: Data Quality Evaluation of Environmental Hazard Studies. Docket # EPA-HQ-OPPT-2016-0742. Washington, DC.
- [Uno, Y; Takasawa, H; Miyagawa, M; Inoue, Y; Murata, T; Yoshikawa, K](#). (1994). An in vivo-in vitro replicative DNA synthesis (RDS) test using rat hepatocytes as an early prediction assay for nongenotoxic hepatocarcinogens screening of 22 known positives and 25 noncarcinogens. *Mutat Res* 320: 189-205. [http://dx.doi.org/10.1016/0165-1218\(94\)90046-9](http://dx.doi.org/10.1016/0165-1218(94)90046-9).
- [USCG](#). (1999). Chemical Hazards Response Information System (CHRIS) Hazardous Chemical Data. (Commandant Instruction 16465.12C). Washington, DC: Department of Transportation. http://www.suttercountyfire.org/YSHMRT/CHRIS%20MANUAL%20CIM_16465_12C.pdf.
- [Versar](#). (2011). External Peer Review of EPA's MS-COMBO Multi-tumor Model and Test Report. (Contract No. EP-C-07-025, Task Order 97).
- [Walker, AI; Thorpe, E; Stevenson, DE](#). (1973). The toxicology of dieldrin (HEOD). I. Long-term oral toxicity studies in mice. *Food Cosmet Toxicol* 11: 415-432.

- [Washburn, S; Arsnow, D; Harris, R.](#) (1998). Risk Analysis - Quantifying uncertainty in human health risk assessment using probabilistic techniques. Southampton: WIT Transactions on Ecology and the Environment.
- [Whalan, JE.](#) (2000). A guide to clinical pathology in animals. Whalan, JE.
- [WHO.](#) (2005). 1,4-Dioxane in drinking water. (WHO/SDE/WSH/05.08/120). Geneva, Switzerland.
- [WHO.](#) (2006). Protecting groundwater for health: Managing the quality of drinking-water sources. London, UK.
http://apps.who.int/iris/bitstream/10665/43186/1/9241546689_eng.pdf.
- [Wilbur, S; Jones, D; Risher, JF; Crawford, J; Tencza, B; Llados, F; Diamond, GL; Citra, M; Osier, MR; Lockwood, LO.](#) (2012). Toxicological Profile for 1,4-Dioxane. Atlanta (GA): Agency for Toxic Substances and Disease Registry (US).
- [Williams, GM; Hirota, N; Rice, JM.](#) (1979). The resistance of spontaneous mouse hepatocellular neoplasms to iron accumulation during rapid iron loading by parenteral administration and their transplantability. *Am J Pathol* 94: 65-74.
- [Wirth, W; Klimmer, O.](#) (1936). [On the toxicology of organic solvents. 1,4 dioxane (diethylene dioxide)]. *Archiv fuer Gewerbepathologie und Gewerbehygiene* 17: 192-206.
- [Won, DNoGYaWCoP.](#) (2014). Material Emissions Testing: VOCs from Wood, Paint, and Insulation Materials. National Research Council of Canada.
<http://dx.doi.org/https://doi.org/10.4224/23002015>.
- [Woo, Yt; Arcos, JC; Argus, MF.](#) (1977a). Metabolism in vivo of dioxane: identification of p-dioxane-2-one as the major urinary metabolite. *Biochem Pharmacol* 26: 1535-1538.
- [Woo, YT; Arcos, JC; Argus, MF; Griffin, GW; K, N.](#) (1977b). Structural identification of p-dioxane-2-one as the major urinary metabolite of p-dioxane. *Naunyn-Schmiedebergs Arch Pharmacol* 299: 283-287. <http://dx.doi.org/10.1007/BF00500322>.
- [Woo, YT; Argus, MF; Arcos, JC.](#) (1977c). Tissue and subcellular distribution of 3H-dioxane in the rat and apparent lack of microsomal-catalyzed covalent binding in the target tissue. *Life Sci* 21: 1447-1456. [http://dx.doi.org/10.1016/0024-3205\(77\)90199-0](http://dx.doi.org/10.1016/0024-3205(77)90199-0).
- [Woo, YT; Argus, MF; Arcos, JC.](#) (1978). Effect of mixed-function oxidase modifiers on metabolism and toxicity of the oncogen dioxane. *Cancer Res* 38: 1621-1625.
- [Yalkowsky, SH; He, Y; Jain, P.](#) (2010). Handbook of aqueous solubility data (2nd ed.). Boca Raton, FL: CRC Press. <http://dx.doi.org/10.1201/EBK1439802458>.
- [Yamazaki, K; Ohno, H; Asakura, M; Narumi, A; Ohbayashi, H; Fujita, H; Ohnishi, M; Katagiri, T; Senoh, H; Yamanouchi, K; Nakayama, E; Yamamoto, S; Noguchi, T; Nagano, K; Enomoto, M; Sakabe, H.](#) (1994). Two-year toxicological and carcinogenesis studies of 1,4-dioxane in F344 rats and BDF1 mice. In K Sumino; S Sato; NG Shinkokai (Eds.), Proceedings: Second Asia-Pacific Symposium on Environmental and Occupational Health 22-24 July, 1993: Kobe (pp. 193-198). Kobe, Japan: Kobe University School of Medicine, International Center for Medical Research.
- [Yant, WP; Schrenk, HH; Waite, CP; Patty, FA.](#) (1930). Acute response of guinea pigs to vapors of some new commercial organic compounds: VI. Dioxan. *Public Health Rep* 45: 2023-2032.
- [Yoon, JS; Mason, JM; Valencia, R; Woodruff, RC; Zimmering, S.](#) (1985). Chemical mutagenesis testing in *Drosophila*. IV. Results of 45 coded compounds tested for the National Toxicology Program. *Environ Mutagen* 7: 349-367.
<http://dx.doi.org/10.1002/em.2860070310>.

- [Young, JD; Braun, WH; Gehring, PJ.](#) (1978a). The dose-dependent fate of 1,4-dioxane in rats. *J Environ Pathol Toxicol* 2: 263-282.
- [Young, JD; Braun, WH; Gehring, PJ.](#) (1978b). Dose-dependent fate of 1,4-dioxane in rats. *J Toxicol Environ Health A* 4: 709-726. <http://dx.doi.org/10.1080/15287397809529693>.
- [Young, JD; Braun, WH; Gehring, PJ; Horvath, BS; Daniel, RL.](#) (1976). 1,4-Dioxane and beta-hydroxyethoxyacetic acid excretion in urine of humans exposed to dioxane vapors. *Toxicol Appl Pharmacol* 38: 643-646. [http://dx.doi.org/10.1016/0041-008X\(76\)90195-2](http://dx.doi.org/10.1016/0041-008X(76)90195-2).
- [Young, JD; Braun, WH; Rampy, LW; Chenoweth, MB; Blau, GE.](#) (1977). Pharmacokinetics of 1,4-dioxane in humans. *J Toxicol Environ Health* 3: 507-520. <http://dx.doi.org/10.1080/15287397709529583>.
- [Zhang, Q; Sharma, G; Wong, JPS; Davis, AY; Black, MS; Biswas, P; Weber, RJ.](#) (2018). Investigating particle emissions and aerosol dynamics from a consumer fused deposition modeling 3D printer with a lognormal moment aerosol model. *Aerosol Sci Technol* 52: 1099-1111. <http://dx.doi.org/http://doi.org/10.1080/02786826.2018.1464115>.
- [Zhang, Q; Wong, JPS; Davis, AY; Black, MS; Weber, RJ.](#) (2017). Characterization of particle emissions from consumer fused deposition modeling 3D printers. *Aerosol Sci Technol* 51: 1275-1286. <http://dx.doi.org/10.1080/02786826.2017.1342029>.
- [Zimmermann, FK; Mayer, VW; Scheel, I; Resnick, MA.](#) (1985). Acetone, methyl ethyl ketone, ethyl acetate, acetonitrile and other polar aprotic solvents are strong inducers of aneuploidy in *Saccharomyces cerevisiae*. *Mutat Res* 149: 339-351. [http://dx.doi.org/10.1016/0027-5107\(85\)90150-2](http://dx.doi.org/10.1016/0027-5107(85)90150-2).
- [WHO.](#) (2005). 1,4-Dioxane in drinking water. (WHO/SDE/WSH/05.08/120). Geneva, Switzerland.
- [WHO.](#) (2006). Protecting groundwater for health: Managing the quality of drinking-water sources. London, UK. http://apps.who.int/iris/bitstream/10665/43186/1/9241546689_eng.pdf
- [Wilbur, S; Jones, D; Risher, JF; Crawford, J; Tencza, B; Lladós, F; Diamond, GL; Citra, M; Osier, MR; Lockwood, LO.](#) (2012). Toxicological Profile for 1,4-Dioxane. Atlanta (GA): Agency for Toxic Substances and Disease Registry (US).
- [Williams, GM; Hirota, N; Rice, JM.](#) (1979). The resistance of spontaneous mouse hepatocellular neoplasms to iron accumulation during rapid iron loading by parenteral administration and their transplantability. *Am J Pathol* 94: 65-74.
- [Wirth, W; Klimmer, O.](#) (1936). [On the toxicology of organic solvents. 1,4 dioxane (diethylene dioxide)]. *Archiv fuer Gewerbepathologie und Gewerbehygiene* 17: 192-206.
- [Woo, Yt; Arcos, JC; Argus, MF.](#) (1977a). Metabolism in vivo of dioxane: identification of p-dioxane-2-one as the major urinary metabolite. *Biochem Pharmacol* 26: 1535-1538.
- [Woo, YT; Arcos, JC; Argus, MF; Griffin, GW; K, N.](#) (1977b). Structural identification of p-dioxane-2-one as the major urinary metabolite of p-dioxane. *Naunyn-Schmiedeberg's Arch Pharmacol* 299: 283-287. <http://dx.doi.org/10.1007/BF00500322>
- [Woo, YT; Argus, MF; Arcos, JC.](#) (1977c). Tissue and subcellular distribution of 3H-dioxane in the rat and apparent lack of microsome-catalyzed covalent binding in the target tissue. *Life Sci* 21: 1447-1456. [http://dx.doi.org/10.1016/0024-3205\(77\)90199-0](http://dx.doi.org/10.1016/0024-3205(77)90199-0)
- [Woo, YT; Argus, MF; Arcos, JC.](#) (1978). Effect of mixed-function oxidase modifiers on metabolism and toxicity of the oncogen dioxane. *Cancer Res* 38: 1621-1625.
- [Yalkowsky, SH; He, Y; Jain, P.](#) (2010). Handbook of aqueous solubility data (2nd ed.). Boca Raton, FL: CRC Press. <http://dx.doi.org/10.1201/EBK1439802458>

- [Yamazaki, K; Ohno, H; Asakura, M; Narumi, A; Ohbayashi, H; Fujita, H; Ohnishi, M; Katagiri, T; Senoh, H; Yamanouchi, K; Nakayama, E; Yamamoto, S; Noguchi, T; Nagano, K; Enomoto, M; Sakabe, H.](#) (1994). Two-year toxicological and carcinogenesis studies of 1,4-dioxane in F344 rats and BDF1 mice. In K Sumino; S Sato; NG Shinkokai (Eds.), Proceedings: Second Asia-Pacific Symposium on Environmental and Occupational Health 22-24 July, 1993: Kobe (pp. 193-198). Kobe, Japan: Kobe University School of Medicine, International Center for Medical Research.
- [Yant, WP; Schrenk, HH; Waite, CP; Patty, FA.](#) (1930). Acute response of guinea pigs to vapors of some new commercial organic compounds: VI. Dioxan. Public Health Rep 45: 2023-2032.
- [Yoon, JS; Mason, JM; Valencia, R; Woodruff, RC; Zimmering, S.](#) (1985). Chemical mutagenesis testing in *Drosophila*. IV. Results of 45 coded compounds tested for the National Toxicology Program. Environ Mutagen 7: 349-367.
<http://dx.doi.org/10.1002/em.2860070310>
- [Young, JD; Braun, WH; Gehring, PJ.](#) (1978a). The dose-dependent fate of 1,4-dioxane in rats. J Environ Pathol Toxicol 2: 263-282.
- [Young, JD; Braun, WH; Gehring, PJ.](#) (1978b). Dose-dependent fate of 1,4-dioxane in rats(b). J Toxicol Environ Health A 4: 709-726. <http://dx.doi.org/10.1080/15287397809529693>
- [Young, JD; Braun, WH; Gehring, PJ; Horvath, BS; Daniel, RL.](#) (1976). 1,4-Dioxane and beta-hydroxyethoxyacetic acid excretion in urine of humans exposed to dioxane vapors. Toxicol Appl Pharmacol 38: 643-646. [http://dx.doi.org/10.1016/0041-008X\(76\)90195-2](http://dx.doi.org/10.1016/0041-008X(76)90195-2)
- [Young, JD; Braun, WH; Rampy, LW; Chenoweth, MB; Blau, GE.](#) (1977). Pharmacokinetics of 1,4-dioxane in humans. J Toxicol Environ Health 3: 507-520.
<http://dx.doi.org/10.1080/15287397709529583>
- [Zhang, Q; Sharma, G; Wong, JPS; Davis, AY; Black, MS; Biswas, P; Weber, RJ.](#) (2018). Investigating particle emissions and aerosol dynamics from a consumer fused deposition modeling 3D printer with a lognormal moment aerosol model. Aerosol Sci Technol 52: 1099-1111. <http://dx.doi.org/http://doi.org/10.1080/02786826.2018.1464115>
- [Zhang, Q; Wong, JPS; Davis, AY; Black, MS; Weber, RJ.](#) (2017). Characterization of particle emissions from consumer fused deposition modeling 3D printers. Aerosol Sci Technol 51: 1275-1286. <http://dx.doi.org/10.1080/02786826.2017.1342029>
- [Zimmermann, FK; Mayer, VW; Scheel, I; Resnick, MA.](#) (1985). Acetone, methyl ethyl ketone, ethyl acetate, acetonitrile and other polar aprotic solvents are strong inducers of aneuploidy in *Saccharomyces cerevisiae*. Mutat Res 149: 339-351.
[http://dx.doi.org/10.1016/0027-5107\(85\)90150-2](http://dx.doi.org/10.1016/0027-5107(85)90150-2)

APPENDICES

Appendix A REGULATORY HISTORY

A.1 Federal Laws and Regulations

Table A-1. Federal Laws and Regulations

Statutes/ Regulations	Description of Authority/Regulation	Description of Regulation
EPA Regulations		
TSCA – Section 6(b)	EPA is directed to identify and begin risk evaluations on 10 chemical substances drawn from the 2014 update of the TSCA Work Plan for Chemical Assessments.	1,4-Dioxane is on the initial list of chemicals to be evaluated for risk under TSCA (81 FR 91927, December 19, 2016).
TSCA – Section 8(a)	The TSCA Section 8(a) CDR Rule requires manufacturers (including importers) to give EPA basic exposure-related information on the types, quantities and uses of chemical substances produced domestically and imported into the United States.	1,4-Dioxane manufacturing (including importing), processing distribution and use information is reported under the CDR rule information about chemicals in commerce in the United States.
TSCA – Section 8(b)	EPA must compile, keep current and publish a list (the TSCA Inventory) of each chemical substance manufactured or processed in the United States.	1,4-Dioxane was on the initial TSCA Inventory and therefore was not subject to EPA’s new chemicals review process.
TSCA – Section 8(e)	Manufacturers (including importers), processors and distributors must immediately notify EPA if they obtain information that supports the conclusion that a chemical substance or mixture presents a substantial risk of injury to health or the environment.	Ten substantial risk reports from 1989 to 2004 U.S. EPA (2014a) Accessed April 13, 2017.
EPCRA – Section 313	Requires annual reporting from facilities in specific industry sectors that employ 10 or more full time equivalent employees and that manufacture, process or otherwise use a TRI-listed chemical in quantities above threshold levels.	1,4-Dioxane is a listed substance subject to reporting requirements under 40 CFR § 372.65 effective as of January 01, 1987.
Federal Food, Drug, and Cosmetic Act	FFDCA governs the allowable residues of pesticides in food. Section 408 of the FFDCA provides EPA with the authority to	In 1998, 1,4-dioxane was removed from the list of pesticide product inert

Statutes/ Regulations	Description of Authority/Regulation	Description of Regulation
(FFDCA) – Section 408	set tolerances (rules that establish maximum allowable residue limits) or exemptions from the requirement of a tolerance, for all residues of a pesticide (including both active and inert ingredients) that are in or on food. Prior to issuing a tolerance or exemption from tolerance, EPA must determine that the tolerance or exemption is “safe.” Sections 408(b) and (c) of the FFDCA define “safe” to mean the Agency has reasonable certainty that no harm will result from aggregate exposures to the pesticide residue, including all dietary exposure and all other exposure (e.g., non-occupational exposures) for which there is reliable information. Pesticide tolerances or exemptions from tolerance that do not meet the FFDCA safety standard are subject to revocation. In the absence of a tolerance or an exemption from tolerance, a food containing a pesticide residue is considered adulterated and may not be distributed in interstate commerce.	ingredients because it was no longer being used in pesticide products. 1,4-Dioxane is also no longer exempt from the requirement of a tolerance (the maximum residue level that can remain on food or feed commodities under 40 CFR Part 180, Subpart D).
CAA – Section 111(b)	Requires EPA to establish new source performance standards (NSPS) for any category of new or modified stationary sources that EPA determines causes, or contributes significantly to, air pollution, which may reasonably be anticipated to endanger public health or welfare. The standards are based on the degree of emission limitation achievable through the application of the best system of emission reduction (BSER) which (considering the cost of achieving reductions and environmental impacts and energy requirements) EPA determines has been adequately demonstrated.	1,4-Dioxane is subject to the NSPS for equipment leaks of volatile organic compounds (VOCs) in the synthetic organic chemicals manufacturing industry for which construction, reconstruction or modification began after 1/5/1981 and on or before 11/7/2006 (40 CFR Part 60, Subpart VV).
CAA – Section 112(b)	Defines the original list of 189 hazardous air pollutants (HAP). Under 112(c) of the CAA, EPA must identify and list source categories that emit HAP and then set	1,4-Dioxane is listed as a HAP under section 112 (42 U.S.C. § 7412) of the CAA.

Statutes/ Regulations	Description of Authority/Regulation	Description of Regulation
	<p>emission standards for those listed source categories under CAA section 112(d). CAA section 112(b)(3)(A) specifies that any person may petition the Administrator to modify the list of HAP by adding or deleting a substance.</p>	
<p>CAA – Section 112(d)</p>	<p>Section 112(d) states that the EPA must establish (NESHAPs for each category or subcategory of major sources and area sources of HAPs [listed pursuant to Section 112(c)]. The standards must require the maximum degree of emission reduction that the EPA determines to be achievable by each particular source category. Different criteria for maximum achievable control technology (MACT) apply for new and existing sources. Less stringent standards, known as generally available control technology (GACT) standards, are allowed at the Administrator's discretion for area sources.</p>	<p>There are a number of source-specific NESHAPs that are applicable to 1,4-dioxane, including: Organic Hazardous Air Pollutants from the Synthetic Organic Chemical Manufacturing Industry (40 CFR Part 63, Subpart F), Organic Hazardous Air Pollutants from the Synthetic Organic Chemical Manufacturing Industry for Process Vents, Storage Vessels, Transfer Operations, and Wastewater (40 CFR Part 63, Subpart G) Off-Site Waste and Recovery Operations (40 CFR Part 63, Subpart DD), Wood Furniture Manufacturing Operations (40 CFR Part 63, Subpart JJ), Pharmaceuticals Production (40 CFR Part 63, Subpart GGG), Group IV Polymers and Resins (thermoplastic product manufacturing) (40 CFR Part 63, Subpart JJJ), Organic Liquids Distribution (Non-gasoline) (40 CFR Part 63, Subpart EEEE), Miscellaneous Organic Chemical Manufacturing (40 CFR Part 63, Subpart FFFF),</p>

Statutes/ Regulations	Description of Authority/Regulation	Description of Regulation
		Site Remediation (40 CFR Part 63, Subpart GGGGG), and Miscellaneous Coating Manufacturing (40 CFR Part 63, Subpart HHHHH).
Comprehensive Environmental Response, Compensation and Liability Act (CERCLA) – Sections 102(a) and 103	Authorizes EPA to promulgate regulations designating as hazardous substances those substances which, when released into the environment, may present substantial danger to the public health or welfare or the environment. EPA must also promulgate regulations establishing the quantity of any hazardous substance the release of which must be reported under Section 103. Section 103 requires persons in charge of vessels or facilities to report to the National Response Center if they have knowledge of a release of a hazardous substance above the reportable quantity threshold.	1,4-Dioxane is a hazardous substance under CERCLA. Releases of 1,4-dioxane in excess of 100 pounds must be reported (40 CFR 302.4).
Safe Drinking Water Act (SDWA) – Section 1412(b)	Every 5 years, EPA must publish a list of contaminants that: (1) are currently unregulated, (2) are known or anticipated to occur in public water systems (PWSs) and (3) may require regulations under SDWA. EPA must also determine whether to regulate at least five contaminants from the list every 5 years.	1,4-dioxane was identified on both the Third (2009) and Fourth (2016) Contaminant Candidate List (CCL) (74 FR 51850, October 8, 2009) (81 FR 81099, November 17, 2016).
SDWA – Section 1445(a)	Every 5 years, EPA must issue a new list of no more than 30 unregulated contaminants to be monitored by PWSs. The data obtained must be entered into the National Drinking Water Contaminant Occurrence Database.	1,4-dioxane was identified in the third Unregulated Contaminant Monitoring Rule (UCMR3), issued in 2012 (77 FR 26072, May 2, 2012).
RCRA – Section 3001	Directs EPA to develop and promulgate criteria for identifying the characteristics of hazardous waste, and for listing hazardous waste, considering toxicity, persistence, and degradability in nature, potential for accumulation in tissue and other related factors such as flammability, corrosiveness, and other hazardous characteristics.	In 1980, 1,4-dioxane became a listed hazardous waste in 40 CFR § 261.33 - Discarded commercial chemical products, off-specification species, container residues, and spill residues thereof (U108) (45 FR 33084).

Statutes/ Regulations	Description of Authority/Regulation	Description of Regulation
Other federal regulations		
FFDCA	Provides the U.S. Food and Drug Administration (FDA) with authority to oversee the safety of food, drugs and cosmetics.	FDA established a limit of 10 mg/kg on the amount of 1,4-dioxane that can be present in the food additive glycerides and polyglycides of hydrogenated vegetable oils (21 CFR § 172.736 and 71 FR 12618, March 13, 2006).
Occupational Safety and Health Act	Requires employers to provide their workers with a place of employment free from recognized hazards to safety and health, such as exposure to toxic chemicals, excessive noise levels, mechanical dangers, heat or cold stress or unsanitary conditions. Under the Act, OSHA can issue occupational safety and health standards including such provisions as PELs, exposure monitoring, engineering and administrative control measures and respiratory protection.	In 1971, OSHA established a PEL for 1,4-dioxane of 100 ppm or 360 mg/m ³ as an 8-hour, TWA (29 CFR § 1910.1001). While OSHA has established a PEL for 1,4-dioxane, OSHA has recognized that many of its PELs are outdated and inadequate for ensuring the protection of worker health. 1,4-Dioxane appears in OSHA's annotated PEL tables, wherein OSHA recommends that employers follow the California OSHA limit of 0.28 ppm, the NIOSH REL of 1 ppm as a 30-minute ceiling or the ACGIH TLV of 20 ppm (8-hour TWA).
Atomic Energy Act	The Atomic Energy Act authorizes the Department of Energy to regulate the health and safety of its contractor employees	10 CFR § 851.23, Worker Safety and Health Program, requires the use of the 2005 ACGIH TLVs if they are more protective than the OSHA PEL.
Federal Hazardous Materials Transportation Act	Section 5103 of the Act directs the Secretary of Transportation to: Designate material (including an explosive, radioactive material, infectious substance, flammable or combustible liquid, solid or gas, toxic, oxidizing or corrosive material and compressed gas) as hazardous when	The Department of Transportation (DOT) has designated 1,4-dioxane as a hazardous material, and there are special requirements for marking, labeling and transporting it (49 CFR Part

Statutes/ Regulations	Description of Authority/Regulation	Description of Regulation
	the Secretary determines that transporting the material in commerce may pose an unreasonable risk to health and safety or property. Issue regulations for the safe transportation, including security, of hazardous material in intrastate, interstate and foreign commerce.	171, 40 CFR § 173.202 and 40 CFR § 173.242).

A.2 State Laws and Regulations

Table A-2. State Laws and Regulations

State Actions	Description of Action
State PELs	California PEL: 0.28 ppm (Cal Code Regs. Title 8, § 5155).
State Right-to-Know Acts	New Jersey (8:59 N.J. Admin. Code § 9.1), Pennsylvania (34 Pa. Code § 323).
State air regulations	Allowable Ambient Levels (AAL): New Hampshire (RSA 125-I:6, ENV-A Chap. 1400), Rhode Island (12 R.I. Code R. 031-022).
State drinking/ground water limits	Massachusetts (310 Code Mass. Regs. § 22.00), Michigan (Mich. Admin. Code r.299.44 and r.299.49, 2017).
Chemicals of high concern to children	Several states have adopted reporting laws for chemicals in children's products that include 1,4-dioxane, such as Oregon (Toxic-Free Kids Act, Senate Bill 478, 2015) Vermont (Code Vt. R. § 13-140-077) and Washington State (Wash. Admin. Code § 173-334-130).
Other	In California, 1,4-dioxane was added to the Proposition 65 list in 1988 (Cal. Code Regs. title 27, § 27001).

A.3 International Laws and Regulations

Table A-3. Regulatory Actions by other Governments and Tribes

Country/Organization	Requirements and Restrictions
Canada	1,4-Dioxane is on the Cosmetic Ingredient Hotlist as a substance prohibited for use in cosmetics. 1,4-Dioxane is also included in Canada's National Pollutant Release Inventory (NPRI), the publicly-accessible inventory of pollutants released, disposed of and sent for recycling by facilities across the country

Country/Organization	Requirements and Restrictions
	[Government of Canada (2010) <i>1,4-Dioxane</i> . Accessed April 18, 2017].
Australia	In 1994, 1,4-dioxane was assessed. A workplace product containing more than 0.1% 1,4-dioxane is classed as a hazardous substance. 1,4-Dioxane is in Class 3, (Packing Group II) under the Australian Dangerous Goods Code [1,4-Dioxane. Priority Existing Chemical No. 7. Full Public Report][1,4-Dioxane. Priority Existing Chemical No. 7. Full Public Report 1998].
Japan	1,4-dioxane is regulated in Japan under the following legislation: Act on the Evaluation of Chemical Substances and Regulation of Their Manufacture, etc. (Chemical Substances Control Law; CSCL) Act on Confirmation, etc. of Release Amounts of Specific Chemical Substances in the Environment and Promotion of Improvements to the Management Thereof Industrial Safety and Health Act (ISHA) Air Pollution Control Law Water Pollution Control Law [National Institute of Technology and Evaluation (NITE) Chemical Risk Information Platform (CHIRP) NITE (2015) , Accessed April 18, 2017].
Republic of Korea	The Ministry of the Environment recently adopted a provisional water quality standard for human health of 50 µg/L 1,4-dioxane in drinking water An et al. (2014) .
Australia, Austria, Belgium, Canada, Denmark, European Union (EU), Finland, France, Germany, Hungary, Ireland, Italy, Japan, Latvia, New Zealand, People's Republic of China, Poland, Singapore, South Korea, Spain, Sweden, Switzerland, The Netherlands, Turkey, United Kingdom	Occupational exposure limits for 1,4-dioxane Insitut fur Arbeitsschutz der (IFA) Deutschen Gesetzlichen Unfallversicherung (2017) (GESTIS International limit values for chemical agents (Occupational exposure limits, OELs) database. Accessed April 18, 2017).
WHO	Established a tolerable daily intake of 16 µg 1,4-dioxane/kg body weight based on a no-observed-adverse-effect level (NOAEL) of 16 mg/kg body weight per day for hepatocellular tumors observed in a long-term drinking-water study in rats.

Country/Organization	Requirements and Restrictions
	The WHO water quality guideline is 0.05 mg/L 1,4-dioxane in drinking water WHO (2005) .

Appendix B EXPOSURE SCENARIO MAPPING TO COU

As part of the Problem Formulation, EPA considered if each unique combination of exposure pathway, route, and receptor in the lifecycle of 1,4-dioxane would be further evaluated and includes all possible exposure scenarios for each condition of use. EPA provided the mapping tables that described all possible scenarios developed during problem formulation in tables B-1 and B2. EPA used readily available fate, engineering, exposure and/or toxicity information to determine whether to conduct further analysis on each exposure scenario.

Industrial and Commercial Occupational Exposure Scenarios for 1,4-Dioxane

EPA has identified release/occupational exposure scenarios and mapped them to relevant conditions of use in Table B-1 below. As presented in the Release/Exposure Scenario column of this table, representative release/exposure scenarios each with 5-6 unique combinations of exposure pathway, route, and receptor will be further analyzed. EPA further refined the mapping/grouping of industrial and commercial occupational exposure scenarios based on factors (*e.g.*, process equipment and handling, magnitude of production volume used, and exposure/release sources) corresponding to conditions of use as additional information is identified during risk evaluation.

Table B-1. Industrial and Commercial Occupational Exposure Scenarios for 1,4-Dioxane

Life Cycle Stage	Category	Subcategory	Release/Exposure Scenario	Exposure Pathway	Exposure Route	Receptor	Further Evaluation?	Rationale for Further Evaluation / no Further Evaluation
Manufacture	Domestic Manufacture or Import	Domestic Manufacture or Import	Manufacture of 1,4-dioxane via acid catalyzed conversion of ethylene glycol by ring closure	Liquid Contact	Dermal	Workers	Yes	Workers are expected to routinely handle liquids containing 1,4-dioxane.
Manufacture	Domestic Manufacture or Import	Domestic Manufacture or Import		Vapor	Dermal	Workers	No	The absorption of 1,4-dioxane vapor via skin is expected to be orders of magnitude lower than via inhalation and will not be further analyzed.
Manufacture	Domestic Manufacture or Import	Domestic Manufacture or Import		Vapor	Inhalation	Workers	Yes	Due to high volatility (VP = 40 mmHg) at room temperature, inhalation exposure from vapor should be further evaluated.
Manufacture	Domestic Manufacture or Import	Domestic Manufacture or Import	Repackaging of import containers	Liquid Contact	Dermal	ONU (Occupational Non-User)	No	Dermal exposure is expected to be primarily to workers directly involved in handling the chemical.

Manufacture	Domestic Manufacture or Import	Domestic Manufacture or Import		Vapor	Dermal	ONU	No	The absorption of 1,4-dioxane vapor via skin is expected to be orders of magnitude lower than via inhalation and will not be further analyzed.
Manufacture	Domestic Manufacture or Import	Domestic Manufacture or Import		Vapor	Inhalation	ONU	Yes	Due to high volatility (VP = 40 mmHg) at room temperature, inhalation exposure from vapor should be further evaluated.
Manufacture	Domestic Manufacture or Import	Domestic Manufacture or Import		Mist	Dermal/Inhalation/Oral	Workers, ONU	No	Mist generation is not expected.
Processing	Processing as a Reactant	Polymerization catalyst	Polymer manufacture	Liquid Contact	Dermal	Workers	Yes	Workers are expected to routinely handle liquids containing 1,4-dioxane.
Processing	Processing as a Reactant			Vapor	Dermal	Workers	No	The absorption of 1,4-dioxane vapor via skin is expected to be orders of magnitude lower than via inhalation and will not be further analyzed.
Processing	Processing as a Reactant			Vapor	Inhalation	Workers	Yes	Due to high volatility at room temperature, inhalation exposure from vapor should be further evaluated. However, potential for exposure may be low in scenarios where 1,4-dioxane is consumed as a chemical intermediate or used as a catalyst.
Processing	Processing as a Reactant			Liquid Contact	Dermal	ONU	No	Dermal exposure is expected to be primarily to workers directly involved in handling the chemical.
Processing	Processing as a Reactant			Vapor	Dermal	ONU	No	The absorption of 1,4-dioxane vapor via skin is expected to be orders of magnitude lower than via inhalation and will not be further analyzed.
Processing	Processing as a Reactant			Vapor	Inhalation	ONU	Yes	Due to high volatility at room temperature, inhalation exposure from vapor should be further evaluated. However, potential for exposure may be low in scenarios where 1,4-dioxane is consumed as a chemical intermediate or used as a catalyst.

Processing	Processing as a Reactant			Mist	Dermal/Inhalation/Oral	Workers, ONU	No	Mist generation is not expected.	
Processing	Non-incorporative	Basic organic chemical manufacturing (process solvent)	Basic organic chemical manufacture	Liquid Contact	Dermal	Workers	Yes	Workers are expected to routinely handle liquids containing 1,4-dioxane.	
Processing				Vapor	Dermal	Workers	No	The absorption of 1,4-dioxane vapor via skin is expected to be orders of magnitude lower than via inhalation and will not be further analyzed.	
Processing				Vapor	Inhalation	Workers	Yes	Due to high volatility at room temperature, inhalation exposure from vapor should be further evaluated.	
Processing				Liquid Contact	Dermal	ONU	No	Dermal exposure is expected to be primarily to workers directly involved in handling the chemical.	
Processing		Repackaging	Bulk to packages, then distribute	Repackaging to large and small containers	Vapor	Dermal	ONU	No	The absorption of 1,4-dioxane vapor via skin is expected to be orders of magnitude lower than via inhalation and will not be further analyzed.
Processing					Vapor	Inhalation	ONU	Yes	Due to high volatility at room temperature, inhalation exposure from vapor should be further evaluated.
Processing					Mist	Dermal/Inhalation/Oral	Workers, ONU	No	Mist generation is not expected.
Processing					Recycling	Recycling	Recycling of process solvents containing 1,4-dioxane	Liquid Contact	Dermal
Processing	Recycling	Recycling	Vapor	Dermal	Workers	No		The absorption of 1,4-dioxane vapor via skin is expected to be orders of magnitude lower than via inhalation and will not be further analyzed.	
Processing	Recycling	Recycling	Vapor	Inhalation	Workers	Yes		Due to high volatility at room temperature, inhalation exposure from vapor should be further evaluated.	
Processing	Recycling	Recycling	Liquid Contact	Dermal	ONU	No		Dermal exposure is expected to be primarily to workers directly involved in handling the chemical.	
Processing	Recycling	Recycling	Vapor	Dermal	ONU	No		The absorption of 1,4-dioxane vapor via skin is expected to be orders of	

								magnitude lower than via inhalation and will not be further analyzed.
Processing	Recycling	Recycling		Vapor	Inhalation	ONU	Yes	Due to high volatility at room temperature, inhalation exposure from vapor should be further evaluated.
Processing	Recycling	Recycling		Mist	Dermal/Inhalation/Oral	Workers, ONU	Yes	EPA requires additional information on industry practices for recycling waste solvents containing 1,4-dioxane to determine if exposures to mists are possible.
Distribution in commerce	Distribution	Distribution	Distribution of bulk shipment of 1,4-dioxane	Liquid Contact, Vapor, Mist	Dermal/Inhalation/Oral	Workers, ONU	Yes	EPA will further analyze activities resulting in exposures associated with distribution in commerce (e.g., loading, unloading) throughout the various lifecycle stages and conditions of use (e.g., manufacturing, processing, industrial use) rather than as a single distribution scenario.
Industrial use	Intermediate Use	Agricultural chemical intermediate	Agricultural product manufacture	Liquid Contact	Dermal	Workers	Yes	Workers are expected to routinely handle liquids containing 1,4-dioxane.
Industrial use				Vapor	Dermal	Workers	No	The absorption of 1,4-dioxane vapor via skin is expected to be orders of magnitude lower than via inhalation and will not be further analyzed.
Industrial use	Processing aids, not otherwise listed	Plasticizer intermediate	Anhydrous acid, bromination and sulfonation chemical manufacture	Vapor	Inhalation	Workers	Yes	Due to high volatility at room temperature, inhalation exposure from vapor should be further evaluated. However, potential for exposure may be low in scenarios where 1,4-dioxane is consumed as a chemical intermediate or used as a catalyst.
Industrial use				Liquid Contact	Dermal	ONU	No	Dermal exposure is expected to be primarily to workers directly involved in handling the chemical.
Industrial use				Polymerization catalyst	Polymer Manufacture	Vapor	Dermal	ONU

								magnitude lower than via inhalation and will not be further analyzed.
Industrial use				Vapor	Inhalation	ONU	Yes	Due to high volatility at room temperature, inhalation exposure from vapor should be further evaluated. However, potential for exposure may be low in scenarios where 1,4-dioxane is consumed as a chemical intermediate or used as a catalyst.
Industrial use				Mist	Dermal/Inhalation/Oral	Workers, ONU	No	Mist generation is not expected.
Industrial use	Processing aids, not otherwise listed	Wood pulping ¹⁹ Extraction of animal and vegetable oils ¹⁵ Wetting and dispersing agent in textile processing ¹⁵	Wood pulping Extraction of animal and vegetable oils Textile processing	Liquid Contact	Dermal	Workers	Yes	Workers are expected to routinely handle liquids containing 1,4-dioxane.
Industrial use	Processing aids, not otherwise listed			Vapor	Dermal	Workers	No	The absorption of 1,4-dioxane vapor via skin is expected to be orders of magnitude lower than via inhalation and will not be further analyzed.
Industrial use	Processing aids, not otherwise listed			Vapor	Inhalation	Workers	Yes	Due to high volatility at room temperature, inhalation exposure from vapor should be further evaluated.
Industrial use	Processing aids, not otherwise listed			Liquid Contact	Dermal	ONU	Yes	Dermal exposure is expected to be primarily to workers directly involved in handling the chemical.
Industrial use	Processing aids, not otherwise listed			Vapor	Dermal	ONU	No	The absorption of 1,4-dioxane vapor via skin is expected to be orders of magnitude lower than via inhalation and will not be further analyzed.
Industrial use	Processing aids, not otherwise listed			Vapor	Inhalation	ONU	Yes	Due to high volatility at room temperature, inhalation exposure from vapor should be further evaluated.

¹⁹ These uses were evaluated but are likely not current uses of 1,4-dioxane.

Industrial use	Processing aids, not otherwise listed			Mist	Dermal/Inhalation/Oral	Workers, ONU	Yes	Mist generation may occur during these processes.
Industrial use	Processing aids, not otherwise listed	Etching of fluoropolymers	Etching of fluoropolymers	Liquid Contact	Dermal	Workers	Yes	Workers are expected to routinely handle liquids containing 1,4-dioxane.
Industrial use	Processing aids, not otherwise listed			Vapor	Dermal	Workers	No	The absorption of 1,4-dioxane vapor via skin is expected to be orders of magnitude lower than via inhalation and will not be further analyzed.
Industrial use	Processing aids, not otherwise listed			Vapor	Inhalation	Workers	Yes	Due to high volatility at room temperature, inhalation exposure from vapor should be further evaluated.
Industrial use	Processing aids, not otherwise listed			Liquid Contact	Dermal	ONU	No	Dermal exposure is expected to be primarily to workers directly involved in handling the chemical.
Industrial use	Processing aids, not otherwise listed			Vapor	Dermal	ONU	No	The absorption of 1,4-dioxane vapor via skin is expected to be orders of magnitude lower than via inhalation and will not be further analyzed.
Industrial use	Processing aids, not otherwise listed			Vapor	Inhalation	ONU	Yes	Due to high volatility at room temperature, inhalation exposure from vapor should be further evaluated.
Industrial use	Processing aids, not otherwise listed			Mist	Dermal/Inhalation/Oral	Workers, ONU	Yes	Mist generation may occur during these processes.
Industrial use	Functional fluids (closed/open system)			Polyalkylene glycol lubricant	Use of lubricants	Liquid Contact	Dermal	Workers
Industrial use	Functional fluids (closed/open system)	Cutting and Tapping Fluid Synthetic metalworking	Use of metalworking	Vapor		Dermal	Workers	No

Industrial use	Functional fluids (closed/open system)	fluid Hydraulic fluid	fluids Servicing hydraulic equipment and charging hydraulic fluids in original equipment manufacture	Vapor	Inhalation	Workers	Yes	Due to high volatility at room temperature, inhalation exposure from vapor should be further evaluated.
Industrial use	Functional fluids (closed/open system)			Liquid Contact	Dermal	ONU	No	Derma exposure is expected to be primarily to workers directly involved in handling the chemical.
Industrial use	Functional fluids (closed/open system)			Vapor	Dermal	ONU	No	The absorption of 1,4-dioxane vapor via skin is expected to be orders of magnitude lower than via inhalation and will not be further analyzed.
Industrial use	Functional fluids (closed/open system)			Vapor	Inhalation	ONU	Yes	Due to high volatility at room temperature, inhalation exposure from vapor should be further evaluated.
Industrial use	Functional fluids (closed/open system)			Mist	Dermal/Inhalation/Oral	Workers, ONU	Yes	Mist exposure can occur during open system uses and potentially while charging and servicing equipment with hydraulic fluid.
Industrial use, potential commercial use	Laboratory chemicals	Chemical reagent Reference material Spectroscopic and photometric measurement Liquid scintillation and counting medium Stable reaction medium Cryoscopic solvent for	Laboratory chemical use	Liquid Contact	Dermal	Workers	Yes	Workers are expected to routinely handle liquids containing 1,4-dioxane.
Industrial use, potential commercial use	Laboratory chemicals			Vapor	Dermal	Workers	No	The absorption of 1,4-dioxane vapor via skin is expected to be orders of magnitude lower than via inhalation and will not be further analyzed.
Industrial use, potential commercial use	Laboratory chemicals			Vapor	Inhalation	Workers	Yes	Due to high volatility at room temperature, inhalation exposure from vapor should be further evaluated.
Industrial use, potential commercial use	Laboratory chemicals			Liquid Contact	Dermal	ONU	No	Derma exposure is expected to be primarily to workers directly involved in handling the chemical.
Industrial use, potential commercial use	Laboratory chemicals			Vapor	Dermal	ONU	No	The absorption of 1,4-dioxane vapor via skin is expected to be orders of magnitude lower than via inhalation and will not be further analyzed.

Industrial use, potential commercial use	Laboratory chemicals	molecular mass determinations		Vapor	Inhalation	ONU	Yes	Due to high volatility at room temperature, inhalation exposure from vapor should be further evaluated.
Industrial use, potential commercial use	Laboratory chemicals	Preparation of histological sections for microscopic examination		Mist	Dermal/Inhalation/Oral	Workers, ONU	No	Mist generation is not expected.
Industrial use, potential commercial use	Adhesives and sealants Other Uses	Film cement	Industrial and commercial small brush application	Liquid Contact	Dermal	Workers	Yes	Workers are expected to routinely handle liquids containing 1,4-dioxane.
Industrial use, potential commercial use				Vapor	Dermal	Workers	No	The absorption of 1,4-dioxane vapor via skin is expected to be orders of magnitude lower than via inhalation and will not be further analyzed.
Industrial use, potential commercial use				Vapor	Inhalation	Workers	Yes	Due to high volatility at room temperature, inhalation exposure from vapor should be further evaluated.
Industrial use, potential commercial use				Liquid Contact	Dermal	ONU	No	Dermal exposure is expected to be primarily to workers directly involved in handling the chemical.
Industrial use, potential commercial use				Vapor	Dermal	ONU	No	The absorption of 1,4-dioxane vapor via skin is expected to be orders of magnitude lower than via inhalation and will not be further analyzed.
Industrial use, potential commercial use				Vapor	Inhalation	ONU	Yes	Due to high volatility at room temperature, inhalation exposure from vapor should be further evaluated.
Industrial use, potential commercial use				Mist	Dermal/Inhalation/Oral	Workers, ONU	No	Mist generation is not expected.
Industrial use, potential commercial use				Other Uses	Spray polyurethane foam	Application of spray polyurethane foam through a	Liquid Contact	Dermal

Industrial use, potential commercial use		Printing and printing compounds	nozzle Use of Printing Inks	Vapor	Dermal	Workers	No	The absorption of 1,4-dioxane vapor via skin is expected to be orders of magnitude lower than via inhalation and will not be further analyzed.
Industrial use, potential commercial use				Vapor	Inhalation	Workers	Yes	Due to high volatility at room temperature, inhalation exposure from vapor should be further evaluated.
Industrial use, potential commercial use				Liquid Contact	Dermal	ONU	No	Dermal exposure is expected to be primarily to workers directly involved in handling the chemical.
Industrial use, potential commercial use				Vapor	Dermal	ONU	No	The absorption of 1,4-dioxane vapor via skin is expected to be orders of magnitude lower than via inhalation and will not be further analyzed.
Industrial use, potential commercial use				Vapor	Inhalation	ONU	Yes	Due to high volatility at room temperature, inhalation exposure from vapor should be further evaluated.
Industrial use, potential commercial use				Mist	Dermal/Inhalation/Oral	Workers, ONU	Yes	Mist generation may occur during these processes.
Manufacture, processing, use, Disposal	Emissions to air			Air	Worker Handling of wastes	Liquid Contact	Dermal	Workers
Manufacture, processing, use, Disposal	Wastewater	Industrial pre-treatment	Vapor	Dermal		Workers	No	The absorption of 1,4-dioxane vapor via skin is expected to be orders of magnitude lower than via inhalation and will not be further analyzed.
Manufacture, processing, use, Disposal	Solid wastes and liquid wastes	Industrial wastewater treatment	Vapor	Inhalation		Workers	Yes	Due to high volatility at room temperature, inhalation exposure from vapor should be further evaluated.
Manufacture, processing, use, Disposal		Publicly owned treatment works (POTW)	Liquid Contact	Dermal		ONU	No	Dermal exposure is expected to be primarily to workers directly involved in handling the chemical.
Manufacture, processing, use, Disposal		Underground Injection	Vapor	Dermal		ONU	No	The absorption of 1,4-dioxane vapor via skin is expected to be orders of

		Municipal landfill						magnitude lower than via inhalation and will not be further analyzed.
Manufacture, processing, use, Disposal		Hazardous landfill		Vapor	Inhalation	ONU	Yes	Due to high volatility at room temperature, inhalation exposure from vapor should be further evaluated.
Manufacture, processing, use, Disposal				Mist	Dermal/Inhalation/Oral	Workers, ONU	No	Mist generation is not expected.

Environmental Releases and Wastes Exposure Scenarios for 1,4-Dioxane

Table B-2. During problem formulation, EPA used readily available fate, exposure and/or toxicity information to determine whether to conduct further analysis on each exposure scenario. EPA has identified release/environmental exposure scenarios and mapped them to relevant conditions of use in the table below.

Table B-2. Environmental Releases and Wastes Exposure Scenarios for 1,4-Dioxane

Lifecycle Stage	Use Category	Release	Exposure Pathway	Exposure Route	Receptor	Further Evaluation?	Rationale for Further Evaluation / no Further Evaluation
Manufacturing and Processing	TBD	Industrial wastewater treatment operations	Water	N/A	Aquatic Species	No	Conservative screening indicates low potential for risk to aquatic organisms.
Manufacturing and Processing	TBD	Industrial wastewater treatment operations	Water, Air	N/A	Terrestrial Species	No	Ingestion of water and inhalation of air are not expected to be primary exposure routes for terrestrial organisms (see OPP tool).
Manufacturing and Processing	TBD	Industrial wastewater treatment operations	Sediment	N/A	Terrestrial Species	No	1,4-Dioxane has low sorption to soil, sludge, and sediment and will instead stay in the associated aqueous phases.
Manufacturing and Processing	TBD	Industrial wastewater treatment operations	Sediment		Aquatic Species	No	
Manufacturing and Processing	TBD	Industrial wastewater treatment operations	Biosolids disposed to soil, migration to groundwater	N/A	Terrestrial Species	No	1,4 dioxane is not expected to remain in soil for long periods of time due to migration to groundwater and volatilization from soil.

Manufacturing and Processing	TBD	Industrial pre-treatment, then transfer to Publicly Owned Treatment Works (POTW)	Water	N/A	Aquatic Species	No	Conservative screening indicates low potential for risk to aquatic organisms.
Manufacturing and Processing	TBD	Industrial pre-treatment, then transfer to Publicly Owned Treatment Works (POTW)	Water, Air	N/A	Terrestrial Species	No	Ingestion of water and inhalation of air are not expected to be primary exposure routes for terrestrial organisms (see OPP tool).
Manufacturing and Processing	TBD	Industrial pre-treatment, then transfer to Publicly Owned Treatment Works (POTW)	Sediment	N/A	Terrestrial Species	No	1,4-Dioxane has low sorption to soil, sludge, and sediment and will instead stay in the associated aqueous phases.
Manufacturing and Processing	TBD	Industrial pre-treatment, then transfer to Publicly Owned Treatment Works (POTW)	Sediment		Aquatic Species	No	
Manufacturing and Processing	TBD	Industrial pre-treatment, then transfer to Publicly Owned Treatment Works (POTW)	Biosolids disposed to soil, migration to groundwater	N/A	Terrestrial Species	No	1,4-dioxane is not expected to remain in soil for long periods of time due to migration to groundwater and volatilization from soil.
Disposal	TBD	Municipal landfill, Hazardous Landfill, and other land disposal	Soil	N/A	Terrestrial Species	No	2015 TRI data indicates 3 sites reporting 13,422 lbs to landfill. However, 1,4-dioxane has low sorption to soil.

Appendix C LIST OF SUPPLEMENTAL DOCUMENTS

1. Summary of External Peer Review and Public Comments and Disposition for 1,4-Dioxane: Response to Support Risk Evaluation for 1,4-Dioxane
2. Final Risk Evaluation for 1,4-Dioxane Systematic Review Supplemental File: Updates to the Data Quality Criteria for Epidemiological Studies
3. Final Risk Evaluation for 1,4-Dioxane Systematic Review Supplemental File: Data Quality Evaluation for Environmental Releases and Occupational Exposure Data Sources
4. Final Risk Evaluation for 1,4-Dioxane Systematic Review Supplemental File: Data Quality Evaluation of Environmental Hazard Studies
5. Final Risk Evaluation for 1,4-Dioxane Systematic Review Supplemental File: Data Quality Evaluation of Environmental Fate and Transport Studies
6. Final Risk Evaluation for 1,4-Dioxane Systematic Review Supplemental File: Data Quality Evaluation of Human Health Hazard Studies, Animal and In Vitro Studies
7. Final Risk Evaluation for 1,4-Dioxane Systematic Review Supplemental File: Data Quality Evaluation of Epidemiological Studies
8. Final Risk Evaluation for 1,4-Dioxane Systematic Review Supplemental File: Data Quality Evaluation of Consumer Exposure Studies
9. Final Risk Evaluation for 1,4-Dioxane Systematic Review Supplemental File: Consumer References, Data Screening
10. Final Risk Evaluation for 1,4-Dioxane Supplemental Information File on Aquatic Exposure Screen Facility Information
11. Final Risk Evaluation for 1,4-Dioxane Supplemental Information File on Occupational Risk Calculations
12. Final Risk Evaluation for 1,4-Dioxane Supplemental Information File on Ambient Water Exposure Modeling Outputs from E-FAST
13. Final Risk Evaluation for 1,4-Dioxane Supplemental Information File on Exposure Modeling Inputs, Results, and Risk Estimates for Incidental Ambient Water Exposure
14. Final Risk Evaluation for 1,4-Dioxane Supplemental Information File on Consumer Exposure Assessment Modeling Input Parameters
15. Final Risk Evaluation for 1,4-Dioxane Supplemental Information File on Consumer Exposure Modeling Results and Risk Estimates
16. Final Risk Evaluation for 1,4-Dioxane Systematic Review Supplemental File: Data Quality Evaluation of Physical-Chemical Properties Studies

Appendix D FATE AND TRANSPORT

EPI Suite™ model inputs

To set up EPI Suite™ for estimating fate properties of 1,4-dioxane, 1,4-dioxane was identified using the “Name Lookup” function. The physical-chemical properties were input based on the values in Table 1-1.. Water solubility was not entered because it is listed as >800 g/L, a value that is not valid to input. EPI Suite™ was run using default settings (*i.e.*, no other parameters were changed or input).

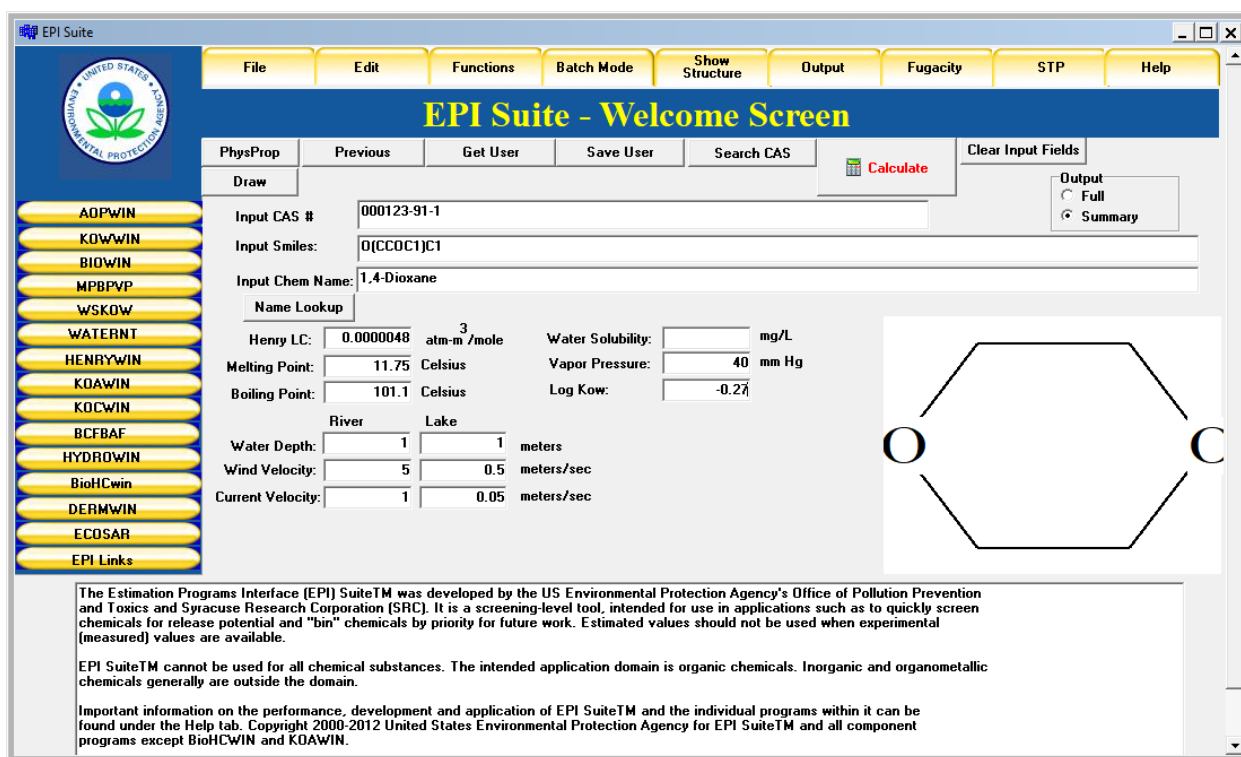


Figure D-1. EPI Suite™ welcome screen set up for 1,4-dioxane model run

As part of problem formulation, EPA also analyzed the sediment, land application and biosolids pathways. The results of the analyses are described in the 2018 problem formulation for 1,4-dioxane [U.S. EPA \(2018c\)](#) and presented below. Fate and transport were not further analyzed in this risk evaluation.

Sediment Pathways

1,4-Dioxane is expected to remain in aqueous phases and not adsorb to sediment due to its water solubility (> 800 g/L) and low partitioning to organic matter ($\log K_{OC} = 0.4$). Limited sediment monitoring data for 1,4-dioxane that are available suggest that 1,4-dioxane is present in sediments, but because 1,4-dioxane does not partition to organic matter ($\log K_{OC} = 0.4$) and biodegrades slowly [$<10\%$ biodegradation in 29 days [ECHA \(1996\)](#)], 1,4-dioxane concentrations in sediment pore water are expected to be similar to the concentrations in the overlying water. Thus, the 1,4-dioxane detected in sediments is likely from the pore water and not 1,4-dioxane that was sorbed to the sediment solids.

Land-Applied Biosolids Pathway

1,4-Dioxane is not expected to adsorb to soil and sediment due to its low partitioning to organic matter (estimated $\log K_{OC} = 0.4$), so 1,4-dioxane in biosolids is expected to be in the aqueous phase associated with the biosolids rather than adsorbed to the organic matter. The aqueous phase represents > 95% of biosolids, or $\geq 70\%$ if the biosolids are dewatered, and at the time of removal the water in the biosolids will contain the same concentration of 1,4-dioxane as the rest of the wastewater at the activated sludge stage of treatment. However, the volume of water removed with biosolids represents < 2% of wastewater treatment plant influent volume [U.S. EPA \(1974\)](#), and is < 1% of influent volume when the sludge is dewatered and the excess water is returned to treatment, a process that is commonly used [NRC \(1996\)](#). Thus, the water released from a treatment plant via biosolids is negligible compared to that released as effluent. By extension the 1,4-dioxane released from wastewater treatment via biosolids is expected to be negligible compared to the 1,4-dioxane released with effluents: of the 1,4-dioxane in influent wastewater, it is expected that < 2% will be removed with biosolids and associated water and > 95% will be present in the effluent (see Section 2.1, Fate and Transport). Further, the concentrations of 1,4-dioxane in biosolids may decrease through volatilization to air during transport, processing (including dewatering and digestion), handling, and application to soil (which may include spraying). When 1,4-dioxane is released in the environment, it is expected to be mobile in soil and migrate to surface waters and groundwater or volatilize to air. 1,4-Dioxane is expected to volatilize readily from dry soil and surfaces due to its vapor pressure (40 mm Hg). Overall, the exposures to surface water from biosolids will be negligible compared to the direct release of WWTP effluent to surface water.

Appendix E ENVIRONMENTAL EXPOSURES

Systematic Review for Environmental Exposures

The flow of publications on environmental exposure through systematic review is illustrated in Section 1.5.1. On-topic literature obtained from Systematic Review were screened via title/abstract screening and full-text screening for relevance and usability. Through scoping and problem formulation, EPA determined that no environmental pathways would be further analyzed. Therefore, none of the 272 studies proceeded to data evaluation per the environmental exposure PECO statement, which was updated to reflect the results of the aquatic exposure screen and the determination not to further analyze this pathway.

First-tier Ecological Aquatic Exposure Assessment for 1,4-Dioxane

While recent monitoring data on ambient surface water levels indicate relatively low levels, EPA used release estimates and measured effluent concentrations from EPA’s Toxics Release Inventory (TRI) and Discharge Monitoring Report (DMR) Pollutant Loading Tool, respectively, to predict surface water concentrations near such discharging facilities. This first-tier aquatic exposure assessment evaluates ecological exposures in the US associated with releases of 1,4-dioxane to surface water. This first-tier, screening approach uses conservative assumptions and readily available data and models. In this assessment, conservative surface water concentrations are estimated for facilities that release the 1,4-dioxane to surface water bodies. The assessment was conducted using the top ten discharging facilities that submit DMRs, as well as the top ten releasers that report to the TRI. The 2015-2016 DMR data with facilities and associated release amounts were identified using EPA’s Enforcement and Compliance History Online (ECHO) [Water Pollutant Loading Tool](#). The 2014-2015 TRI dataset was updated using data from [TRI Explorer](#). In response to public comment, the TRI analysis was also augmented to include the top indirect discharging sites, *i.e.*, those reporting off-site waste transfers to POTWs for treatment. Surface water concentrations were estimated using EPA’s [Exposure and Fate Assessment Screening Tool, Version 2014 U.S. EPA \(2014c\)](#). The two most recent years with complete data at the time of the problem formulation analysis were 2014 and 2015 for TRI and 2015 and 2016 for DMR. In Section 2.2, more recent 2018 TRI and DMR data were used to estimate surface water releases for Occupational Exposure Scenarios (OES) within the scope of this evaluation. These estimated releases ranged from 0-67.7 kg/site/day across all OES, with the highest release volume associated with Industrial Uses. The releases modeled as part of this first-tier aquatic exposure assessment were within this range, as they were based on top direct and indirect dischargers. It is not expected that the incorporation of the more recent OES release estimated would have altered the conclusions of the screening-level aquatic exposure assessment undertaken during problem formulation.

Table E-1 shows the environmental release data from TRI reported in the 1,4-Dioxane Problem Formulation document.

Table E-1. Summary of 1,4-Dioxane TRI Releases to the Environment in 2015 (lbs)

	Number of Facilities	Air Releases		Water Releases	Land Disposal			Other Releases ^a	Total On- and Off-site Disposal or Other Releases ^{b,c}
		Stack Air Releases	Fugitive Air Releases		Class I Underground Injection	RCRA Subtitle C Landfills	All other Land Disposal ^a		
Subtotal		46,219	16,377		563,976	13,376	49		
Totals	49	62,596		35,402	577,400			0	675,399

Data source: 2015 TRI Data (updated March 2017) [U.S. EPA \(2017g\)](#).

^a Terminology used in these columns may not match the more detailed data element names used in the TRI public data and analysis access points.

^b These release quantities include releases due to one-time events not associated with production such as remedial actions or earthquakes.

^c Counts release quantities once at final disposition, accounting for transfers to other TRI reporting facilities that ultimately dispose of the chemical waste.

Predicted surface water concentrations ranged from 1.26 to 11,500 ug/L for acute scenarios and 2.37E-08 to 5,762 µg/L for chronic release scenarios for the set of top dischargers modeled, based on the two complete years of most recent data available at the time the analysis was conducted during problem formulation (2014-2016). These concentrations were predicted using conservative assumptions to inform whether further evaluation of the aquatic exposure pathway is supported.

Facility Selection

This assessment predicts conservative surface water concentrations for a set of facilities reporting recent releases of 1,4-dioxane via DMR and/or TRI. The DMR dataset of facilities were queried from ECHO's Water Pollutant Loading Tool. DMR includes pollutant loading information for more than 60,000 DMR reporting facilities (industrial and municipal point source dischargers) regulated under the Clean Water Act. It contains wastewater monitoring and other facility data, as reported on facility-specific DMRs. TRI data were retrieved from TRI Explorer for TRI reporters. TRI contains reporting information on facilities in specific industry sectors which employ more than 10 full-time equivalent employees and manufacture, process, or use more than 25,000 lbs per year of a TRI-listed chemical.

The analysis was conducted using the top direct and indirect dischargers of 1,4-dioxane from DMR and TRI covering the two most current and complete reporting years available at the time of problem formulation (*i.e.*, 2015 and 2016 for DMR and 2014 and 2015 for TRI). As many of the facilities overlapped between the DMR and TRI sets, and between the assessment years, a total of 24 unique facilities were assessed. Table E-2 below summarizes characterizing information.

Table E-2. Facility Selection Characterization

Parameter	DMR - 2015	DMR - 2016	TRI - 2014 ¹	TRI - 2015 ¹
Universe of Facilities				
No. of Facilities	54	61	56	50
No. of Facilities with annual loading >0	26	31	21	22
Annual Loading:				
Maximum	20,974	30,319	122,130.36	165,416.24
95 th percentile	20,733	25,047	26,962.0	21,349.2
50 th percentile	38.6	16.6	184.0	544.5
Minimum	0.000074	0.15	0.01	0.000132
No. of Facilities in Top 5 th percentile for discharging	1	2	2	2
Facilities Selected				
Number Selected	10	10	18	20
Annual Loading/Release Percentile % (Range)	64-100%	70-100%	0-100%	0-100%
SIC Represented	N=5 2821, 4952, 2869, 2899, 3861	N=5 2821, 4952, 2869, 3861, blank (landfill)	N=3 2821, 2869, 2899, 2879, 2865, 2599, 3569, 3599, 3821, 3841, 3081, 2843	N=14 2821, 2869, 2865, 2899, 2599, 3569, 3599, 3821, 3841, 3081, 2834, 2835, 2843, 4953
NAICS Represented	--	--	N=7 325211, 325199, 325320, 325110, 333999, 326113, 325613	N=8 325211, 325199, 325110, 333999, 326113, 325412, 325613, 562213
No. of POTWs	4	5	0	0
No. of non-POTWs	6	5	18	20
--No. of direct dischargers (non- POTW)	6	4	10	10
--No of indirect dischargers (non- POTW)	0	1 (Beacon landfill - discharges to POTW)	8	10
States Represented	N=5 CA, NY, MO, SC, WV	N=6 CA, CT, PA, NY, SC, WV	N=10 WV, SC, LA, NC, TN, AL, MN, MS, MD, WI	N=13 WV, SC, LA, TX, NC, TN, AL, MN, NY, MD, MS, WI, OH

¹ TRI facility counts include indirect and direct dischargers.

As described, this approach used only the top ten dischargers for a given release data source and reporting year. However, for the TRI direct surface water releases, the top ten facilities modeled represented > 99% of the total releases to surface water for all reporting sites during the time period modeled. Because there were at most ten facilities reporting off-site waste transfer to POTW – treatment during the years examined, all of those were captured in this effort. Additionally, the top ten dischargers modeled based on DMR reporting represented >95% of the total releases to surface water reported across all sites for the years modeled. Therefore, most reported surface water releases were captured in this first-tier assessment. Furthermore, the modeled sites reflect a variety of watersheds in 18 states.

The following basic information was collected for each facility and is shown in the supplemental file titled 1,4-D Supplemental – Aq Screen Facility Information 062419:

- **DMR:** Site name, location (city, state, latitude, longitude), NPDES code, SIC code, NAICS Code, FRS ID, average effluent concentration (mg/L), maximum effluent concentration (mg/L), total pounds (lbs/yr), average flow (MGD), flag for potential outlier, and max allowable load (lbs/yr).
- **TRI:** Site name, location (city, state, latitude, longitude), NPDES code, NAICS Code, FRS ID, TRI Facility ID, and Direct TRI Pounds (lbs/yr).
- **Receiving Water Information:** Waterbody Number (REACH code) and Waterbody Name (from GNIS).

Estimating Surface Water Concentrations

Surface water concentrations were estimated for multiple scenarios using E-FAST [U.S. EPA \(2014c\)](#), which can be used to estimate site-specific, near-facility surface water concentrations based on estimated loadings of 1,4-dioxane into receiving water bodies. Both direct discharges (*i.e.*, facility releases to surface water) and indirect discharges (*i.e.*, facility transfers to other sites/POTWs for treatment and subsequent release to surface water) were included based on TRI reporting. DMR reporting includes direct discharges only, as volumes are being reported under a facility's NPDES permit. The reported annual loading estimates for DMR facilities are calculated by using the reported effluent concentrations and facility effluent flows. For TRI, the reported releases are based on monitoring, emission factors, mass balance and/or other engineering calculations. These reported annual loading amounts (lbs/year) were first converted to release inputs required by E-FAST (kg/day) by converting from lbs to kgs and dividing by the number of release days for a given scenario. The reported annual loading amounts (lbs/year) are shown in the supplemental file, Supplemental File: Aquatic Exposure Screen Facility Information, while the release inputs (kg/day) are shown in Tables E-3, E-4, and E-5. The referenced supplemental file also provides a column showing the reported release converted from lbs to kgs and an example EFAST output file for one of the sites modeled.

E-FAST [U.S. EPA \(2014c\)](#) incorporates stream dilution at the point of release using stream flow distribution data contained within the model. The stream flow data have not been updated recently and may differ from current values obtained from NHD or USGS gages. Site-specific stream flow data are applied using a National Pollutant Discharge Elimination System (NPDES) code. If a specific discharger's NPDES code could not be identified within the E-FAST database, a surrogate site or generic Standard Industrial Classification (SIC) code was applied (*i.e.*, Industrial POTW).

E-FAST 2014 can incorporate wastewater treatment removal efficiencies. Wastewater treatment removal is assumed to be 0% for all direct discharges this exercise, as reported direct loadings/releases are assumed to account for any pre-release treatment. Indirect releases were assessed using TRI Explorer data on transfers to POTW using 2% wastewater treatment removal based on fate predictions. Therefore, for volumes transferred off-site to POTWs, a 2% wastewater treatment removal rate was applied within E-FAST. Because the days of release and/or operation are not reported in these sources, E-FAST [U.S. EPA \(2014c\)](#) is run assuming hypothetical release-day scenarios (*i.e.*, assuming 1, 20, and 250 days for most facilities and 250 days for Wastewater/Sewage Treatment Plants/Publicly Owned Treatment Works [WWT/STP/POTW]). For WWTP/STP/POTW facilities, it is assumed that a lower number of release and/or operation days is unlikely. Refer to the E-FAST 2014 Documentation Manual for equations used in the model to estimate surface water concentrations [U.S. EPA \(2014c\)](#).

The modeled surface water concentrations presented in Tables E-3, Table **E-4**, and E-5 are associated with a low flow – 7Q10, which is an annual minimum seven-day average stream flow over a ten-year recurrence interval. The 7Q10 stream flow is used to derive the presented surface water concentrations.

No post-release degradation or removal mechanisms (e.g., hydrolysis, aerobic degradation, photolysis, volatilization) are applied in the calculation of the modeled surface water concentrations.

Modeled Surface Water Concentrations

Tables E-3, E-4, and E-5 present the results of this first-tier aquatic exposure assessment. Based on the top ten DMR discharging facilities in 2015 and 2016, predicted surface water concentrations, which were based on the 7Q10 stream flow, ranged from 18.8 to 11,500 µg/L for acute release scenarios and 0.095 to 5,762 µg/L for chronic release scenarios. Based on the top TRI discharging facilities in 2014 and 2015 (including direct and indirect dischargers), predicted surface water concentrations ranged from 1.26 to 9,734 µg/L for acute release scenarios and 2.37E-08 to 4,879 µg/L for chronic release scenarios. The estimated surface water concentrations derived from chronic release scenarios (i.e., those assuming 20 days or more of annual release days) were compared against the chronic COC of 14,500 µg/L using E-FAST's high-end Probabilistic Dilution Model (PDM).

It is assumed that these modeled surface water concentrations are higher than those that would be present from non-point sources based on the conservative nature of the estimation approaches including the following: surface water concentrations would be expected to decrease downstream and this modeling analysis does not account for downstream transport and fate processes; non-zero wastewater removal rates would be applied for any indirect releases that pass through a treatment facility before release; and assuming a low-end number of release days (i.e., 1 day per year) assumes the total annual loading estimate occurs over 1 day. Furthermore, the modeled levels, for some sites, exceed the maximum levels reported in the literature cited in Section 2.3.1.

Table E-3. Summary of Modeled Surface Water Concentrations for DMR Facilities

Facility		E-FAST Inputs and Results			
NPDES Used in E-FAST	Name	Days of Release ^a	Release ^a (kg/day)	7Q10 Concentration (µg/L)	Days Exceedance (days/yr) COC = 14,500 µg/L
Reporting Year 2016					
WV0000132 (SIC 2821)	M and G Polymers USA, LLC	1	13,753	968.17	NA
		20	688	48.41	0
		250	55	3.87	0
SC0026506 (SIC 2821)	Dak Americas LLC	10 ^b	977	11,500	NA
		20	488	5,761.65	0
		250	39	461.36	0
SC0046311 ^c (SIC 4952)	Lake City Wastewater Treatment Plant	250	5.4	695.88	0
WV0000086 (SIC 2869)	Institute Plant	1	271	81.19	NA
		20	14	4.07	0
		250	1.1	0.33	0
NY0001643 (SIC 3861)	Eastman Kodak	1	79	74.46	NA
		20	3.9	3.7	0
		250	0.3	0.28	0
PA0026492 (SIC 4952)	The Scranton Sewer Authority	250	0.2	1.85	0
CA0054011 (SIC 4952)	Los Coyotes Water Reclamation Plant	250	0.2	1.45	20
CTMIU0161	Beacon Heights	250	0.2	1.10	0

Facility		E-FAST Inputs and Results			
NPDES Used in E-FAST	Name	Days of Release ^a	Release ^a (kg/day)	7Q10 Concentration (µg/L)	Days Exceedance (days/yr) COC = 14,500 µg/L
(SIC Blank) ⇒ CT0101061 ^d	Landfill ⇒ Beacon Falls WPCF				
CA0053911 (SIC 4952)	San Jose Creek Water Reclamation Plant	250	0.1	0.47	20
CA0056227 (SIC 4952)	Donald C Tillman WRP	250	0.1	1.49	0
Reporting Year 2016			Min	74.46 (acute) 0.28 (chronic)	
			Max	11,500 (acute) 5,762 (chronic)	
Reporting Year 2015					
WV0000132 (SIC 2821)	M and G Polymers USA, LLC	1	9,514	669.75	NA
		20	476	33.49	0
		250	38	2.68	0
SC0026506 (SIC 2821)	Dak Americas LLC	10 ^b	920	10,900	NA
		20	460	5,428.91	0
		250	37	434.22	0
SC0046311 ^c (SIC 4952)	Lake City Wastewater Treatment Plant	250	4.3	554.12	0
SC0002798 (SIC 2821)	Auriga Polymers, Inc.	1	155	521.38	NA
		20	7.8	26.22	0
		250	0.6	2.02	0
WV0000086 (SIC 2869)	Institute Plant	1	92	27.42	NA
		20	4.6	1.38	0
		250	0.4	0.12	0
CA0054011 (SIC 4952)	Los Coyotes Water Reclamation Plant	250	0.1	0.73	20
CA0053953 (SIC 4952)	LA-Glendale WRP	250	0.1	2.93	0
CA0056227 (SIC 4952)	Donald C Tillman WRP	250	0.1	1.49	0
MO0101184 (SIC 2899)	Buckman Laboratories, Inc.	1	20	1,819.84	NA
		20	1	90.99	0
		250	0.1	9.1	0
NY0001643 (SIC 3861)	Eastman Kodak	1	20	18.78	NA
		20	1	0.95	0
		250	0.1	0.0949	0
Reporting Year 2015			Min	18.78 (acute) 0.0949 (chronic)	
			Max	10,900 (acute) 5,429 (chronic)	

- a. Days of release (1, 20, or 250) are EPA assumptions that provide a range of potential surface water concentrations; days of release were not reported in DMR. The release (kg/day) is based on the per day based on total annual loading (lbs/yr), as reported in DMR Pollutant Loading Tool, and is divided by the assumed number of release days prior to modeling.
- b. The Dak chemicals site acute scenario was re-run for a 10-day acute scenario based on input from EPA engineers related to the lowest number of operating days assumed for facilities falling within this standard industrial category (*i.e.*, 10 days per year). Therefore, maximum surface water concentrations based on this site reflect an assumed 10 days per year of release instead of 1 day.
- c. Flow data were not available in E-FAST 2014 for NPDES SC0046311 (Lake City Wastewater Treatment Plant) and an appropriate surrogate was not readily identified. Therefore, a generic SIC code (4952 – Industrial POTW) was applied in E-FAST.

d. NPDES CTMIU0161 (Beacon Heights Landfill) is not in the E-FAST 2014 database. This site is a landfill and is in the Superfund program. Leachate collected from this site is sent through a leachate transportation line to the local sewer system and to the Beacon Falls Treatment Plant (Beacon Falls WPCF; NPDES CT0101061). <https://cumulis.epa.gov/supercpad/SiteProfiles/index.cfm?fuseaction=second.Cleanup&id=0100180#bkground>

Table E-4. Summary of Modeled Surface Water Concentrations for TRI Facilities – Direct

NPDES Used in E-FAST	Name	Days of Release ^a	Release ^a (kg/day)	7Q10 Concentration (µg/L)	Days Exceedance (days/yr) COC = 14,500 µg/L
Reporting Year 2015^b					
WV0000132	APG Polytech LLC	1	9767	687.59	NA
		20	488	34.35	0
		250	39	2.75	0
SC0026506	DAK Americas LLC Cooper River Plant	10 ^c	810	9,557	NA
		20	405	4778.76	0
		250	32	377.58	0
LA0036421 ^d	BASF Corp.	1	5361	21.7	NA
		20	268	1.09	0
		250	21	0.0868	0
LA0000191	St Charles Operations (TAFT/STAR) Union Carbide Corp.	1	817	3.31	NA
		20	41	0.17	0
		250	3.3	0.0134	0
TX0002844 ^e	Union Carbide Corp. Seadrift Plant	1	640	7685.62	NA
		20	32	96.07	NA
		250	2.6	7.81	NA
NC0003719	DAK Americas LLC	10 ^c	44	56.19	NA
		20	22	28.16	0
		250	1.8	2.30	0
LA0003301 ^f	The DOW Chemical Co. – Louisiana Operations	1	337	1.36	NA
		20	17	0.0688	0
		250	1	0.00405	0
SC0002798	Auriga Polymers Inc.	1	157	527.77	NA
		20	8	26.89	0
		250	1	3.36	0
NC0001112	Invista SA RL – Wilmington	1	99	480.86	NA
		20	5	24.29	0
		250	0.4	1.94	0
TN0002640	Eastman Chemical Co.	1	56	28.91	NA
		20	3	1.55	0
		250	0.2	0.10	0
Reporting Year 2015			Min	1.36 (acute) 0.00405 (chronic)	
			Max	9,557 (acute) 4,778.76 (chronic)	
Reporting Year 2014^g					
WV0000132	APG Polytech LLC	1	12,200	858.87	NA
		20	611	43.01	0
		250	49	3.45	0
SC0026506	DAK Americas LLC Cooper River Plant	10 ^c	825	9,734	NA
		20	412	4,861.36	0
		250	33	389.4	0
LA0036421 ^d	BASF Corp.	1	1199	4.85	NA

NPDES Used in E-FAST	Name	Days of Release ^a	Release ^a (kg/day)	7Q10 Concentration (µg/L)	Days Exceedance (days/yr) COC = 14,500 µg/L
		20	60	0.24	0
		250	4.8	0.0194	0
LA0000191	St Charles Operations (TAFT/STAR) Union Carbide Corp.	1	784	3.17	NA
		20	39	0.16	0
		250	3.1	0.012	0
LA0003301 ^f	The DOW Chemical Co. – Louisiana Operations	1	312	1.26	NA
		20	16	0.0648	0
		250	1	0.00405	0
NC0003719	DAK Americas LLC. Cedar Creek	10 ^c	17	22.14	NA
		20	9	11.52	0
		250	0.7	0.9	0
SC0002798	Auriga Polymers Inc.	1	83	279.01	NA
		20	4	13.45	0
		250	0.3	1.01	0
TN0002640	Eastman Chemical Co.	1	67	34.58	NA
		20	3	1.55	0
		250	0.3	0.15	0
WV0000086	Bayer Crop Science LP.	1	66	19.76	NA
		20	3	0.90	0
		250	0.3	0.0898	0
NC0001112	Invista SA RL – Wilmington	1	44	213.72	NA
		20	2	9.71	0
		250	0.2	0.97	0
Reporting Year 2014			Min	1.26 (acute) 0.00405 (chronic)	
			Max	9,734 (acute) 4,861.36 (chronic)	

- Days of release (1, 20, or 250) are EPA assumptions that provide a range of potential surface water concentrations; days of release were not reported to TRI. The release (kg/day) is based on the per day based on annual releases to surface water (lbs/yr), as reported to TRI, and is divided by the assumed number of release days prior to modeling.
- ARKEMA Inc (KY0003603), Dow Chemical Co Freeport (TX0006483), Honeywell International (LA0000329), and Westlake Vinyls Inc (KY0003484) facilities, which were included in the draft risk evaluation based on previous data extraction, did not have reported surface water discharges in TRI explorer per 2015 release report and were therefore removed from the list of assessed sites.
- The Dak chemicals site acute scenario was re-run for a 10-day acute scenario based on input from EPA engineers related to the lowest number of operating days assumed for facilities falling within this standard industrial category (*i.e.*, 10 days per year). Therefore, maximum surface water concentrations based on this site reflect an assumed 10 days per year of release instead of 1 day.
- For facility BASF CORP (LA0004057), E-FAST appears to show that this facility discharging to Bayou Baton Rouge. Communications with the Louisiana Department of Environmental Quality confirmed this site discharges process waters to the Mississippi River via pipeline, so an appropriate surrogate, the Baton Rouge POTW (NPDES LA0036421), was used in E-FAST for the purposes of applying stream flow.
- The facility UNION CARBIDE CORP SEADRIFT PLANT does not have a NPDES listed in DMR; however, a facility name and location search within E-FAST 2014 returned a NPDES (TX0002844), which was used for modeling.
- The NPDES provided in DMR's Pollutant Loading Tool for the facility THE DOW CHEMICAL CO - LOUISIANA OPERATIONS (NPDES LA0116602) was not found in E-FAST 2014; however, a facility name and location search within E-FAST 2014 returned a different NPDES (LA0003301) associated with this facility name and location, so it was applied for modeling.
- ARKEMA Inc (KY0003603), Catlettsburg Refining LLC (KY0070718), Dow Chemical Co Freeport (TX0006483), Eagle US 2 LLC (LA0000761), Honeywell International (LA0000329), and Westlake Vinyls Inc (KY0003484) facilities, which were included in the draft risk evaluation based on previous data extraction, did not have reported surface water discharges in TRI explorer per 2014 release report and were therefore removed from the list of assessed sites.

Table E 5. Summary of Modeled Surface Water Concentrations for Facilities - Indirect

NPDES Used in E-FAST	Facility Name	Receiving POTW	Days of Release ^a	Release ^a (kg/day)	7Q10 Concentration (µg/L)	Days Exceedance (days/yr) COC = 14,500 µg/L
Reporting Year 2015						
AL0048593	Indorama Ventures	Decatur Utilities Dry Creek WWTP	250	300	15.95	0
Ind. POTW (SIC 4952) ^b	SUEZ WTS Solutions USA Inc.	Blue Lake WWTP	250	27	3409.79	3
Ind. POTW (SIC 4952) ^c	Nan Ya Plastics Corp. America	Lake City WWTP	250	7	884.02	0
Ind. POTW (SIC 4952) ^b	Mitsubishi Polyester Film Inc.	Pelham WWTP	250	2	252.58	0
NY0087971	AMRI Rensselaer Inc.	Rensselaer Co.	250	0.4	0.0573	0
MD0021601	Solvay USA Inc.	Patapsco WWTP	250	0.1	0.76	0
Ind. POTW (SIC 4952) ^b	DAK Americas Mississippi Inc.	Hancock County Port and Harbor Commission	250	0.1	12.63	0
WI0025411	Aldrich Chemical Co. LLC	Sheboygan Regional WWTP	250	0.004	0.012	NA
WI0060453	Evonik Materials Corp.	Milton Waterworks	250	0.001	0.0586	0
OH0024970	Heritage Thermal Services	East Liverpool WWTP	250	2.39E-07	2.37E-08	0
Reporting Year 2015				Min	2.37E-08 (chronic)	
				Max	3,410 (chronic)	
Reporting Year 2014						
AL0048593	Indorama Ventures	Decatur Utilities Dry Creek WWTP	250	222	11.8	0
Ind. POTW (SIC 4952) ^b	SUEZ WTS Solutions USA Inc.	Blue Lake WWTP	250	30	3788.66	4
Ind. POTW (SIC 4952) ^c	Nan Ya Plastics Corp. America	Lake City WWTP	250	8	1010.31	0
Ind. POTW (SIC 4952) ^b	Mitsubishi Polyester Film Inc.	Pelham WWTP	250	1	126.29	0
Ind. POTW (SIC 4952) ^b	DAK Americas Mississippi Inc.	Hancock County Port and Harbor Commission	250	0.1	12.63	0
MD0021601	Solvay USA Inc.	Patapsco WWTP	250	0.1	0.76	0
WI0025411	Aldrich Chemical Co. LLC	Sheboygan Regional WWTP	250	0.004	0.012	NA
WI0060453	Evonik Materials Corp.	Milton Waterworks	250	0.001	0.00586	0
Reporting Year 2014				Min	0.0059 (chronic)	
				Max	3,789 (chronic)	

a. Days of release (250) are EPA assumptions that provide a range of potential surface water concentrations; days of release were not reported to TRI. The release (kg/day) is based on the per day based on annual releases to surface water (lbs/yr), as reported to TRI, and is divided by the assumed number of release days prior to modeling.

b. SIC for industrial POTWs was used for the facility because the facility was not found in E-FAST 2014.

- c. SIC for industrial POTWs was used for NAN YA PLASTICS CORP AMERICA because flow data were not available in E-FAST 2014 for NPDES SC0046311 (Lake City Wastewater Treatment Plant) and an appropriate surrogate was not readily identified.

Appendix F ENVIRONMENTAL RISK

F.1 Environmental Risk Tables

Table F-1. Environmental Risk Estimation of 1,4-Dioxane from Industrial Releases into Surface Water from DMR Facilities in Year 2015

Name, Location, and ID of Active Releaser Facility	E-FAST Inputs and Results				RQ	
	Days of Release ^a	Release ^a (kg/day)	10 th Percentile 7Q10 Concentration (µg/L)	Days Exceedance (days/yr)	Algae COC = 57,500 µg/L	Fish Chronic COC = 14,500 µg/L
M and G Polymers USA, LLC WV0000132 (SIC 2821)	1	9,514	669.75	NA	0.0328069	0.008273
	20	476	33.49	0	0.0026276	0.0006626
	250	38	2.68	0	0.0634621	0.0160035
Dak Americas LLC SC0026506 (SIC 2821)	10 ^b	920	10,900 ^b	NA	0.031731	0.0080017
	20	460	5,428.91	0	0.0025379	0.00064
	250	37	434.22	0	0.0002966	7.48E-05
Lake City Wastewater Treatment Plant SC0046311 ^c (SIC 4952)	250	4.3	554.12	0	0.0106966	0.0026974
Auriga Polymers, Inc. SC0002798 (SIC 2821)	1	155	521.38	NA	0.0005379	0.0001357
	20	7.8	26.22	0	4.14E-05	1.04E-05
	250	0.6	2.02	0	0.0063172	0.001593
Institute Plant WV0000086 (SIC 2869)	1	92	27.42	NA	0.0003172	0.00008
	20	4.6	1.38	0	2.76E-05	6.96E-06
	250	0.4	0.12	0	6.90E-06	1.74E-06
Los Coyotes Water Reclamation Plant CA0054011 (SIC 4952)	250	0.1	0.73	20	6.90E-06	1.74E-06
LA-Glendale WRP CA0053953 (SIC 4952)	250	0.1	2.93	0	6.90E-06	1.74E-06
Donald C Tillman WRP CA0056227 (SIC 4952)	250	0.1	1.49	0	0.0013793	0.0003478
Buckman Laboratories, Inc. MO0101184 (SIC 2899)	1	20	1,819.84	NA	6.90E-05	1.74E-05
	20	1	90.99	0	6.90E-06	1.74E-06
	250	0.1	9.1	0	0.0013655	0.0003443
Eastman Kodak NY0001643 (SIC 3861)	1	20	18.78	NA	6.90E-05	1.74E-05
	20	1	0.95	0	6.90E-06	1.74E-06
	250	0.1	0.0949	0	0	0

- c. Days of release (1, 20, or 250) are EPA assumptions that provide a range of potential surface water concentrations; days of release were not reported in DMR. The release (kg/day) is based on the per day based on total annual loading (lbs/yr), as reported in DMR Pollutant Loading Tool, and is divided by the assumed number of release days prior to modeling.
- d. The Dak chemicals site acute scenario was re-run for a 10-day acute scenario based on input from EPA engineers related to the lowest number of operating days assumed for facilities falling within this standard industrial category (*i.e.*, 10 days per year). Therefore, maximum surface water concentrations based on this site reflect an assumed 10 days per year of release instead of 1 day.
- e. Flow data were not available in E-FAST 2014 for NPDES SC0046311 (Lake City Wastewater Treatment Plant) and an appropriate surrogate was not readily identified. Therefore, a generic SIC code (4952 – Industrial POTW) was applied in E-FAST.
- f. NPDES CTMIU0161 (Beacon Heights Landfill) is not in the E-FAST 2014 database. This site is a landfill and is in the Superfund program. Leachate collected from this site is sent through a leachate transportation line to the local sewer system and to the Beacon Falls Treatment Plant (Beacon Falls WPCF; NPDES CT0101061).

<https://cumulis.epa.gov/supercpad/SiteProfiles/index.cfm?fuseaction=second.Cleanup&id=0100180#bkground>

Name, Location, and ID of Active Releaser Facility	E-FAST Inputs and Results				RQ	
	Days of Release ^a	Release ^a (kg/day)	10 th Percentile 7Q10 Concentration (µg/L)	Days Exceedance (days/yr)	Algae COC = 57,500 µg/L	Fish Chronic COC = 14,500 µg/L

Table F-2. Environmental Risk Estimation of 1,4-Dioxane from Industrial Releases into Surface Water from DMR Facilities in Year 2016

Name, Location, and ID of Active Releaser Facility	E-FAST Inputs and Results				RQ	
	Days of Release ^a	Release ^a (kg/day)	10 th Percentile 7Q10 Concentration (µg/L)	Days Exceedance (days/yr)	Algae COC = 57,500 µg/L	Fish Chronic COC = 14,500 µg/L
M and G Polymers USA, LLC WV0000132 (SIC 2821)	1	13,753	968.17	NA	0.0168377	0.0667703
	20	688	48.41	0	0.0008419	0.0033386
	250	55	3.87	0	6.73E-05	0.0002669
Dak Americas LLC SC0026506 (SIC 2821)	10^b	977	11,500	NA	0.2	0.7931034
	20	488	5,761.65	0	0.1002026	0.3973552
	250	39	461.36	0	0.0080237	0.0318179
Lake City Wastewater Treatment Plant SC0046311 ^c (SIC 4952)	250	5.4	695.88	0	0.0121023	0.0479917
Institute Plant WV0000086 (SIC 2869)	1	271	81.19	NA	0.001412	0.0055993
	20	14	4.07	0	7.07826 E-05	0.0002807
	250	1.1	0.33	0	5.73913 E-06	2.27586 E-05
Eastman Kodak NY0001643 (SIC 3861)	1	79	74.46	NA	0.001295	0.0051352
	20	3.9	3.7	0	6.43478 E-05	0.0002552
	250	0.3	0.28	0	4.86957 E-06	1.93103 E-05
The Scranton Sewer Authority PA0026492 (SIC 4952)	250	0.2	1.85	0	3.21739 E-05	0.0001276
Los Coyotes Water Reclamation Plant CA0054011 (SIC 4952)	250	0.2	1.45	20	2.52174 E-05	0.0001
Beacon Heights Landfill Beacon Falls WPCF CTMIU0161 (SIC Blank) CT0101061 ^d	250	02	1.10	0	1.91E-05	7.59E-05
San Jose Creek Water Reclamation Plant CA0053911 (SIC 4952)	250	0.1	0.47	20	8.17E-06	3.24138 E-05
Donald C Tillman WRP CA0056227 (SIC 4952)	250	0.1	1.49	0	2.59E-05	0.0001028

Name, Location, and ID of Active Releaser Facility	E-FAST Inputs and Results				RQ	
	Days of Release ^a	Release ^a (kg/day)	10 th Percentile 7Q10 Concentration (µg/L)	Days Exceedance (days/yr)	Algae COC = 57,500 µg/L	Fish Chronic COC = 14,500 µg/L

- e. Days of release (1, 20, or 250) are EPA assumptions that provide a range of potential surface water concentrations; days of release were not reported in DMR. The release (kg/day) is based on the per day based on total annual loading (lbs/yr), as reported in DMR Pollutant Loading Tool, and is divided by the assumed number of release days prior to modeling.
- f. The Dak chemicals site acute scenario was re-run for a 10-day acute scenario based on input from EPA engineers related to the lowest number of operating days assumed for facilities falling within this standard industrial category (*i.e.*, 10 days per year). Therefore, maximum surface water concentrations based on this site reflect an assumed 10 days per year of release instead of 1 day.
- g. Flow data were not available in E-FAST 2014 for NPDES SC0046311 (Lake City Wastewater Treatment Plant) and an appropriate surrogate was not readily identified. Therefore, a generic SIC code (4952 – Industrial POTW) was applied in E-FAST.
- h. NPDES CTMIU0161 (Beacon Heights Landfill) is not in the E-FAST 2014 database. This site is a landfill and is in the Superfund program. Leachate collected from this site is sent through a leachate transportation line to the local sewer system and to the Beacon Falls Treatment Plant (Beacon Falls WPCF; NPDES CT0101061).
- <https://cumulis.epa.gov/supercpad/SiteProfiles/index.cfm?fuseaction=second.Cleanup&id=0100180#bkground>

Table F-3. Environmental Risk Estimation of 1,4-Dioxane from Direct Industrial Releases into Surface Water from TRI Facilities in Year 2014^a

Name, Location, and ID of Active Releaser Facility	E-FAST Inputs and Results				RQ	
	Days of Release ^b	Release ^b (kg/day)	7Q10 Concentration (µg/L)	Days Exceedance (days/yr) COC = 14,500 µg/L	Algae COC = 57,500 µg/L	Fish Chronic COC = 14,500 µg/L
NPDES Used in E-FAST APG Polytech LLC WV0000132	1	12,200	858.87	NA	1.49E-02	5.92E-02
	20	611	43.01	0	7.48E-04	2.97E-03
	250	49	3.45	0	6.00E-05	2.38E-04
DAK Americas LLC Cooper River Plant SC0026506	10 ^c	825	9,734	NA	1.69E-01	6.71E-01
	20	412	4,861.36	0	8.45E-02	3.35E-01
	250	33	389.4	0	6.77E-03	2.69E-02
BASF Corp. LA0036421 ^d	1	1199	4.85	NA	8.43E-05	3.34E-04
	20	60	0.24	0	4.17E-06	1.66E-05
	250	4.8	0.0194	0	3.37E-07	1.34E-06
St Charles Operations (TAFT/STAR) Union Carbide Corp. LA0000191	1	784	3.17	NA	5.51E-05	2.19E-04
	20	39	0.16	0	2.78E-06	1.10E-05
	250	3.1	0.012	0	2.09E-07	8.28E-07
The DOW Chemical Co. Louisiana Operations LA0003301 ^e	1	312	1.26	NA	2.19E-05	8.69E-05
	20	16	0.0648	0	1.13E-06	4.47E-06
	250	1	0.00405	0	7.04E-08	2.79E-07
DAK Americas LLC. Cedar Creek NC0003719	10 ^c	17	22.14	NA	3.85E-04	1.53E-03
	20	9	11.52	0	2.00E-04	7.94E-04
	250	0.7	0.9	0	1.57E-05	6.21E-05
Auriga Polymers Inc. SC0002798	1	83	279.01	NA	4.85E-03	1.92E-02
	20	4	13.45	0	2.34E-04	9.28E-04
	250	0.3	1.01	0	1.76E-05	6.97E-05
Eastman Chemical Co. TN0002640	1	67	34.58	NA	6.01E-04	2.38E-03
	20	3	1.55	0	2.70E-05	1.07E-04
	250	0.3	0.15	0	2.61E-06	1.03E-05
Bayer Crop Science LP. WV0000086	1	66	19.76	NA	3.44E-04	1.36E-03
	20	3	0.90	0	1.57E-05	6.21E-05
	250	0.3	0.0898	0	1.56E-06	6.19E-06
Invista SA RL – Wilmington NC0001112	1	44	213.72	NA	3.72E-03	1.47E-02
	20	2	9.71	0	1.69E-04	6.70E-04
	250	0.2	0.97	0	1.69E-05	6.69E-05

Name, Location, and ID of Active Releaser Facility NPDES Used in E-FAST	E-FAST Inputs and Results				RQ	
	Days of Release ^b	Release ^b (kg/day)	7Q10 Concentration (µg/L)	Days Exceedance (days/yr) COC = 14,500 µg/L	Algae COC = 57,500 µg/L	Fish Chronic COC = 14,500 µg/L

- d. ARKEMA Inc (KY0003603), Catlettsburg Refining LLC (KY0070718), Dow Chemical Co Freeport (TX0006483), Eagle US 2 LLC (LA0000761), Honeywell International (LA0000329), and Westlake Vinyls Inc (KY0003484) facilities, which were included in the risk evaluation based on previous data extraction, did not have reported surface water discharges in TRI explorer per 2014 release report and were therefore removed from the list of assessed sites.
- e. Days of release (1, 20, or 250) are EPA assumptions that provide a range of potential surface water concentrations; days of release were not reported to TRI. The release (kg/day) is based on the per day based on annual releases to surface water (lbs/yr), as reported to TRI, and is divided by the assumed number of release days prior to modeling.
- f. ARKEMA Inc (KY0003603), Dow Chemical Co Freeport (TX0006483), Honeywell International (LA0000329), and Westlake Vinyls Inc (KY0003484) facilities, which were included in the risk evaluation based on previous data extraction, did not have reported surface water discharges in TRI explorer per 2015 release report and were therefore removed from the list of assessed sites.
- g. For facility BASF CORP (LA0004057), E-FAST appears to show that this facility discharging to Bayou Baton Rouge. Communications with the Louisiana Department of Environmental Quality confirmed this site discharges process waters to the Mississippi River via pipeline, so an appropriate surrogate, the Baton Rouge POTW (NPDES LA0036421), was used in E-FAST for the purposes of applying stream flow.
- h. The NPDES provided in DMR's Pollutant Loading Tool for the facility THE DOW CHEMICAL CO - LOUISIANA OPERATIONS (NPDES LA0116602) was not found in E-FAST 2014; however, a facility name and location search within E-FAST 2014 returned a different NPDES (LA0003301) associated with this facility name and location, so it was applied for modeling.

Table F-5. Environmental Risk Estimation of 1,4-Dioxane from Direct Industrial Releases into Surface Water from TRI Facilities in Year 2015^b

Name, Location, and ID of Active Releaser Facility NPDES Used in E-FAST	E-FAST Inputs and Results				RQ	
	Days of Release ^a	Release ^a (kg/day)	7Q10 Concentration (µg/L)	Days Exceedance (days/yr) COC = 14,500 µg/L	Algae COC = 57,500 µg/L	Fish Chronic COC = 14,500 µg/L
APG Polytech LLC WV0000132	1	9767	687.59	NA	1.20E-02	4.74E-02
	20	488	34.35	0	5.97E-04	2.37E-03
	250	39	2.75	0	4.78E-05	1.90E-04
DAK Americas LLC Cooper River Plant SC0026506	10 ^c	810	9,557	NA	1.66E-01	6.59E-01
	20	405	4778.76	0	8.31E-02	3.30E-01
	250	32	377.58	0	6.57E-03	2.60E-02
BASF Corp. LA0036421 ^d	1	5361	21.7	NA	3.77E-04	1.50E-03
	20	268	1.09	0	1.90E-05	7.52E-05
	250	21	0.0868	0	1.51E-06	5.99E-06
St Charles Operations (TAFT/STAR) Union Carbide Corp LA0000191	1	817	3.31	NA	5.76E-05	2.28E-04
	20	41	0.17	0	2.96E-06	1.17E-05
	250	3.3	0.0134	0	2.33E-07	9.24E-07
Union Carbide Corp. Seadrift Plant TX0002844 ^e	1	640	7685.62	NA	1.34E-01	5.30E-01
	20	32	96.07	NA	1.67E-03	6.63E-03
	250	2.6	7.81	NA	1.36E-04	5.39E-04
DAK Americas LLC NC0003719	10 ^c	44	56.19	NA	9.77E-04	3.88E-03
	20	22	28.16	0	4.90E-04	1.94E-03
	250	1.8	2.30	0	4.00E-05	1.59E-04
The DOW Chemical Co. Louisiana Operations LA0003301 ^f	1	337	1.36	NA	2.37E-05	9.38E-05
	20	17	0.0688	0	1.20E-06	4.74E-06
	250	1	0.00405	0	7.04E-08	2.79E-07
Auriga Polymers Inc. SC0002798	1	157	527.77	NA	9.18E-03	3.64E-02
	20	8	26.89	0	4.68E-04	1.85E-03
	250	1	3.36	0	5.84E-05	2.32E-04
Invista SA RL – Wilmington NC0001112	1	99	480.86	NA	8.36E-03	3.32E-02
	20	5	24.29	0	4.22E-04	1.68E-03
	250	0.4	1.94	0	3.37E-05	1.34E-04
Eastman Chemical Co. TN0002640	1	56	28.91	NA	5.03E-04	1.99E-03
	20	3	1.55	0	2.70E-05	1.07E-04
	250	0.2	0.10	0	1.74E-06	6.90E-06

Name, Location, and ID of Active Releaser Facility NPDES Used in E-FAST	E-FAST Inputs and Results				RQ	
	Days of Release ^a	Release ^a (kg/day)	7Q10 Concentration (µg/L)	Days Exceedance (days/yr) COC = 14,500 µg/L	Algae COC = 57,500 µg/L	Fish Chronic COC = 14,500 µg/L

- h. Days of release (1, 20, or 250) are EPA assumptions that provide a range of potential surface water concentrations; days of release were not reported to TRI. The release (kg/day) is based on the per day based on annual releases to surface water (lbs/yr), as reported to TRI, and is divided by the assumed number of release days prior to modeling.
- i. ARKEMA Inc (KY0003603), Dow Chemical Co Freeport (TX0006483), Honeywell International (LA0000329), and Westlake Vinyls Inc (KY0003484) facilities, which were included in the risk evaluation based on previous data extraction, did not have reported surface water discharges in TRI explorer per 2015 release report and were therefore removed from assessed sites.
- j. The Dak chemicals site acute scenario was re-run for a 10-day acute scenario based on input from EPA engineers related to the lowest number of operating days assumed for facilities falling within this standard industrial category (*i.e.*, 10 days per year). Therefore, maximum surface water concentrations based on this site reflect an assumed 10 days per year of release instead of 1 day.
- k. For facility BASF CORP (LA0004057), E-FAST appears to show that this facility discharging to Bayou Baton Rouge. Communications with the Louisiana Department of Environmental Quality confirmed this site discharges process waters to the Mississippi River via pipeline, so an appropriate surrogate, the Baton Rouge POTW (NPDES LA0036421), was used in E-FAST for the purposes of applying stream flow.
- l. The facility UNION CARBIDE CORP SEADRIFT PLANT does not have a NPDES listed in DMR; however, a facility name and location search within E-FAST 2014 returned a NPDES (TX0002844), which was used for modeling.
- m. The NPDES provided in DMR's Pollutant Loading Tool for the facility THE DOW CHEMICAL CO - LOUISIANA OPERATIONS (NPDES LA0116602) was not found in E-FAST 2014; however, a facility name and location search within E-FAST 2014 returned a different NPDES (LA0003301) associated with this facility name and location, so it was applied for modeling.

Table 4-5. Summary of Modeled Surface Water Concentrations for Facilities – Indirect – Reporting Year 2014

Name, Location, and ID of Active Releaser Facility NPDES Used in E-FAST	Receiving POTW	E-FAST Inputs and Results				RQ	
		Days of Release ^a	Release ^a (kg/day)	7Q10 Concentration (µg/L)	Days Exceedance (days/yr) COC = 14,500 µg/L	Algae COC = 57,500 µg/L	Fish Chronic COC = 14,500 µg/L
Reporting Year 2014							
Indorama Ventures AL0048593	Decatur Utilities Dry Creek WWTP	250	222	11.8	0	2.05E-04	8.14E-04
SUEZ WTS Solutions USA Inc. Ind. POTW (SIC 4952) ^b	Blue Lake WWTP	250	30	3788.66	4	6.59E-02	2.61E-01
Nan Ya Plastics Corp. America Ind. POTW (SIC 4952) ^c	Lake City WWTP	250	8	1010.31	0	1.76E-02	6.97E-02
Mitsubishi Polyester Film Inc. Ind. POTW (SIC 4952) ^b	Pelham WWTP	250	1	126.29	0	2.20E-03	8.71E-03
DAK Americas Mississippi Inc. Ind. POTW (SIC 4952) ^b	Hancock County Port and Harbor Commission	250	0.1	12.63	0	2.20E-04	8.71E-04
Solvay USA Inc. MD0021601	Patapsco WWTP	250	0.1	0.76	0	1.32E-05	5.24E-05
Aldrich Chemical Co. LLC WI0025411	Sheboygan Regional WWTP	250	0.004	0.012	NA	2.09E-07	8.28E-07
Evonik Materials Corp. WI0060453	Milton Waterworks	250	0.001	0.00586	0	1.02E-07	4.04E-07

- d. Days of release (250) are EPA assumptions that provide a range of potential surface water concentrations; days of release were not reported to TRI. The release (kg/day) is based on the per day based on annual releases to surface water (lbs/yr), as reported to TRI, and is divided by the assumed number of release days prior to modeling.
- e. SIC for industrial POTWs was used for the facility because the facility was not found in E-FAST 2014.
- f. SIC for industrial POTWs was used for NAN YA PLASTICS CORP AMERICA because flow data were not available in E-FAST 2014 for NPDES SC0046311 (Lake City Wastewater Treatment Plant) and an appropriate surrogate was not readily identified.

Table F-6. Environmental Risk Estimation of 1,4-Dioxane from Direct Industrial Releases into Surface Water from TRI Facilities in Year 2014

Name, Location, and ID of Active Releaser Facility NPDES Used in E-FAST	Receiving POTW	E-FAST Inputs and Results				RQ	
		Days of Release ^a	Release ^a (kg/day)	7Q10 Concentration (µg/L)	Days Exceedance (days/yr) COC = 14,500 µg/L	Algae COC = 57,500 µg/L	Fish Chronic COC = 14,500 µg/L
Indorama Ventures AL0048593	Decatur Utilities Dry Creek WWTP	250	300	15.95	0	2.77E-04	1.10E-03
SUEZ WTS Solutions USA Inc. Ind. POTW (SIC 4952) ^b	Blue Lake WWTP	250	27	3409.79	3	5.93E-02	2.35E-01
Nan Ya Plastics Corp. America Ind. POTW (SIC 4952) ^c	Lake City WWTP	250	7	884.02	0	1.54E-02	6.10E-02
Mitsubishi Polyester Film Inc. Ind. POTW (SIC 4952) ^b	Pelham WWTP	250	2	252.58	0	4.39E-03	1.74E-02
AMRI Rensselaer Inc. NY0087971	Rensselaer Co.	250	0.4	0.0573	0	9.97E-07	3.95E-06
Solvay USA Inc. MD0021601	Patapsco WWTP	250	0.1	0.76	0	1.32E-05	5.24E-05
DAK Americas Mississippi Inc. Ind. POTW (SIC 4952) ^b	Hancock County Port and Harbor Commission	250	0.1	12.63	0	2.20E-04	8.71E-04
Aldrich Chemical Co. LLC WI0025411	Sheboygan Regional WWTP	250	0.004	0.012	NA	2.09E-07	8.28E-07
Evonik Materials Corp. WI0060453	Milton Waterworks	250	0.001	0.0586	0	1.02E-06	4.04E-06
Heritage Thermal Services OH0024970	East Liverpool WWTP	250	2.39E-07	2.37E-08	0	4.12E-13	1.63E-12

- a. Days of release (250) are EPA assumptions that provide a range of potential surface water concentrations; days of release were not reported to TRI. The release (kg/day) is based on the per day based on annual releases to surface water (lbs/yr), as reported to TRI, and is divided by the assumed number of release days prior to modeling.
- b. SIC for industrial POTWs was used for the facility because the facility was not found in E-FAST 2014.
- c. SIC for industrial POTWs was used for NAN YA PLASTICS CORP AMERICA because flow data were not available in E-FAST 2014 for NPDES SC0046311 (Lake City Wastewater Treatment Plant) and an appropriate surrogate was not readily identified.

Appendix G OCCUPATIONAL EXPOSURES

G.1 Systematic Review Summary Tables

G.1.1 Evaluation of Inhalation Data Sources Specific to 1,4-Dioxane

EPA has reviewed acceptable sources for 1,4-dioxane inhalation exposure data according to the data quality evaluation criteria found in [The Application of Systematic Review in TSCA Risk Evaluations U.S. EPA \(2018b\)](#). Table G-1 summarizes the results of this evaluation. The data quality evaluation indicated the sources included are of medium to high confidence and are used to characterize the occupational inhalation exposures of 1,4-dioxane.

Table G-1. Summary of Inhalation Monitoring Data Sources Specific to 1,4-Dioxane

Row	Occupational Exposure Scenario	Type of Sample	Worker Activity or Sampling Location	1,4-Dioxane Airborne Concentration (mg/m ³) ^a	Number of Samples	Type of Measurement	Sample Time	Source	Data Identifier from Data Extraction and Evaluation	Overall Data quality rating from Data Extraction and Evaluation	Rationale for Inclusion / Exclusion
1	Laboratory Chemicals	Personal	Solvent extraction and TLC	1.8 ppm (highest value)	Unknown	Unknown	Unknown	NICNAS, 1998	NICNAS (1998)	High	Included – Referenced in comparison to other available data in the Laboratory Chemical OES.
2	Film Cement	Personal	Film cement application	<1 ppm	Unknown	Unknown	Unknown	NICNAS, 1998	NICNAS (1998)	High	Included – Referenced in comparison to other available data in the Film Cement OES.
3	Industrial Use	Area and Personal	Metal cleaning surface, Medicine manufacture, Shirt cleaning area, textile industry, Pharmaceutical production Manufacture of magnetic tapes, Use (e.g., as solvent) in other productions	Central Tendency: 5 mg/m ³ High-end: 20 mg/m ³	Eight datasets – each has between 2 and 194 samples per set	Full-shift and Short term	6-8 hour for full shift, 0-0.5 hour for short term	ECJRC, 2002	ECJRC (2002)	High	Included – Recommended central tendency and high-end values used to estimate inhalation exposures for industrial use
4	Industrial Use	EASE Modeling	Extractant in medicine manufacturing	36-180 mg/m ³	Not applicable – estimates from modeling	unknown	Not applicable – estimates from modeling	ECJRC, 2002	ECJRC (2002)	High	Included – Modeling estimates are considered/referenced, but not used in exposure calculations.

Row	Occupational Exposure Scenario	Type of Sample	Worker Activity or Sampling Location	1,4-Dioxane Airborne Concentration (mg/m ³) ^a	Number of Samples	Type of Measurement	Sample Time	Source	Data Identifier from Data Extraction and Evaluation	Overall Data quality rating from Data Extraction and Evaluation	Rationale for Inclusion / Exclusion
5	Laboratory Chemicals	Area and Personal	Laboratory Work	0-166 mg/m ³	Three datasets – each has between 1 and 305 samples per set	Full-shift and Short term	6-8 hour for full shift, 0-0.5 hour for short term	ECJRC, 2002	ECJRC (2002)	High	Included – Mean, 90 th percentile, and short-term peak values used to estimate inhalation exposures for laboratory chemical use
6	Open System Functional Fluids	Area and Personal	Threader, broaching, Apex drill, lunch tables (for area) Transfer lines, roughing, four-way, multiple, screw machine-lathing, and apex drill (for pbz)	0.14 to 0.23 mg/m ³ (area) 0.24 to 0.53 (PBZ) These are exposures to MWF, not dioxane specifically	6 PBZ, 4 area	Full-shift	~ 7 hours sample time	Burton, 1997	Burton and Driscoll (1997)	High	Included – Used in conjunction with 1,4-dioxane weight fraction to estimate inhalation exposures during use of metalworking fluids
7	Printing Inks (3D)	Area	3-D printing	27 ppbv	1	Full-shift	8	Ryan & Hubbard , 2016	Ryan and Hubbard (2016)	High	Included – Used to estimate inhalation exposures for 3-D printing ink use
8	Film Cement	Area and Personal	Splicing	less than 1 ppm	4 pbz, 1 area	Full-shift	6 hours	Okawa, 1982	Okawa and Coye (1982)	High	Included – Data used to estimate exposures for film cement application.

Row	Occupational Exposure Scenario	Type of Sample	Worker Activity or Sampling Location	1,4-Dioxane Airborne Concentration (mg/m ³) ^a	Number of Samples	Type of Measurement	Sample Time	Source	Data Identifier from Data Extraction and Evaluation	Overall Data quality rating from Data Extraction and Evaluation	Rationale for Inclusion / Exclusion
9	Manufacturing	Personal	Unknown	provided in report, most less than 2 ug/sample	28	Full-shift	Time listed for each sample	BASF, 2016	BASF (2016)	High	Included – Data used to estimate exposures for manufacturing
10	Manufacturing	Personal	Routine duties, neutralization, evaporator dump	0.39 ppm (15-min STEL) <0.056 ppm (8-hour TWA) 38 ppm (15-min STEL) 0.23 ppm (8-hour TWA)	4	Short-term, Full-shift	15-min STEL, 8-hour TWA	BASF, 2017	BASF (2017)	High	Included – Data used to estimate exposures for manufacturing
11	Spray Foam Application	Not applicable – Monitoring data not provided	a typical two-story, 2,300-square-foot house with a medium-pitch roof — has a roof area of about 1,500 square feet	Not applicable – Monitoring data not provided	Not applicable – Monitoring data not provided	Not applicable – Monitoring data not provided	Not applicable – Monitoring data not provided	Huber, 2018	Huber (2018)	Medium	Included – Used as an input in calculations to model exposures during spray foam use
12	Spray Foam Application	Not applicable – Monitoring data not provided	an average size house is 1,500 square feet of roofing	Not applicable – Monitoring data not provided	Not applicable – Monitoring data not provided	Not applicable – Monitoring data not provided	Not applicable – Monitoring data not provided	HomeAdvisor, 2018	HomeAdvisor (2018)	Medium	Included – Used as an input in calculations to model exposures during spray foam use
13	Spray Foam Application	Not applicable – Monitoring data not provided	Mix A-side and B-side in 1:1 ratio	Not applicable – Monitoring data not provided	Not applicable – Monitoring data not provided	Not applicable – Monitoring data not provided	Not applicable – Monitoring data not provided	OMG Roofing Products, 2018	OMG Roofing Products (2018)	High	Included – Used as an input in calculations to model exposures

Row	Occupational Exposure Scenario	Type of Sample	Worker Activity or Sampling Location	1,4-Dioxane Airborne Concentration (mg/m ³) ^a	Number of Samples	Type of Measurement	Sample Time	Source	Data Identifier from Data Extraction and Evaluation	Overall Data quality rating from Data Extraction and Evaluation	Rationale for Inclusion / Exclusion
											during spray foam use
14	Spray Foam Application	Not applicable – Monitoring data not provided	0.1% 1,4-dioxane in B-Side	Not applicable – Monitoring data not provided	Not applicable – Monitoring data not provided	Not applicable – Monitoring data not provided	Not applicable – Monitoring data not provided	GAF, 2014	GAF (2014)	High	Included – Used as an input in calculations to model exposures during spray foam use
15	Dry Film Lubrication	Area and personal	Manufacture, Application - also provides specific activity descriptions	<0.031 to 50 ppm	25	8-hour TWA, Short-term tasks	8 hours, varied	DOE, 2018a	DOE (2018a)	High	Included – Data used to estimate exposures for dry film lubrication manufacture and use
16	Dry Film Lubrication	Not applicable – Monitoring data not provided	Up to 10 workers potentially exposed.	Not applicable – Monitoring data not provided	Not applicable – Monitoring data not provided	Not applicable – Monitoring data not provided	Not applicable – Monitoring data not provided	DOE, 2018b	DOE (2018b)	High	Included – Used in dry film lubrication scenario

G.1.2 Evaluation of Cross-Cutting Data Sources

EPA has reviewed acceptable sources for data that are relevant to all chemicals in this first wave of risk evaluations under the amended TSCA according to the data quality evaluation criteria found in [The Application of Systematic Review in TSCA Risk Evaluations U.S. EPA \(2018b\)](#). Table G-2 summarizes the results of this evaluation. The data quality evaluation indicated the sources included are of medium to high confidence and are used to characterize the occupational inhalation exposures of 1,4-dioxane.

Table G-2. Summary of Cross-Cutting Data Sources

Row	Data Source	Reference	Overall Data quality rating from Data Extraction and Evaluation
1	Chemical Data Reporting (CDR) Data	U.S. EPA (2016c)	High
2	RY 2016 Toxics Release Inventory (TRI) Data	U.S. EPA (2016e)	Medium
3	Defense Occupational and Environmental Health Readiness System – Industrial Hygiene (DOEHRS-IH); Provided to EPA from DOD; 2018	DoD (2018)	High
4	Bureau of Labor Statistics (BLS). 2014b. Employee Tenure News Release, September 18, 2014. http://www.bls.gov/news.release/archives/tenure_09182014.htm (Accessed February 19, 2016).	BLS (2014)	High
5	Bureau of Labor Statistics (BLS). 2015. Hours and Employment by Industry Tables - August 6, 2015. Available at http://www.bls.gov/lpc/tables.htm (Accessed December 30, 2015).	BLS (2015)	High
6	Census Bureau. 2012b. Code Lists and Crosswalks - Census 2012 Detailed Industry Code List. Available at http://www.census.gov/people/io/methodology/ (Accessed January 28, 2016).	U.S. Census Bureau (2012)	N/A ^a
7	Census Bureau. 2016a. Survey of Income and Program Participation - Data. Available at http://www.census.gov/programs-surveys/sipp/data.html (Accessed February 1, 2016).	U.S. Census Bureau (2016a)	High
8	Census Bureau. 2016b. Survey of Income and Program Participation - SIPP Introduction and History. Available at http://www.census.gov/programs-surveys/sipp/about/sipp-introduction-history.html (Accessed February 1, 2016).	U.S. Census Bureau (2016b)	N/A ^b
9	Bureau of Labor Statistics (BLS). 2016. May 2016 Occupational Employment and Wage Estimates: National Industry-Specific Estimates. Available at http://www.bls.gov/oes/tables.htm (Accessed May 14, 2018).	BLS (2016)	High

10	Census Bureau. 2015. Statistics of U.S. Businesses (SUSB). Available at https://www.census.gov/data/tables/2015/econ/susb/2015-susb-annual.html (Accessed May 14, 2018).	U.S. Census Bureau (2015)	High
11	Cherrie JW, Semple S, Brouwer D (2004) Gloves and dermal exposure to chemicals: Proposals for Evaluating Workplace Effectiveness. <i>Annals of Occupational Hygiene</i> 48: 607-615.	Cherrie et al. (2004)	High
12	Dancik Y, Bigliardi PL, Bigliardi-Qi M (2015) What happens in the skin? Integrating skin permeation kinetics into studies of developmental and reproductive toxicity following topical exposure. <i>Reproductive Toxicology</i> . 58: 252-281.	Dancik et al. (2015)	High
13	Environmental Protection Agency [EPA] (2013) ChemSTEER User Guide: Chemical Screening Tool for Exposures and Environmental Release.	U.S. EPA (2013b)	High
14	Frasch HF, Bunge AL (2015). The Transient Dermal Exposure II: Post-Exposure Absorption and Evaporation of Volatile Compounds. <i>Journal of Pharmaceutical Sciences</i> 104: 1499-1507.	Frasch and Bunge (2015)	High
15	Frasch HF (2012). Dermal Absorption of Finite Doses of Volatile Compounds. <i>J Pharm Sci</i> . 2012 July; 101(7): 2616-2619.	Frasch (2012)	High
16	Frasch HF, Dotson GS, Barbero AM (2011). <i>In Vitro</i> Human Epidermal Penetration of 1-Bromopropane. <i>Journal of Toxicology and Environmental Health, Part A</i> , 74:1249-1260.	Frasch et al. (2011)	High
17	Garrod ANI, Phillips AM, Pemberton JA (2001). Potential Exposure of Hands Inside Protective Gloves - a Summary of Data from Non-Agricultural Pesticide Surveys. <i>Ann. Occup Hyg.</i> , Vol. 45, No. 1, pp. 55-60.	Garrod et al. (2001)	High
18	Kasting GB, Miller MA (2006) Kinetics of finite dose absorption through skin 2: Volatile Compounds. <i>Journal of Pharmaceutical Sciences</i> 95: 268-280.	Kasting and Miller (2006)	High
19	Marquart H, Franken R, Goede H, Fransman W, Schinkel (2017) Validation of the dermal exposure model in ECETOC TRA. <i>Annals of Work Exposures and Health</i> . 61: 854-871.	Marquart et al. (2017)	High
20	Baldwin, P. E., and A. D. Maynard. 1998. A Survey of Wind Speeds in Indoor Workplaces. <i>The Annals of Occupational Hygiene</i> , 42(5), 303-313.	Baldwin and Maynard (1998)	High

^a This is a crosswalk of codes. Does not provide data. Does not need to be evaluated.

^b This is a history and introduction of the U.S. Census Bureau's SIPP program. Does not provide data. Does not need to be evaluated.

G.2 Equations for Calculating Acute and Chronic Inhalation Exposures

This report assessed 1,4-dioxane exposures to workers in occupational settings, presented as 8-hour time weighted average (TWA). The 8-hour TWA exposures were used to calculate acute exposure, average daily concentration (ADC) for chronic, non-cancer risks, and lifetime average daily concentration (LADC) for chronic, cancer risks.

Acute workplace exposures were assumed to be equal to the contaminant concentration in air (8-hour TWA), per Equation G-1.

Equation G-1

$$AEC = \frac{C \times ED}{AT_{acute}}$$

Where:

- AEC** = acute exposure concentration
- C** = contaminant concentration in air (8-hour TWA)
- ED** = exposure duration (8 hour/day)
- AT_{acute}** = acute averaging time (8 hour/day)

ADC and LADC were used to estimate workplace chronic exposures for non-cancer and cancer risks, respectively. These exposures were estimated as follows:

Equation G-2

$$ADC \text{ or } LADC = \frac{C \times ED \times EF \times WY}{AT \text{ or } AT_c}$$

Where:

- ADC** = average daily concentration (8-hour TWA) used for chronic non-cancer risk calculations
- LADC** = lifetime average daily concentration (8-hour TWA) used for chronic cancer risk calculations
- C** = contaminant concentration in air (8-hour TWA)
- ED** = exposure duration (8 hour/day)
- EF** = exposure frequency (250 days/year, except where noted)
- WY** = exposed working years per lifetime (50th percentile = 31; 95th percentile = 40)
- AT** = averaging time, non-cancer risks (WY × 260 days/yr × 8 hour/day)
- AT_c** = averaging time, cancer risks (LT × 260 days/year × 8 hour/day; where LT = 78 years)

Exposure Duration (ED)

EPA used an exposure duration of 8 hours per day for averaging full-shift exposures.

Exposure Frequency (EF)

Exposure frequency (EF) is expressed as the number of days per year a worker is exposed to the chemical being assessed. In some cases, it could be reasonable to assume a worker is exposed to the chemical on each working day. In other cases, it could be more appropriate to estimate a worker's exposure to the chemical occurs during a subset of the worker's annual working days. The relationship between exposure frequency and annual working days could be described as follows:

Equation G-3

$$EF = f \times AWD$$

Where:

EF = exposure frequency, the number of days per year a worker is exposed to the chemical (day/yr)

f = fractional number of annual working days during which a worker is exposed to the chemical (dimensionless)

AWD = annual working days, the number of days per year a worker works (day/yr)

BLS [2015](#)) provides data on the total number of hours worked and total number of employees by each industry NAICS code²⁰. These data are available from the 3- to 6-digit NAICS level. Dividing the total, annual hours worked by the number of employees yields the average number of hours worked per employee per year for each NAICS.

EPA has identified approximately 140 NAICS codes applicable to the multiple conditions of use for the ten chemicals currently undergoing risk evaluation. For each NAICS code of interest, EPA looked up the average hours worked per employee per year at the more specific NAICS code hierarchy (*i.e.*, 4-digit, 5-digit, or 6-digit). EPA converted the working hours per employee to working days per year per employee assuming employees work an average of eight hours per day. The average number of days per year worked, or AWD, ranged from 169 to 282 days per year, with a 50th percentile value of 250 days per year. EPA repeated this analysis for all NAICS codes at the 4-digit level. The average AWD for all 4-digit NAICS codes ranges from 111 to 282 days per year, with a 50th percentile value of 228 days per year. Two hundred fifty days per year is approximately the 75th percentile.

In the absence of industry-specific data, EPA assumed that the fractional number of annual working days during which a worker is exposed to the 1,4-dioxane (f) is equal to one for all conditions of use.

EPA used an exposure frequency of 250 days per year for all exposure scenarios in this assessment with the exception of the import and re-packaging scenario. EPA estimated 1 to 18 sites could import and re-package 1,4-dioxane (see Section 2.4.1.1.2 for additional details).

²⁰ NAICS is a 2- through 6-digit hierarchical classification system, offering five levels of detail. Each digit in the code is part of a series of progressively narrower categories, and the more digits in the code signify greater classification detail. The first two digits designate the economic sector, the third digit designates the subsector, the fourth digit designates the industry group, the fifth digit designates the NAICS industry, and the sixth digit designates the national industry.

These sites could receive the chemical in totes and may re-package it in bottles or drums. For central tendency exposures, EPA assumed 18 sites and that each site repackaged into either bottles or drums. Based on standard loading and unloading rates, EPA used an exposure frequency of 2 days for sites that repackaged into bottles and 3 days for sites that repackaged into drums to calculate ADC and LADC. For high-end exposures, EPA assumed 1 site re-packaged into both bottles and drums. EPA used a weighted exposure frequency the account for 32 days for re-packaging into bottles and 58 days for re-packaging into drums to calculate ADC and LADC.

Working Years (WY)

Table G-3 lists the various worker exposure durations considered/recommended for risk and exposure assessments. The variations in worker exposure duration could be caused by various factors including issues of individual risk, population risk, type and nature of exposure, duration of time at a single location, activity patterns, and other factors. A more realistic portrayal of the reasonable length of exposure that would occur at the location(s) of maximal impact requires consideration of newer data and assessment of more realistic exposure scenario.

Table G-3. Representative Worker Exposure Durations Considered for Risk Assessments

Worker Exposure Duration (years)	Remarks	Reference
45	OSHA performed critical analysis and addressed comments of American Chemistry Council (ACC), Chamber of Commerce, and others.	Federal Register, 2016
40	Based on threshold of toxicological concern classification to Cramer classes that requires detailed knowledge about structural chemical classes. Protective for a worker population, which consists typically of people who are healthy and within certain age limits.	ECETOC (2006)
30	-	Mallongi et al. (2018; NRC (1994))
25 – 30	-	Baclocchi et al. (2010)
25	Supplemental guidance to provide a standard set of default values that were intended to be used for calculating reasonable maximum exposure levels for use in exposure assessments when site-specific data are lacking. Exposure assessments were based on recommendations in <i>Exposure Factors Handbook U.S. EPA (2011a)</i> .	U.S. EPA (2014f, 1991)
25	Offsite worker based on point estimate and stochastic risks. Risk assessments were conducted	OEHHA (2012)

	for different durations of exposure based on estimates of how long people live at a single location (9 years for the average, 30 years for a high-end estimate, and 70 years for a lifetime).	
20	Monte Carlo Analysis	Washburn et al. (1998)

EPA utilized a triangular distribution for exposed working years per lifetime (also could be referred as worker exposure duration) values considering the recent information available at the Current Population Survey (CPS) from the Bureau of Labor Statistics (BLS), Survey of Income and Program Participation (SIPP) and relevant resources from U.S. Census Bureau (Census). The key parameters of the triangular distribution are following:

Minimum value: BLS CPS tenure data with current employer as a low-end estimate of the number of lifetime working years: 10.4 years;

Mode value: The 50th percentile tenure data with all employers from SIPP as a mode value for the number of lifetime working years: 36 years; and

Maximum value: The maximum average tenure data with all employers from SIPP as a high-end estimate on the number of lifetime working years: 44 years.

This triangular distribution revealed a 50th percentile value of 31 years and a 95th percentile value of 40 years. These values were used for central tendency and high-end ADC and LADC calculations, respectively (see Appendix G.4 on Modeling Approach and Parameters for High-end and Central Tendency Inhalation Exposure Estimates).

The BLS [2014](#)) provided information on employee tenure with *current employer* obtained from the CPS. The CPS is a monthly sample survey of about 60,000 households that provides information on the labor force status of the civilian non-institutional population age 16 and over; CPS data are released every two years. The data are available by demographics and by generic industry sectors but are not available by NAICS codes.

The U.S. Census' [2016a](#)) SIPP provided information on *lifetime tenure with all employers*. SIPP is a household survey that collects data on income, labor force participation, social program participation and eligibility, and general demographic characteristics through a continuous series of national panel surveys of between 14,000 and 52,000 households [U.S. Census Bureau \(2016b\)](#). EPA analyzed the 2008 SIPP Panel Wave²¹ 1, a panel that began in 2008 and covers the interview months of September 2008 through December 2008 [U.S. Census Bureau \(2016a, b\)](#). For this panel, lifetime tenure data are available by Census Industry Codes, which could be cross-walked with NAICS codes.

²¹ SIPP is administered in panels and conducted in waves. Within a SIPP panel, the entire sample is interviewed over a 4-year period which includes a group of annual interviews conducted during a 4-month period. These groups of interviews are called waves. The first time an interviewer contacts a household is Wave 1; the second time is Wave 2, and so forth.

SIPP data included fields for the industry in which each surveyed, size and characteristics of this population, work patterns, worker age, and years of work experience *with all employers* over the surveyed individual’s lifetime.²² Census household surveys used different industry codes than the NAICS codes used in its firm surveys, so these were converted to NAICS using a published crosswalk [U.S. Census Bureau \(2012\)](#). EPA calculated the average tenure for the following age groups: 1) workers age 50 and older; 2) workers age 60 and older; and 3) workers of all ages employed at time of survey. EPA used tenure data for age group “50 and older” to determine the high-end lifetime working years, because the sample size in this age group is often substantially higher than the sample size for age group “60 and older”. For some industries, the number of workers surveyed, or the *sample size*, was too small to provide a reliable representation of the worker tenure in that industry. The data with sample size of less than five were excluded from this analysis.

Table G-4 summarized the average tenure for workers age 50 and older from SIPP data. Although the tenure could differ for any given industry sector, no significant variability was observed between the 50th and 95th percentile values of average tenure across manufacturing and non-manufacturing sectors.

Table G-4. Overview of Average Worker Tenure from U.S. Census SIPP (Age Group 50+)

Industry Sectors	Working Years			
	Average	50 th Percentile	95 th Percentile	Maximum
All industry sectors relevant to the 10 chemicals undergoing risk evaluation	35.9	36	39	44
Manufacturing sectors (NAICS 31-33)	35.7	36	39	40
Non-manufacturing sectors (NAICS 42-81)	36.1	36	39	44

Source: [U.S. Census Bureau \(2016a\)](#)

Note: Industries where sample size is less than five are excluded from this analysis.

BLS CPS data provided the median years of tenure that wage and salary workers had been with their current employer. Table G-5 presented CPS data for all demographics (men and women) by age group from 2008 to 2012. To estimate the low-end value on number of working years, EPA used the available recent [U.S. EPA \(2014e\)](#) CPS data for workers age 55 to 64 years, which indicated a median tenure of 10.4 years with their current employer. The use of this low-end value represented a scenario where workers were only exposed to the chemical of interest for a portion of their lifetime working years, as they could change job(s) or move from one industry to another throughout their career.

²² The number of years of work experience was calculated considering the difference between the year first worked and the current data year (*i.e.*, 2008). Any intervening months, when not working, were subtracted thereafter.

Table G-5. Median Years of Tenure with Current Employer by Age Group

Age	January 2008	January 2010	January 2012	January 2014
16 years and over (<25)	4.1	4.4	4.6	4.6
16 to 17 years	0.7	0.7	0.7	0.7
18 to 19 years	0.8	1.0	0.8	0.8
20 to 24 years	1.3	1.5	1.3	1.3
25 years and over (<65)	5.1	5.2	5.4	5.5
25 to 34 years	2.7	3.1	3.2	3.0
35 to 44 years	4.9	5.1	5.3	5.2
45 to 54 years	7.6	7.8	7.8	7.9
55 to 64 years	9.9	10.0	10.3	10.4
65 years and over	10.2	9.9	10.3	10.3

Source: [BLS \(2014\)](#)

G.3 Sample Calculations for Calculating Acute and Chronic Inhalation Exposures

Sample calculations for high-end and central tendency acute and chronic exposure concentrations for one setting, Industrial Uses, are demonstrated below. The explanation of the equations and parameters used is provided in Appendix G.2. The final values will have two significant figures since they are based on values from modeling.

G.3.1 Example High-End ADC and LADC

Calculate AEC_{HE} :

$$AEC_{HE} = \frac{C_{HE} \times ED}{AT_{acute}}$$

$$AEC_{HE} = \frac{20 \frac{mg}{m^3} \times 8 \frac{hr}{day}}{8 \frac{hr}{day}}$$

$$AEC_{HE} = 20 \frac{mg}{m^3}$$

Calculate ADC_{HE} :

$$ADC_{HE} = \frac{C_{HE} \times ED \times EF \times EWY}{AT}$$

$$ADC_{HE} = \frac{20 \frac{mg}{m^3} \times 8 \frac{hr}{day} \times 250 \frac{days}{year} \times 40 \text{ years}}{\left(40 \text{ years} \times 260 \frac{days}{year} \times 8 \frac{hours}{day}\right)} = 19 \frac{mg}{m^3}$$

Calculate LADC_{HE}:

$$LADC_{HE} = \frac{C_{HE} \times ED \times EF \times EWY}{AT_{LADC}}$$

$$LADC_{HE} = \frac{20 \frac{mg}{m^3} \times 8 \frac{hr}{day} \times 250 \frac{days}{year} \times 40 \text{ years}}{\left(78 \text{ years} \times 260 \frac{days}{year} \times 8 \frac{hours}{day}\right)} = 9.9 \frac{mg}{m^3}$$

G.3.2 Example Central Tendency ADC and LADC

Calculate AEC_{CT}:

$$AEC_{CT} = \frac{C_{CT} \times ED}{AT_{acute}}$$

$$AEC_{CT} = \frac{5 \frac{mg}{m^3} \times 8 \frac{hr}{day}}{8 \frac{hr}{day}}$$

$$AEC_{CT} = 5 \frac{mg}{m^3}$$

Calculate ADC_{CT}:

$$ADC_{CT} = \frac{C_{CT} \times ED \times EF \times EWY}{AT_{ADC}}$$

$$ADC_{CT} = \frac{5 \frac{mg}{m^3} \times 8 \frac{hr}{day} \times 250 \frac{days}{year} \times 31 \text{ years}}{\left(31 \text{ years} \times 260 \frac{days}{year} \times 8 \frac{hours}{day}\right)} = 4.8 \frac{mg}{m^3}$$

Calculate LADC_{CT}:

$$LADC_{CT} = \frac{C_{CT} \times ED \times EF \times EWY}{AT_{LADC}}$$

$$LADC_{CT} = \frac{5 \frac{mg}{m^3} \times 8 \frac{hr}{day} \times 250 \frac{days}{year} \times 31 \text{ years}}{\left(78 \text{ years} \times 260 \frac{days}{year} \times 8 \frac{hours}{day}\right)} = 1.9 \frac{mg}{m^3}$$

G.4 Modeling Approach and Parameters for High-End and Central Tendency Inhalation Exposure Estimates for Import and Repackaging, Functional Fluids (Open System), Spray Foam Application, and Disposal

This appendix presents the approach for high-end and typical inhalation exposure estimation. This approach is based on the application of established *EPA AP-42 Loading Model*, *EPA Mass Balance Model* (Fehrenbacher, M.C.), and Monte Carlo simulation.

This approach is intended to assess air releases and associated inhalation exposures associated with interior container loading scenarios at industrial and commercial facilities. Inhalation exposure to chemical vapor is a function of physical properties of substance, various EPA default constants, and other model parameters. While physical properties are fixed for a substance, some model parameters, such as ventilation rate (Q), mixing factor (k) and vapor saturation factor (f), are expected to vary from one facility to another. This approach addresses variability for these parameters using a Monte Carlo simulation.

An individual model input parameter could either have a discrete value or a distribution of values. EPA assigned statistical distributions based on available literature data or engineering judgment to address the variability in Q, k, f, and exposed working years per lifetime (WY). A Monte Carlo simulation (a type of stochastic simulation) was conducted to capture variability in the model input parameters. The simulation was conducted using the Latin hypercube sampling, a statistical method for generating a near-random sample of parameter values from a multidimensional distribution, in @RISK Industrial Edition, Version 7.0.0 (Palisade, Ithaca, New York). The Latin hypercube sampling method is a statistical method for generating a sample of possible values from a multi-dimensional distribution forces the samples drawn to correspond more closely with the input distribution and thus converges faster on the true statistics of the input distribution. Latin hypercube sampling is a stratified method, meaning it guarantees that its generated samples are representative of the probability density function (variability) defined in the model. EPA performed 100,000 iterations of the model to capture the range of possible input values (*i.e.*, including values with low probability of occurrence).

From the distribution resulted from the Monte Carlo simulation, the 95th and 50th percentile values are selected to represent a high-end exposure, and central tendency exposure level respectively. The statistics were calculated directly in @RISK. The following subsections detail the model design equations and parameters used for Inhalation exposure estimates.

G.4.1 Model Design Equations

The *EPA Mass Balance Model* includes the following equations for estimating mass concentration of the chemical vapor in air (mg/m³):

Equation G-4

$$C_m = C_v \times \frac{MW}{V_m}$$

Where

- C_m = mass concentration of chemical vapor in air [mg/m³]
 C_v = volumetric concentration of chemical vapor in air [ppm]
 MW = molecular weight of chemical [g/mol]
 V_m = molar volume [L/mol]

Equation G-5

$$C_v = \frac{170,000 \times T \times G}{MW \times Q \times k}$$

- T = temperature [K]
 G = average vapor generation rate [gm/sec]
 MW = molecular weight of chemical [g/mol]
 Q = ventilation rate [ft³/min]
 k = mixing factor [Dimensionless]

Average vapor generation rate needed for *EPA Mass Balance Model*, is calculated from following *EPA AP-42 Loading Model*:

Equation G-6

$$G = \frac{f \times MW \times (3,785.4 \times V_c) \times r \times X \times \left(\frac{VP}{760}\right)}{3,600 \times T \times R}$$

- G = average vapor generation rate [gm/sec]
 f = saturation factor [Dimensionless]
 MW = molecular weight of chemical [g/mol]
 V_c = container volume [gallon]
 r = container loading/unloading rate [number of containers/hr]
 X = vapor pressure correction factor [Dimensionless], assumed to be equal to weight fraction of component
 VP = vapor pressure (at temperature, T) [mm Hg]
 T = temperature [K]
 R = universal gas constant [atm-cm³/mol-K]

Mass concentration of the chemical vapor in air calculated from Equation G-4, subsequently used in following equations to estimate acute exposure concentration (AEC), average daily concentration (8-hour TWA) used for chronic non-cancer risk calculations (ADC) and lifetime average daily concentration (8-hour TWA) used for chronic cancer risk calculations (LADC):

Equation G-7

$$AEC = \frac{C \times ED}{AT_{acute}}$$

Where:

- AEC** = acute exposure concentration [mg/m³]
- C** = contaminant concentration in air (8-hour TWA) [mg/m³]
- ED** = exposure duration [hr/day]
- AT_{acute}** = acute averaging time [hr/day]

ADC and LADC are used to estimate workplace chronic exposures for non-cancer and cancer risks, respectively. These exposures are estimated as follows:

Equation G-8

$$ADC \text{ or } LADC = \frac{C \times ED \times EF \times WY}{AT \text{ or } AT_c}$$

Where:

- ADC** = average daily concentration (8-hour TWA) used for chronic non-cancer risk calculations [mg/m³]
- LADC** = lifetime average daily concentration (8-hour TWA) used for chronic cancer risk calculations [mg/m³]
- C** = contaminant concentration in air (8-hour TWA) [mg/m³]
- ED** = exposure duration [hour/day]
- EF** = exposure frequency [days/yr]
- WY** = exposed working years per lifetime [yr/LT]
- AT** = averaging time, non-cancer risks [hr]
- AT_c** = averaging time, cancer risks [hr]

Equation G-9

$$AT = WY \times 260 \left[\frac{d}{yr} \right] \times 8 \left[\frac{hr}{day} \right]$$

- AT** = averaging time, non-cancer risks [hr]
- WY** = exposed working years per lifetime [yr/LT]

Equation G-10

$$AT_c = LT \times 260 \left[\frac{d}{yr} \right] \times 8 \left[\frac{hr}{day} \right]$$

- AT_c** = averaging time, cancer risks [hr]
- LT** = lifetime = 78 [yr]

Refer to Appendix G.2 for equations used to calculate acute and chronic inhalation exposures, details about Equation G-8 and Equation G-9, and the basis for various parameters used in the calculations.

G.4.2 Model Parameters

Table G-6 summarizes the model parameters and their values for the Monte Carlo simulation. High-end and typical exposure are estimated by selecting the 50th and 95th percentile values from the output distribution.

Table G-6. Summary of Parameter Values and Distributions Used in the Inhalation Exposure Model

Input Parameter	Symbol	Unit	Constant Model Parameter Values		Variable Model Parameter Values				Rational / Basis
			Value	Basis	Lower Bound	Upper Bound	Mode	Distribution Type	
Molecular Weight	<i>MW</i>	g/mol	88.1	—	—	—	—	—	Physical Property
Vapor Pressure	<i>VP</i>	mm Hg		—	30	40	—	—	Physical Property. The vapor pressure of 1,4-dioxane was needed at 293K (30 mmHg) and at 298K (40 mmHg).
Molar Volume at 298 K	<i>V_m</i>	L/mol	24.45	—	—	—	—	—	Physical Constant
Gas Constant	<i>R</i>	atm-cm ³ /mol-K	82.05	—	—	—	—	—	
Temperature	<i>T</i>	K	298	—	—	—	—	—	Process Parameter
Container Volume	<i>V_c</i>	gallons	1 or 55	—	—	—	—	—	Value is determined by the selected container type for given exposure scenario
Container Loading/Unloading Rate	<i>r</i>	Containers / hr	20 or 60	—	—	—	—	—	Value is determined by the selected container type
Ventilation Rate ²³	<i>Q</i>	ft ³ /min	—	—	500	10000	3000	Triangular	1. General ventilation rates in industry ranges from a low of 500 ft ³ /min to over 10,000 ft ³ /min; a typical value is 3,000. 2. Mixing Factor ranges from 0.1 to 1. 3. Saturation factor ranges from 0.5 for submerged loading to 1.45 for splash loading.
Mixing Factor	<i>k</i>	Dimensionless	—	—	0.1	1	0.5	Triangular	
Saturation Factor	<i>f</i>	Dimensionless	—	—	0.5	1.45	0.5	Triangular	Underlying distribution of these parameters are not known, EPA assigned triangular distributions, since triangular distribution requires least assumptions and is completely defined by range and mode of a parameter.

²³ Ventilation rate procedure is a prescriptive design procedure in which air rates are dependent on space type, occupancy, and floor area. Airflow for ventilation could be calculated by various methods including area method, air change method, occupancy method, and heat removal method.

Input Parameter	Symbol	Unit	Constant Model Parameter Values		Variable Model Parameter Values				Rational / Basis
			Value	Basis	Lower Bound	Upper Bound	Mode	Distribution Type	
									(ASHRAE, 2016 ; ACGIH, 2019)
Vapor Pressure Correction Factor	<i>X</i>	Dimensionless	1	—	—	—	—	—	For Import & Repackaging and Disposal
Vapor Pressure Correction Factor	<i>X</i>	Dimensionless	0.001	—	—	—	—	—	For Functional Fluids (open System) and Spray Foam Application
Exposed Working Years per Lifetime	<i>WY</i>	years	—	—	10	44	31	Triangular	See Appendix G.2 of this Report
Contaminant concentration in air (8-hour TWA)	<i>C</i>	mg/m ³	—	—	—	—	—	Calculated	Refer Appendix G.2 for “Equations for Calculating Acute and Chronic Inhalation Exposures”
Exposure Duration	<i>ED</i>	hr/day	8	—	—	—	—	—	
Acute averaging Time	<i>AT_{acute}</i>	hr/day	8	—	—	—	—	—	
Averaging Time, non-cancer risks	<i>AT</i>	hr	—	—	—	—	—	Calculated	
Averaging Time, cancer risks	<i>AT_c</i>	hr	—	—	—	—	—	Calculated	
Exposure Frequency	<i>EF</i>	days/yr	250	—			—	—	

—: Not Applicable

G.4.3 Sample Monte Carlo Simulation Result

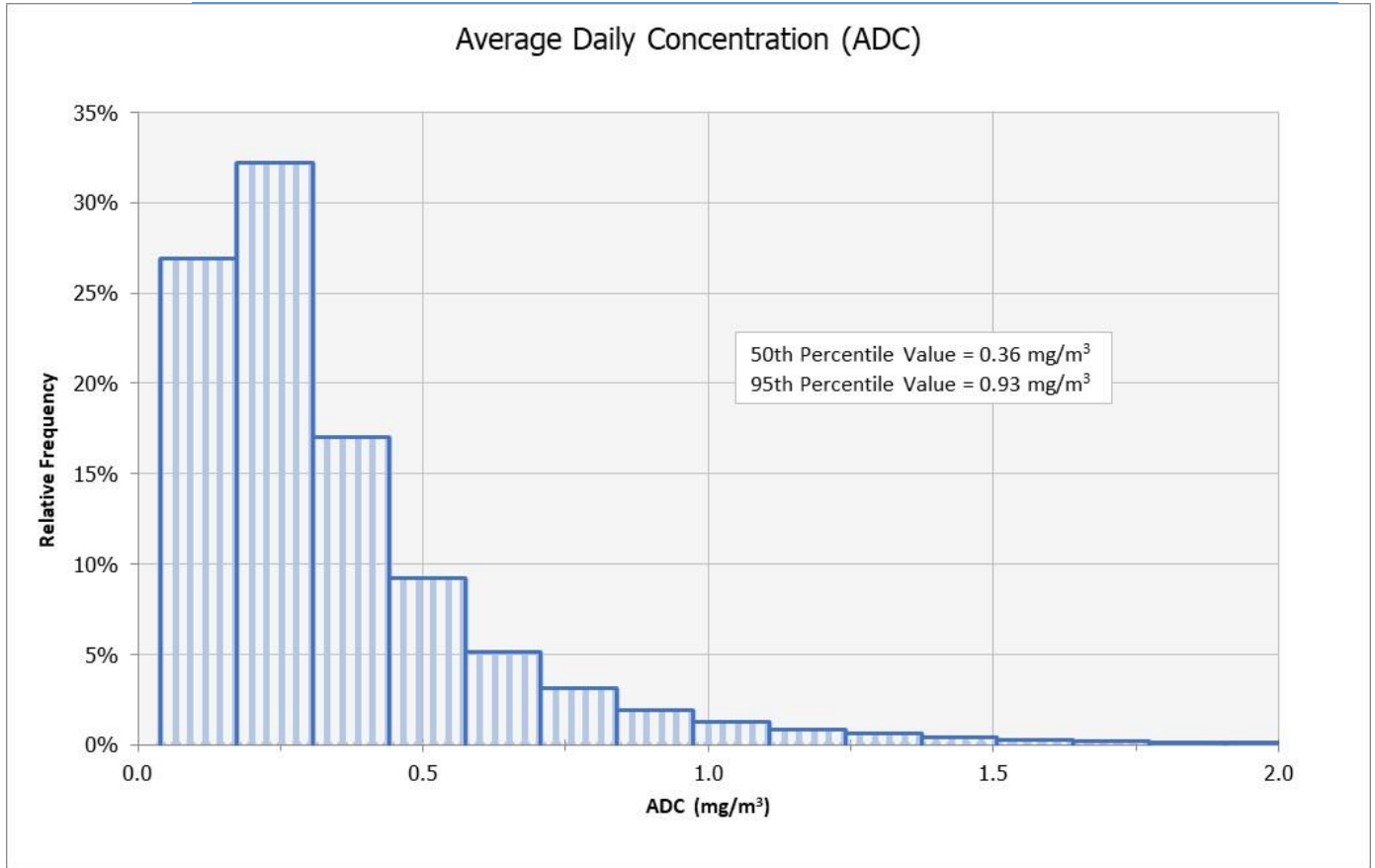


Figure G-1. Example of Monte Carlo Simulation results for the Disposal Scenario

G.5 Approach for Estimating the Number of Workers

This appendix summarizes the methods that EPA used to estimate the number of workers who are potentially exposed to 1,4-dioxane in each of its conditions of use. The method consists of the following steps:

Identify the North American Industry Classification System (NAICS) codes for the industry sectors associated with each condition of use.

Estimate total employment by industry/occupation combination using the Bureau of Labor Statistics' Occupational Employment Statistics (OES) data [BLS \(2016\)](#).

Refine the OES estimates where they are not sufficiently granular by using the U.S. Census' [2016b](#)) Statistics of U.S. Businesses (SUSB) data on total employment by 6-digit NAICS.

Estimate the percentage of employees likely to be using 1,4-dioxane instead of other chemicals (*i.e.*, the market penetration of 1,4-dioxane in the condition of use).

Estimate the number of sites and number of potentially exposed employees per site.

Estimate the number of potentially exposed employees within the condition of use.

Step 1: Identifying Affected NAICS Codes

As a first step, EPA identified NAICS industry codes associated with each condition of use. EPA generally identified NAICS industry codes for a condition of use by:

Querying the [U.S. Census Bureau's NAICS Search tool](#) using keywords associated with each condition of use to identify NAICS codes with descriptions that match the condition of use.

Referencing EPA Generic Scenarios (GS's) and Organisation for Economic Co-operation and Development (OECD) Emission Scenario Documents (ESDs) for a condition of use to identify NAICS codes cited by the GS or ESD.

Reviewing Chemical Data Reporting (CDR) data for the chemical, identifying the industrial sector codes reported for downstream industrial uses, and matching those industrial sector codes to NAICS codes using Table D-2 provided in the [CDR reporting instructions](#).

Each condition of use section in the main body of this report identifies the NAICS codes EPA identified for the respective condition of use.

Step 2: Estimating Total Employment by Industry and Occupation

BLS's [2016](#)) OES data provide employment data for workers in specific industries and occupations. The industries are classified by NAICS codes (identified previously), and occupations are classified by Standard Occupational Classification (SOC) codes.

Among the relevant NAICS codes (identified previously), EPA reviewed the occupation description and identified those occupations (SOC codes) where workers are potentially exposed to 1,4-dioxane. Table G-7 shows the SOC codes EPA classified as occupations potentially exposed to 1,4-dioxane. These occupations are classified into workers (W) and occupational non-users (O). All other SOC codes are assumed to represent occupations where exposure is unlikely.

Table G-7. SOC with Worker and ONU Designations for All Conditions of Use Except Dry Cleaning

SOC	Occupation	Designation
11-9020	Construction Managers	O
17-2000	Engineers	O
17-3000	Drafters, Engineering Technicians, and Mapping Technicians	O
19-2031	Chemists	O
19-4000	Life, Physical, and Social Science Technicians	O
47-1000	Supervisors of Construction and Extraction Workers	O
47-2000	Construction Trades Workers	W
49-1000	Supervisors of Installation, Maintenance, and Repair Workers	O
49-2000	Electrical and Electronic Equipment Mechanics, Installers, and Repairers	W
49-3000	Vehicle and Mobile Equipment Mechanics, Installers, and Repairers	W
49-9010	Control and Valve Installers and Repairers	W
49-9020	Heating, Air Conditioning, and Refrigeration Mechanics and Installers	W
49-9040	Industrial Machinery Installation, Repair, and Maintenance Workers	W
49-9060	Precision Instrument and Equipment Repairers	W

49-9070	Maintenance and Repair Workers, General	W
49-9090	Miscellaneous Installation, Maintenance, and Repair Workers	W
51-1000	Supervisors of Production Workers	O
51-2000	Assemblers and Fabricators	W
51-4020	Forming Machine Setters, Operators, and Tenders, Metal and Plastic	W
51-6010	Laundry and Dry-Cleaning Workers	W
51-6020	Pressers, Textile, Garment, and Related Materials	W
51-6030	Sewing Machine Operators	O
51-6040	Shoe and Leather Workers	O
51-6050	Tailors, Dressmakers, and Sewers	O
51-6090	Miscellaneous Textile, Apparel, and Furnishings Workers	O
51-8020	Stationary Engineers and Boiler Operators	W
51-8090	Miscellaneous Plant and System Operators	W
51-9000	Other Production Occupations	W

W = worker designation

O = ONU designation

For dry cleaning facilities, due to the unique nature of work expected at these facilities and that different workers may be expected to share among activities with higher exposure potential (e.g., unloading the dry-cleaning machine, pressing/finishing a dry-cleaned load), EPA made different SOC code worker and ONU assignments for this condition of use. Table G-8 summarizes the SOC codes with worker and ONU designations used for dry cleaning facilities.

Table G-8. SOCs with Worker and ONU Designations for Dry Cleaning Facilities

SOC	Occupation	Designation
41-2000	Retail Sales Workers	O
49-9040	Industrial Machinery Installation, Repair, and Maintenance Workers	W
49-9070	Maintenance and Repair Workers, General	W
49-9090	Miscellaneous Installation, Maintenance, and Repair Workers	W
51-6010	Laundry and Dry-Cleaning Workers	W
51-6020	Pressers, Textile, Garment, and Related Materials	W
51-6030	Sewing Machine Operators	O
51-6040	Shoe and Leather Workers	O
51-6050	Tailors, Dressmakers, and Sewers	O
51-6090	Miscellaneous Textile, Apparel, and Furnishings Workers	O

W = worker designation

O = ONU designation

After identifying relevant NAICS and SOC codes, EPA used BLS data to determine total employment by industry and by occupation based on the NAICS and SOC combinations. For example, there are 110,640 employees associated with 4-digit NAICS 8123 (*Drycleaning and Laundry Services*) and SOC 51-6010 (*Laundry and Dry-Cleaning Workers*).

Using a combination of NAICS and SOC codes to estimate total employment provides more accurate estimates for the number of workers than using NAICS codes alone. Using only NAICS codes to estimate number of workers typically result in an overestimate, because not all workers employed in that industry sector will be exposed. However, in some cases, BLS only provide

employment data at the 4-digit or 5-digit NAICS level; therefore, further refinement of this approach may be needed (see next step).

Step 3: Refining Employment Estimates to Account for lack of NAICS Granularity

The third step in EPA’s methodology was to further refine the employment estimates by using total employment data in the U.S. Census Bureau’s [2016b](#) SUSB. In some cases, BLS OES’s occupation-specific data are only available at the 4-digit or 5-digit NAICS level, whereas the SUSB data are available at the 6-digit level (but are not occupation-specific). Identifying specific 6-digit NAICS will ensure that only industries with potential 1,4-dioxane exposure are included. As an example, OES data are available for the 4-digit NAICS 8123 *Drycleaning and Laundry Services*, which includes the following 6-digit NAICS:

NAICS 812310 Coin-Operated Laundries and Drycleaners;

NAICS 812320 Drycleaning and Laundry Services (except Coin-Operated);

NAICS 812331 Linen Supply; and

NAICS 812332 Industrial Launderers.

In this example, only NAICS 812320 is of interest. The Census data allow EPA to calculate employment in the specific 6-digit NAICS of interest as a percentage of employment in the BLS 4-digit NAICS.

The 6-digit NAICS 812320 comprises 46% of total employment under the 4-digit NAICS 8123. This percentage can be multiplied by the occupation-specific employment estimates given in the BLS OES data to further refine our estimates of the number of employees with potential exposure.

Table G-9 illustrates this granularity adjustment for NAICS 812320.

Table G-9. Estimated Number of Potentially Exposed Workers and ONUs under NAICS 812320

NAICS	SOC CODE	SOC Description	Occupation Designation	Employment by SOC at 4-digit NAICS level	% of Total Employment	Estimated Employment by SOC at 6-digit NAICS level
8123	41-2000	Retail Sales Workers	O	44,500	46.0%	20,459

8123	49-9040	Industrial Machinery Installation, Repair, and Maintenance Workers	W	1,790	46.0%	823
8123	49-9070	Maintenance and Repair Workers, General	W	3,260	46.0%	1,499
8123	49-9090	Miscellaneous Installation, Maintenance, and Repair Workers	W	1,080	46.0%	497
8123	51-6010	Laundry and Dry-Cleaning Workers	W	110,640	46.0%	50,867
8123	51-6020	Pressers, Textile, Garment, and Related Materials	W	40,250	46.0%	18,505
8123	51-6030	Sewing Machine Operators	O	1,660	46.0%	763
8123	51-6040	Shoe and Leather Workers	O	Not Reported for this NAICS Code		
8123	51-6050	Tailors, Dressmakers, and Sewers	O	2,890	46.0%	1,329
8123	51-6090	Miscellaneous Textile, Apparel, and Furnishings Workers	O	0	46.0%	0
Total Potentially Exposed Employees				206,070		94,740
Total Workers						72,190
Total Occupational Non-Users						22,551

Note: numbers may not sum exactly due to rounding.

W = worker

O = occupational non-user

Source: [BLS \(2016\)](#); [U.S. Census Bureau \(2016b\)](#)

Step 4: Estimating the Percentage of Workers Using 1,4-Dioxane Instead of Other Chemicals

In the final step, EPA accounted for the market share by applying a factor to the number of workers determined in Step 3. This accounts for the fact that 1,4-dioxane may be only one of multiple chemicals used for the applications of interest. EPA was unable to identify market penetration data for any of the conditions of use. In the absence of market penetration data for a given condition of use, EPA assumed 1,4-dioxane may be used at up to all sites and by up to all workers calculated in this method as a bounding estimate. This assumes a market penetration of 100%. Market penetration is discussed for each condition of use in the main body of this report.

Step 5: Estimating the Number of Workers per Site

EPA calculated the number of workers and occupational non-users in each industry/occupation combination using the formula below (granularity adjustment is only applicable where SOC data are not available at the 6-digit NAICS level):

$$\text{Number of Workers or ONUs in NAICS/SOC (Step 2)} \times \text{Granularity Adjustment Percentage (Step 3)} = \text{Number of Workers or ONUs in the Industry/Occupation Combination}$$

EPA then estimated the total number of establishments by obtaining the number of establishments reported in the U.S. Census Bureau's SUSB [2016b](#)) data at the 6-digit NAICS level.

EPA then summed the number of workers and occupational non-users over all occupations within a NAICS code and divided these sums by the number of establishments in the NAICS code to calculate the average number of workers and occupational non-users per site.

Step 6: Estimating the Number of Workers and Sites for a Condition of Use

EPA estimated the number of workers and occupational non-users potentially exposed to 1,4-dioxane and the number of sites that use 1,4-dioxane in a given condition of use through the following steps:

Obtaining the total number of establishments by:

Obtaining the number of establishments from SUSB [2016b](#)) at the 6-digit NAICS level (Step 5) for each NAICS code in the condition of use and summing these values; or

Obtaining the number of establishments from the Toxics Release Inventory (TRI), Discharge Monitoring Report (DMR) data, National Emissions Inventory (NEI), or literature for the condition of use.

Estimating the number of establishments that use 1,4-dioxane by taking the total number of establishments from Step 6.A and multiplying it by the market penetration factor from Step 4.

Estimating the number of workers and occupational non-users potentially exposed to 1,4-dioxane by taking the number of establishments calculated in Step 6.B and multiplying it by the average number of workers and occupational non-users per site from Step 5.

G.6 Occupational Exposure Scenario Grouping

OES grouping corresponds to the defined use scenarios for the occupational exposure assessment.

Table G-10. Occupational Exposure Scenario Groupings

Life Cycle Stage	Category	Subcategory	OES Grouping	
Manufacture	Domestic Manufacture	Domestic Manufacture	Manufacturing	
Manufacture	Import	Import	Import and Repackaging	
		Repackaging		
Processing	Recycling	Recycling	Industrial Use	
Processing	Non-Incorporative	Pharmaceutical and medicine manufacturing (process solvent)		
		Basic organic chemical manufacturing (process solvent)		
	Processing as a reactant	Pharmaceutical intermediate		
		Polymerization catalyst		
Industrial Use	Intermediate Use	Agricultural chemical intermediate		
		Plasticizer intermediate		
		Catalysts and reagents for anhydrous acid reactions, brominations and sulfonations		
	Processing aids, not otherwise listed	Wood pulping ²⁴		
		Extraction of animal and vegetable oils ²⁰		
		Wetting and dispersing agent in textile processing ²⁰		
		Purification of pharmaceuticals		
		Etching of fluoropolymers		
	Industrial Use			Metalworking fluid

²⁴ These uses were evaluated but are likely not current uses of 1,4-dioxane.

	Functional Fluids, Open System	Cutting and Tapping Fluid Polyalkylene Glycol Fluid	Functional Fluids, Open System
Industrial Use	Functional Fluids, Closed System ^a	Hydraulic Fluid ^a	Functional Fluids, Closed System ^a
Industrial Use, Potential Commercial Use	Laboratory Chemicals	Chemical Reagent	Laboratory Chemicals
		Reference material	
		Spectroscopic and photometric measurement	
		Liquid scintillation counting medium	
		Stable Reaction medium	
		Cryoscopic solvent for molecular mass determinations	
		Preparation of histological sections for microscopic examination	
Industrial Use, Potential Commercial Use	Adhesives and Sealants	Film Cement	Film Cement
Industrial Use, Potential Commercial Use	Other Uses	Spray Polyurethane Foam	Spray Application
Industrial Use, Potential Commercial Use	Other Uses	Printing and Printing Compositions	Use of Printing Inks (3D)
Industrial Use, Potential Commercial Use	Other Uses	Dry Film Lubricant	Dry Film Lubricant
Disposal	Disposal	Wastewater	Disposal
		Underground Injection	
		Landfill	
		Recycling	
		Incineration	

^a EPA did not find evidence to support the intended use of 1,4-dioxane in closed-system functional fluids; therefore, occupational exposures and environmental releases were not assessed for this scenario. See Section 2.4.1.1.6.

G.6.1 Manufacturing

There are three methods to produce 1,4-dioxane, but it is typically manufactured for industrial purposes via an acid-catalyzed conversion of ethylene glycols in a closed system. The other two methods²⁵ are used to make substituted 1,4-dioxane and are not known to be used for industrial production [ECJRC \(2002\)](#).

A typical acid-catalyzed conversion of ethylene glycols process is carried out in a heated vessel at a temperature between 266 and 392 °F (130 and 200 °C) and a pressure between 0.25 and 1.1 atm (25 and 110 kPa) [ECJRC \(2002\)](#). At the BASF Facility in Zachary, Louisiana, 1,4-dioxane is produced using this method with diethylene glycol and concentrated sulfuric acid (Figure G-2). After synthesis, 1,4-dioxane is further purified in a multi-step process that includes multiple distillation and neutralization steps to remove water and volatile byproducts [BASF \(2017\)](#).

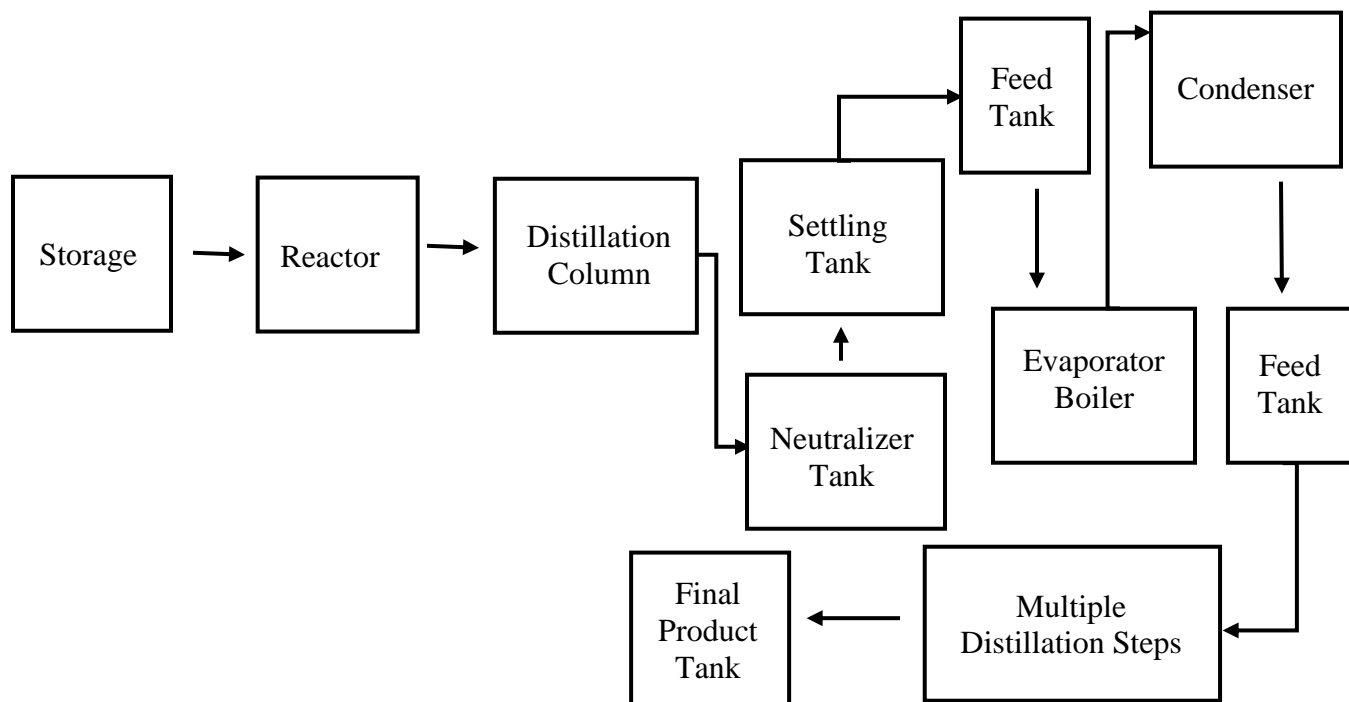


Figure G-2. Generic Manufacturing Process Flow Diagram

Source: Modeled after [BASF \(2017\)](#)

Number of Potentially Exposed Workers and Occupational Non-Users

The CDR [U.S. EPA \(2016c\)](#) reports two manufacturing sites, each reporting 50 to 100 workers. Based on data from the Bureau of Labor Statistics (BLS) for NAICS code 325199 (All Other Basic Organic Chemical Manufacturing and related SOC codes), there could be an average of 39 workers and 19 ONUs per site [U.S. EPA \(2016c\)](#). The BLS data indicated that there could be an

²⁵ Substituted 1,4-Dioxane can be prepared by ring closure of 2-chloro-2'-hydroxydiethyl ether through heating with 20% sodium hydroxide, and by catalyzed cyclo-dimerization of ethylene oxide either over NaHSO₄, SiF₄, or BF₃, or at an elevated temperature with an acidic cation-exchange resin.

average of 57 potentially exposed workers and ONUs per site, which is consistent with the range reported in CDR [2016c](#)). Using the BLS data, EPA estimated that 78 workers and 36 ONUs could be exposed over all sites that manufacture 1,4-dioxane in the U.S., 2018, BASF provided additional information regarding the manufacture of 1,4-dioxane. In this public comment, BASF indicated that the Zachary, Louisiana site would cease manufacturing of 1,4-dioxane by the end of 2018; and BASF might direct its customers to import the chemical from a BASF site in Germany. Though the public comment stated that BASF is the sole domestic producer of 1,4-dioxane, CDR [2016c](#)) lists a second domestic manufacturer; therefore, EPA assesses exposures from the two 1,4-dioxane manufacturing sites in the US [BASF \(2018a\)](#); [U.S. EPA \(2016c\)](#).

Worker and Occupational Non-User Activities

BASF provided limited monitoring data related to certain steps in the production process, such as neutralization and evaporator dumping. However, specific descriptions of these worker tasks were not provided [BASF \(2017\)](#). The European Union Risk Assessment Report [ECJRC \(2002\)](#) provided detailed description of the 1,4-Dioxane manufacturing processes at the sites in Europe. The report stated that the primary ways workers could be exposed are during drumming, maintenance, sampling, and from the system “breathing.” Dermal and inhalation exposures are expected during drumming from connecting and disconnecting the transfer line, and during any leakages [ECJRC \(2002\)](#).

ONUs include employees that work at the site where 1,4-dioxane is manufactured, but they do not directly handle the chemical and are therefore expected to have lower exposures. ONUs for manufacturing include supervisors, managers, and tradesmen that may be in the manufacturing area, but do not perform tasks that result in the same level of exposures as production workers.

Worker and Occupational Non-User Exposure Assessment

EPA used full-shift, personal breathing zone (PBZ) monitoring data provided by BASF to assess occupational inhalation exposures. These data ranged from 2006 to 2011 and covered the manufacturing facility under two different corporate ownerships, Ferro Corp and BASF. BASF also provided monitoring data in a public comment from 2017. The public comment states that these data are from “*periodic monitoring of employees performing tasks that could present exposure to Dioxane*” [BASF \(2017\)](#). EPA assumed that these monitoring data were originated via PBZ measurements. In addition, EPA reviewed European manufacturing monitoring data cited in the European Union Risk Assessment [ECJRC \(2002\)](#) for 1,4-dioxane ranging between 1976 to 1998. After the review, EPA chose monitoring data from the more recent time period in this risk evaluation that are representative of U.S. manufacturing over the older European data.

The production monitoring data of 1,4-dioxane from BASF plant at Zachary, Louisiana is summarized in Table G-11 [BASF \(2017\)](#). [BASF \(2016\)](#) provided additional monitoring data from multiple Industrial Hygiene Analyses (IHA) reports from 2008 to 2011. It also provided monitoring data from 2006 and 2007 from the previous owner of the manufacturing site (Ferro Corp), but did not provide job descriptions, exposure sources, or possible engineering controls used in relation to these data points to refine the exposure assessment [BASF \(2016\)](#). The data are summarized in Table G-12.

Table G-11 2017 1,4-Dioxane Production Monitoring Data [BASF \(2017\)](#)

Date Monitored	Process Task Monitored	Results		Sample Type
		ppm	mg/m ³ ^a	
2/24/2017	Neutralization step	0.39	1.4	15-min TWA
2/24/2017	Routine duties during production (including neutralization step)	<0.056	<0.20	8-hour TWA
2/28/2017	Evaporator dump step	38	137	15-min TWA
2/28/2017	Routine duties during production (including evaporator dump step)	0.23	0.828	8-hour TWA

^a Calculated using 3.6 (mg/m³)/ppm conversion factor [NIOSH \(2005\)](#)

Source: [BASF \(2017\)](#)

Table G-12. 2007-2011 1,4-Dioxane Production Monitoring Data [BASF \(2016\)](#)

Report	Mass of 1,4-dioxane (µg)	Sampling time (min)	Flow rate (cm ³ /min)	Total air volume sampled (L)	Raw air concentration (mg/m ³) ^a	Raw air concentration (ppm) ^a	Adjusted air concentration (mg/m ³) ^{a, f}
IHA 12/18/2008	13	487	34.5	16.8	0.77	0.21	0.85
	26	484	34.5	16.7	1.56	0.43	1.71
IHA 01/12/2010	<2	490	34.5	16.9	<0.12	<0.04	<0.13
	6	508	34.5	17.5	0.34	0.1	0.38
	6	397	34.5	13.7	0.44	0.12	0.48
	<2	487	34.5	16.8	<0.12	0.04	<0.13
	<2	471	34.5	16.2	<0.12	0.04	<0.14
IHA 05/14/2010	<2	480	34.5 ^c	-	<0.12 ^d	0.0335	<0.13
	7	480	34.5 ^c	-	0.42 ^d	0.117	0.46
	120	483	34.5 ^c	-	7.20 ^d	2.00	7.91
IHA 11/09/2010	<2	419	34.5 ^c	-	<0.14 ^d	<0.038	<0.15
	<2	445	34.5 ^c	-	<0.13 ^d	<0.036	<0.14
	<2	443	34.5 ^c	-	<0.13 ^d	<0.036	<0.14
	<2	450	34.5 ^c	-	<0.13 ^d	<0.036	<0.14
IHA 08/05/2011	21	493	34.5 ^c	-	1.23 ^d	0.342	1.36
	6	443	34.5 ^c	-	0.39 ^d	0.109	0.43
	<2	474	34.5 ^c	-	<0.12 ^d	<0.033	<0.13
Ferro summary (2006 – 2007)	-	480	-	-	0.25 ^e	0.07	0.28
	-	480	-	-	3.63 ^e	1.01	4.00
	-	480	-	-	0.36 ^e	0.1	0.40
	-	480	-	-	1.8 ^e	0.5	1.98

Report	Mass of 1,4-dioxane (µg)	Sampling time (min)	Flow rate (cm ³ /min)	Total air volume sampled (L)	Raw air concentration (mg/m ³) ^a	Raw air concentration (ppm) ^a	Adjusted air concentration (mg/m ³) ^{a, f}
	-	480	-	-	0.43 ^e	0.12	0.47
	-	480	-	-	0.9 ^e	0.25	0.99
	-	480	-	-	6.84 ^e	1.9	7.52
	-	480	-	-	24.1 ^e	6.7	26.5
	<2 ^{b, c}	480	34.5 ^c	-	<0.14 ^e	0.04 ^c	<0.16
	<2 ^{b, c}	480	34.5 ^c	-	<0.14 ^e	0.04 ^c	<0.16
	-	-	-	-	1.55	0.43	1.7

^a The duration corresponds to the sample time listed for this concentration.

^b Non-detect

^c Assumed values

^d EPA calculated raw air concentrations in mg/m³ by using sampling durations on the associated chain of custody sheets and assuming the same sampling rate (34.5 cc/min) given in the other two IHA reports.

^e Converted ppm results to units of mg/m³ by multiplying by 3.60 mg/m³ per ppm.

^f EPA divided the 28 raw TWA air concentrations by 0.91 (assuming the same desorption efficiency for all samples) to generate adjusted air concentrations in mg/m³.

The cells marked “-” are not available and/or not applicable.

Source: [BASF \(2016\)](#)

BASF provided data from 28 PBZ samples [BASF \(2016\)](#). Based on the provided sampling durations, EPA assumed that these samples were 8-hour TWAs. Of the 28 samples, the 11 samples dated 2006 and 2007 showed results only in units of ppm in a tabular summary from the previous owner of the manufacturing site (Ferro Corp). EPA converted these ppm results to units of mg/m³ by multiplying by 3.60 mg/m³ per ppm for 1,4-dioxane.

The two BASF Industrial Hygiene Analysis (IHA) reports dated 12/18/2008 and 1/12/2010 showed a total of 7 samples with mass units in µg, sampling rates of 34.5 cc/min, sampling durations in minutes (ranging from 6.5 to >8 hours) and calculated sample volumes in units of liters and TWA air concentrations in ppm.

The remaining 10 samples in the three IHA reports dated 05/14/2010, 11/09/2010 and 08/05/2011 were given as µg/sample mass results only without sampling rates, sample volumes, or other parameters or units. EPA calculated raw air concentrations in mg/m³ by using sampling durations on the associated chain of custody sheets and assuming the same sampling rate (34.5 cc/min) given in the two older IHA reports (dated 12/18/2008 and 1/12/2010).

The IHA report (dated 12/18/2008) indicates that the sampling results do not account for desorption efficiency, shown as 0.91. It appears that none of the reports make such a correction. EPA divided the 28 raw TWA air concentrations by 0.91 (assuming the same desorption efficiency for all samples) to generate adjusted air concentrations in mg/m³.

To assess occupational inhalation exposures, EPA assembled the BASF 8-hour TWA monitoring data from Table G-11 and the adjusted air concentration values from Table G-12 to a single sample set with 30 data points. EPA calculated the 95th percentile and 50th percentile of this data

set to assess the high-end and central tendency exposures, respectively. EPA estimated acute and chronic inhalation exposures using these values and the equations in Appendix G.2. The EU Risk Assessment [ECJRC \(2002\)](#) estimated that the central tendency inhalation exposure was 0.2 mg/m³ and a reasonable high-end exposure was 10 mg/m³ (full-shift) [ECJRC \(2002\)](#). These values were based on measured data and support the values that EPA calculated for this assessment. These values are summarized in Section 2.4.1.1.1.

BASF reported two 15-minute short-term exposures (refer Table G-11). EPA used the higher of these two values, 137 mg/m³ from the evaporator dump step, as a high-end short-term exposure value in this risk assessment. EPA did not use the other short-term exposure value (1.4 mg/m³) to estimate a central tendency, short-term exposure, since the statistical significance of this sample is unclear (*i.e.*, low end of range, median, etc.).

Although BASF stated that they would cease manufacturing 1,4-dioxane at their Zachary, Louisiana site by the end of 2018, EPA used the exposure monitoring data from this site as representative of 1,4-dioxane manufacturing across the U.S. manufacturing facilities.

G.6.2 Import and Repackaging

Commodity chemicals are typically imported into the United States in bulk via water, air, land, and intermodal shipments [Tomer and Kane \(2015\)](#). These shipments take the form of oceangoing chemical tankers, railcars, tank trucks, and intermodal tank containers. Chemicals shipped in bulk containers may be repackaged into smaller containers for resale, such as drums or bottles. Domestically manufactured commodity chemicals may be shipped within the United States in liquid cargo barges, railcars, tank trucks, tank containers, intermediate bulk containers (IBCs)/totes, and drums. Both imported, and domestically manufactured commodity chemicals may be repackaged by wholesalers for resale; for example, repackaging bulk packaging into drums or bottles. The exact shipping and packaging methods specific to 1,4-dioxane are not known, so for this risk evaluation, EPA assessed the repackaging of 1,4-dioxane from bulk packaging to drums and bottles at wholesale repackaging sites (see Figure G-3). The import and repackaging uses are grouped because repackaging is the only routine activity of an importer that would lead to an exposure.

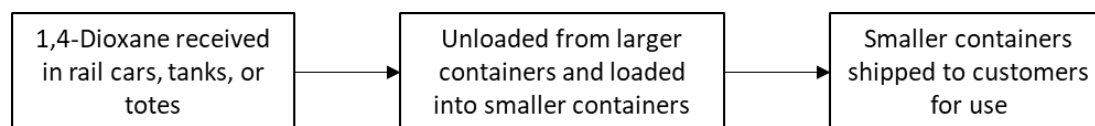


Figure G-3. General Process Flow Diagram for Import and Repackaging

During repackaging, workers could be exposed while connecting and disconnecting hoses and transfer lines to containers and packaging to be unloaded (*e.g.*, railcars, tank trucks, totes), intermediate storage vessels (*e.g.*, storage tanks, pressure vessels), and final packaging containers (*e.g.*, drums, bottles). Workers near loading racks and container filling stations are potentially exposed to fugitive emissions from equipment leaks and displaced vapor as containers are filled. These activities are potential sources of worker exposure through dermal contact with liquid and inhalation of vapors. In addition, ONUs may include employees that work at the site where 1,4-dioxane is repackaged, but they do not directly handle the chemical and are therefore expected to

have lower inhalation exposures and are not expected to have dermal exposures. ONUs for repackaging include supervisors, managers, and tradesmen that may be in the repackaging area but do not perform tasks that result in the same level of exposures as repackaging workers.

Number of Potentially Exposed Workers and Occupational Non-Users

Two companies reported selling a portion of their PV to Industry Sector (IS) code IS46 for wholesale and retail sale in the 2016 CDR. While one CDR submitter reported the industrial use type for the wholesale sites as “processing – repackaging”, the other reported “not known or reasonably ascertainable.” EPA assumes both sets of wholesale sites repackage their shipments of 1,4-dioxane. Each CDR submitter reported selling 1,4-dioxane to fewer than 10 wholesale sites with at least 50 but less than 100 workers potentially exposed. It is possible some portion of the wholesale sites indicated by the two CDR submitters may overlap; for example, both CDR submitters may sell to the same wholesaler. Two facilities in the 2018 TRI with NAICS Code 325199, all other basic organic chemical manufacturing, reported a TRI activity of repacking. A third facility did not report any TRI activities but had the same NAICS Code, and is assumed to repackage 1,4-dioxane as well. Therefore, EPA assesses an overall range of wholesale sites repackaging 1,4-dioxane of three to 18. Similarly, the range of reported potentially exposed workers is 50 to 198 [U.S. EPA \(2016c\)](#).

CDR IS code IS46 corresponds to NAICS codes for wholesale and retail trade and transportation and warehousing. EPA assumes NAICS Code 424690, other chemical and allied products merchant wholesalers, is the most relevant NAICS code for wholesalers who repackage and sell 1,4-dioxane. Using U.S. Census and BLS data, EPA estimates a total of 9,517 establishments, 27,214 workers, 10,359 ONUs, a ratio of 3:1 workers to ONUs for this NAICS code. Using the range of three to 18 sites, EPA calculates a range of nine to 51 workers and three to 20 ONUs over all sites (a total of 12 to 71 potentially exposed employees). This range is less than the estimated range reported to CDR of 50 to 198 potentially exposed employees. Therefore, EPA assesses the range of total potentially exposed employees of 50 to 198 and applies the ratio of 3:1 workers to ONUs to estimate a range of 38 to 149 workers and 12 to 49 ONUs.

Worker and Occupational Non-User Exposure Assessment

Exposure data for this scenario are not available. Therefore, EPA modeled inhalation exposures using the *EPA AP-42 Loading Model* and the *EPA Mass Balance Inhalation Model* and varied the saturation factor (f), ventilation rate (Q), mixing factor (k) using a Monte Carlo simulation. See Appendix G.4 for more information about the Monte Carlo simulation. These models use default parameter values and standard assumptions to develop estimates of inhalation exposures for container loading and unloading operations.

Table G-13 summarizes the 2016 CDR data reported for the PV of 1,4-dioxane sold to wholesalers and the container types assumed by EPA for the purposes of this risk evaluation [U.S. EPA \(2016c\)](#). EPA assumed Tedia and BASF both ship 1,4-dioxane to wholesalers using 550-gal totes. This assumption yields a similar order of magnitude of the number of shipping containers sent to wholesalers: approximately 32 totes for Tedia and approximately 58 totes for BASF. EPA assumes Tedia’s shipments are repackaged into 1-gal bottles since this volume is often sold for laboratory use. EPA assumes BASF’s shipments are repackaged into 55-gal drums as the market for this volume is unknown. Table G-14 estimates the number of each type of container per site.

Table G-13. 2016 CDR Data and Assumed Container Types for Repackaging

Company	PV (lb/yr)	% of PV Sold to Wholesalers and Repackaged	Assumed Initial Container Type and Volume ^b	Assumed Repackaged Container Type and Volume	Number of Repackaged Containers
Tedia	151,265	Up to 100% ^a	Totes (550 gal)	Bottles (1 gal)	17,598
BASF	908,710	30%	Totes (550 gal)	Drums (55 gal)	577

^a In the 2016 CDR, Tedia appears to report that up to 100% of its PV is shipped to each of its two end-use markets: shipped directly to pharmaceutical and medicine manufacturing and shipped to wholesalers for resale to laboratory use. Therefore, EPA assesses the entire PV (Manufacture + Imports) as the upper bound for repackaging for laboratory use.

^b Container types are not specified. These types are assumed based on PV and market.

Source: [U.S. EPA \(2016c\)](#)

Table G-14. Number of Totes and Containers per Site

Company	Number of Totes Unloaded per Site		Number of Repackaged Containers per Site	
	1 site	18 sites	1 site	18 sites
Tedia	32	2	17,598	978
BASF	58	3	577	32

To calculate central tendency and high-end exposures from repackaging 1,4-dioxane from totes to drums and small containers, EPA modeled full-shift and short-term exposures using the equations and parameters in Appendix G.2 and a Monte Carlo simulation. EPA assumed that workers may be exposed to vapors from the breathing of smaller containers as they are loaded; therefore, EPA assessed exposures for loading bottles and drums.

EPA assumed that one tote could be unloaded per day and the totes could be loaded directly into the bottles or drums; therefore, the rate of unloading would be equal to the rate at which the bottles or drums are loaded. Assuming default loading rates of 60 bottles per hour and 20 drums per hour, it would take an estimated 9.2 hours to unload one tote into 550 bottles and 0.5 hours to unload one tote into 10 drums. EPA assumed the bottles are loaded over the course of a full-shift. Using the Monte Carlo simulation, EPA estimated the central tendency and high-end exposures for unloading totes into bottles were 9.3 and 33 mg/m³, respectively. For repackaging into drums, EPA averaged the 30-minute exposure over an 8-hour shift, assuming the workers are exposed to 1,4-dioxane while repackaging and then not exposed for the rest of the shift. The central tendency and high-end 8-hour TWA exposures for unloading from totes into drums are 11 and 38 mg/m³, respectively. EPA also considered the 30-minute exposures of 170 and 610 mg/m³ to be central tendency and high-end short-term exposures.

Since different container types may be used, the number of sites may range from 1 to 18 sites, which also affects the number of days used to calculate acute and chronic inhalation exposures. To account for this, EPA used the equations in Appendix G.4 along with a Monte Carlo

simulation to vary the number of sites using a uniform distribution (*i.e.*, integers only). The results of these calculations are summarized in Section 2.4.1.1.2.

G.6.3 Industrial Uses

In the absence of available information, EPA assumes that industrial operations are similar in this category. For uses grouped in the Industrial Uses category, EPA expected that 1,4-dioxane is received as a solvent, intermediate, or catalyst in its final formulation and requires no further processing. The 1,4-dioxane is then unloaded and sent to intermediate storage or used immediately in the process. If used as an intermediate, 1,4-dioxane is likely consumed during the reaction. For solvents or catalysts, spent 1,4-dioxane would be collected at the end of the process for reuse, disposal, or recycling. Figure G-4 shows a basic process flow diagram for Industrial Use.

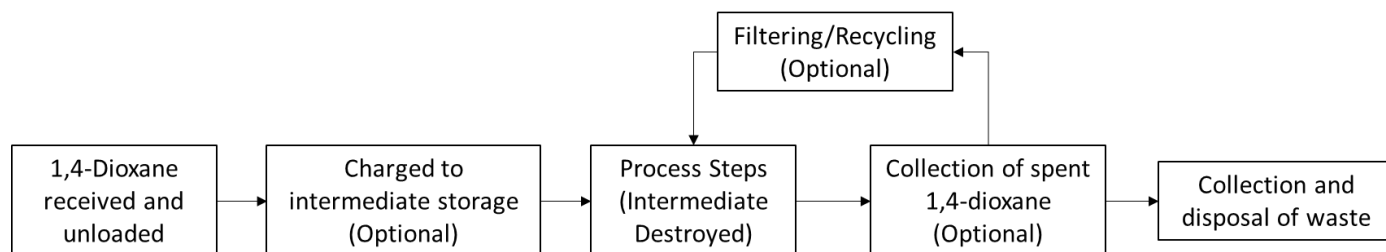


Figure G-4. Generic Industrial Use Process Flow Diagram

Specific process description information is available for some uses of 1,4-dioxane. For example, during wood pulping, 1,4-dioxane is used in an aqueous solution in organosolv pulping to extract lignin from chipped wood. The solution is usually mixed in a ratio of 96 parts 1,4-dioxane to four parts water (by volume). A ratio of 9:1, 1,4-dioxane to water, may also be used to increase lignin yield, but the product will also have a higher carbohydrate content. During this process, milled wood is mechanically stirred in an aqueous dioxane solution. The wood chip-dioxane suspension is centrifuged and the remaining solids are washed again in a fresh aqueous dioxane solution. The extract is dried to produce crude milled wood lignin [Obst and Kirk \(1988\)](#).

In pharmaceutical and medicine manufacturing, 1,4-dioxane is used as an intermediate, a process solvent, and a solvent for purification. Pharmaceutical processes vary across the industry, but nearly all process are batch operations. In general, pharmaceutical manufacture includes one or more chemical reactions, followed by product separation, purification, and drying [U.S. EPA \(1978\)](#).

Specific worker exposure scenarios in the US are unknown but could be similar to those described in the 2002 EU Risk Assessment for 1,4-Dioxane. Possible exposure scenarios described in this assessment in industrial processes that use 1,4-dioxane as a solvent include unloading 1,4-dioxane, sampling, maintenance activities, and drumming or loading spent 1,4-dioxane for disposal [ECJRC \(2002\)](#). These exposure activities are related to the process flow diagram shown in Figure G-4.

ONUs include employees that work at the site where 1,4-dioxane is used in an industrial setting as a solvent, chemical intermediate, or catalyst, but they do not directly handle the chemical and are therefore expected to have lower exposures. ONUs for industrial use include supervisors,

managers, and tradesmen that may be in the processing area, but do not perform tasks that result in the same level of exposures as production workers.

In Table 2-9 of *Problem Formulation of the Risk Evaluation for 1,4-Dioxane* [U.S. EPA \(2018e\)](#), EPA identified several conditions of use that may produce a mist. Some of those uses were included within this Industrial Uses group; namely, wood pulping²⁶, extraction of animal and vegetable oils²², wetting and dispersing agent in textile processing²², etching of fluoropolymers, and recycling. Mist generation is not expected from the process steps shown in Figure G-4 or the wood pulping process description. Therefore, exposures to mists from any use within the industrial uses group were not assessed for workers or ONUs.

Number of Potentially Exposed Workers and Occupational Non-Users

The two listed manufacturers in the 2016 Chemical Data Reporting (CDR) database reported three downstream industrial uses in the following two sectors; pharmaceutical and medicine manufacturing, and all other basic inorganic chemical manufacturing. Each sector is listed as having fewer than 10 sites, with one industrial use employing 50 to 100 workers and two with 100 to 500 workers each [U.S. EPA \(2016c\)](#). These three sectors only estimate workers for two of the industries that may fall in the industrial uses category, therefore, this range of 250 to 1,100 total workers could underrepresent the workers exposed in all the industries related to this use category.

EPA identified NAICS codes that were relevant to this condition of use and refined the number of workers using relevant SOC codes. Table G-15 identifies the relevant NAICS. BLS data indicate an average of 32 workers and 13 ONUs per site. The number of establishments within these NAICS codes that use 1,4-dioxane-based solvents, intermediates, and catalysts are unknown. A total of 24 sites in these NAICS codes reported discharging 1,4-dioxane in the 2018 TRI and 2018 DMR. EPA assumed this represents the total number of sites that use 1,4-dioxane in this condition of use and estimates a total of 768 workers and 312 ONUs may be exposed during these operations.

²⁶ These uses were evaluated but are likely not current uses of 1,4-dioxane.

Table G-15. Industrial Use NAICS Codes

NAICS Code	NAICS Description
311224	Soybean and Other Oilseed Processing
311613	Rendering and Meat Byproduct Processing
313110	Fiber, Yarn and Thread Mills
322121	Pulp and Paper (except groundwood, newsprint) combined Manufacturing
325180	Other Basic Inorganic Chemical Manufacturing
325199	All Other Basic Organic Chemical Manufacturing
325320	Pesticide and Other Agricultural Chemical Manufacturing
325411 ^a	Medicinal and Botanical Manufacturing
325412	Pharmaceutical Preparation Manufacturing
325510	Paint and Coating Manufacturing
325992 ^a	Photographic Film, Paper, Plate, and Chemical Manufacturing
325998	All Other Miscellaneous Chemical Product and Preparation Manufacturing
326130 ^a	Laminated Plastics Plate, Sheet (except Packaging), and Shape Manufacturing
327910 ^b	Abrasive Product Manufacturing
334413	Semiconductor and Related Device Manufacturing
335991 ^a	Carbon and Graphite Product Manufacturing

a - Data only available at the 4-digit NAICS level. Workers/site and ONUs/site numbers account for %granularity.

b - BLS data unavailable (total workers and ONUs). Averaged workers/site and ONUs/site for the other NAICS Codes.

Worker and Occupational Non-User Exposure Assessment

The 2002 EU Risk Assessment provided a summary of some exposure data relevant to the conditions of use outlined in Section 2.4.1.1.4. The Finnish Environmental Institute and an unnamed company provided the datasets, and the data provided ranged from 1989 to 1998. Some of the exposure data cover uses that are not applicable to this Industrial Uses group; therefore, EPA selected data for the uses related to this group. Select data specific to this Industrial Uses group are summarized in Table G-16.

Table G-16. DoD and 2002 EU Risk Assessment Industrial Use Inhalation Exposure Data

Industries or Task	Number of Samples	Exposure Levels (mg/m ³)			Source
		Range	Average	90 th percentile	
Medicine manufacture ^a	20 ^b	1.8-18	6.5		ECJRC (2002)
Pharmaceutical production ^a	<30 ^c	<3.6			ECJRC (2002)
Use (e.g., as solvent) in other productions ^d	194 ^c	<0.01-184	0.11 ^e	1.8	ECJRC (2002)
Use (e.g., as solvent) in other productions ^d	49 ^c	<0.04-7.2	0.07 ^e	0.62	ECJRC (2002)
Plastic Thermoforming	1	<72			DoD (2018)

^a The 2002 EU Risk Assessment does not provide information about these uses to describe the difference between medicine and pharmaceutical manufacture. EPA assumes the processes are similar. These datasets also come from different sources in the report.

^b Fixed and personal samples.

^c Personal samples.

^d These datasets were provided by the same company, but as separate datasets from different time periods.

^e These were medians.

The 2002 European Union Risk Assessment provided calculated exposure estimates using exposure data from similar scenarios and the Estimation and Assessment of Substance Exposure (EASE) model. The EASE model was developed by the US Health and Safety Executive with the Health and Safety Laboratory. It predicts expected dermal and inhalation exposures for a wide range of substances and scenarios using situational information related to the chemical [Tickner et al. \(2005\)](#). The scenario considers exposures specifically from activities related to the use of 1,4-dioxane as an extractant medicine manufacturing. The assessment assumes that it is an essentially closed system which may be breached and local exhaust ventilation (LEV) is used. Using these assumptions, the model calculated an inhalation exposure of 36 to 180 mg/m³ [ECJRC \(2002\)](#).

EPA reached out to the Department of Defense (DoD) for monitoring data for TSCA chemicals. The DoD provided monitoring data from its Defense Occupational and Environmental Health Readiness System – Industrial Hygiene (DOEHRS-IH), which collects occupational and environmental health risk data from each service branch. The dataset provided by the DoD to EPA included one sample for 1,4-dioxane exposure. The sample was a personal sample taken December 4, 2015 from a plastic thermoforming process. The total sampling time was 104 minutes and the measured result was <20,000 ppb (72 mg/m³) [DoD \(2018\)](#).

The 2002 EU Risk Assessment states that the inhalation estimates from EASE appear to considerably overestimate the exposures and recommends a central tendency exposure of 5 mg/m³ (full- shift) and a reasonable high-end exposure of 20 mg/m³ (full-shift) for the end use of 1,4-dioxane, mainly based on the highest exposure level during medicine manufacture [ECJRC \(2002\)](#). This recommended range agrees well with the exposure data in Table G-16, except for

one of the data points. The exposure level of 184 mg/m³ is likely an outlier because the value is two magnitudes larger than the 90th percentile of the range; 1.8 mg/m³. Therefore, the proposed range of 5 to 20 mg/m³ was used to estimate the inhalation exposures for the Industrial Uses group. These central tendency and reasonable high-end estimates were assumed to be equivalent to central tendency and high-end values, respectively and representing an 8-hour TWA value. Acute and chronic inhalation exposures for Industrial Uses were calculated using the equations in Appendix G.2. Results of these calculations are summarized in Section 2.4.1.1.4.

G.6.4 Functional Fluids (Open System)

EPA assessed the industrial use of metalworking fluids in the metal products and machinery (MP&M) industry [U.S. EPA \(2017d\)](#). Metalworking fluids (formulations ranging from straight oils to water-based fluids, which include soluble oils and semisynthetic/synthetic fluids) are used to reduce heat and friction and to remove metal particles in industrial machining and grinding operations. Cutting and tapping fluids are a subset of metalworking fluids that are used for the machining of internal and external threads using cutting tools like taps and thread-mills. In general, industrial metal shaping operations include machining, grinding, deformation, blasting, and other operations and may use different types of metalworking fluids to provide cooling and lubrication and to assist in metal shaping and protect the part being shaped from oxidation [OECD \(2011\)](#). Of the three open-system functional fluids identified in the *Preliminary Information on Manufacturing, Processing, Distribution, Use, and Disposal: 1,4-Dioxane* [U.S. EPA \(2017d\)](#), only one (a cutting and tapping fluid) has a safety data sheet (SDS) with information indicating the 1,4-dioxane content ranges from 0.01 to 0.1 wt%. While some cutting and tapping fluids may be used by consumers in a DIY setting, there are no consumer uses reported to the CDR [U.S. EPA \(2017d\)](#).

The Emission Scenario Document (ESD) on the Use of Metalworking Fluids provided a generic process description of the industrial use of metalworking fluids in the metal products and machinery (MP&M) industries [OECD \(2011\)](#). Metalworking fluids are typically received in containers ranging from 5-gallon pails to bulk containers. Water-based metalworking fluids are unloaded and diluted with water on-site before being transferred into the trough of the metalworking machine. Straight oils are not diluted and instead transferred directly into the trough. The metalworking fluids are pumped from the trough and usually sprayed directly on the part during metal shaping. The fluid stays on the part and may drip dry before being rinsed or wiped clean. Any remaining metalworking fluid is usually removed during a cleaning or degreasing operation [OECD \(2011\)](#). A generic process flow diagram is shown in Figure G-5.

Workers could unload the metalworking fluid from containers; clean containers; dilute water-based metalworking fluids; transfer fluids to the trough; perform metal shaping operations; rinse, wipe, and/or transfer the completed part; change filters; transfer spent fluids; and clean equipment [OECD \(2011\)](#).

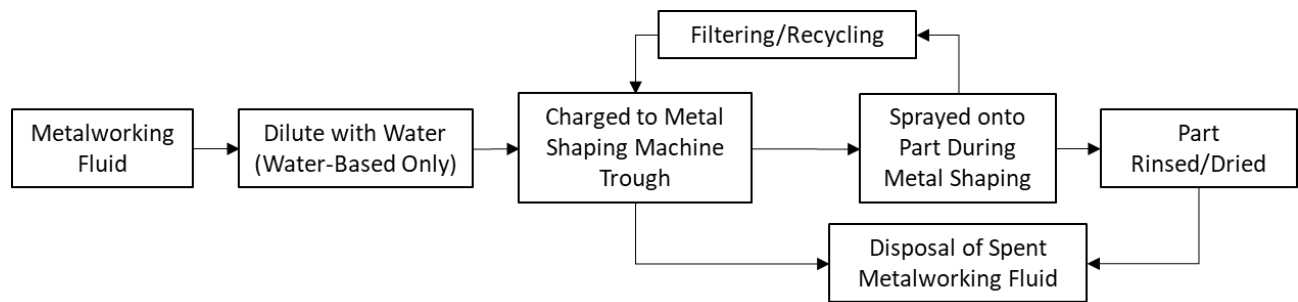


Figure G-5. Process Flow Diagram for Open System Functional Fluids

ONUs include employees that work at the site where 1,4-dioxane is used in an industrial setting as an open-system functional fluid, but these employees typically do not directly handle the chemical and are therefore expected to have lower exposures. ONUs for open-system functional fluids include supervisors, managers, and tradesmen that may be in the processing area but do not perform tasks that result in the same level of exposures as machinists.

Since 1,4-dioxane has a high vapor pressure (40 mm Hg at 2525°C), workers could be exposed to 1,4-dioxane when handling liquid metalworking fluid, such as unloading, transferring, and diluting neat fluids, and disposing spent fluids and cleaning machines and troughs. However, due to 1,4-dioxane’s low content in metalworking fluids (0.01 to 0.1 wt%), the 1,4-dioxane partial pressure could be low and would reduce exposure to 1,4-dioxane vapors.

The greatest source of potential exposure is during metal shaping operations. The high machine speeds can generate airborne mists of the metalworking fluids to which workers could be exposed. Additionally, the high vapor pressure of 1,4-dioxane could lead to its evaporation from the airborne mist droplets, potentially creating a fog of vapor and mist. However, the low concentration of 1,4-dioxane in metalworking fluids could lead to a low partial pressure, which would mitigate the evaporation of the 1,4-dioxane from the mist droplets.

Number of Potentially Exposed Workers and Occupational Non-Users

Three facilities reported 1,4-dioxane releases in the 2018 DMR, but due to the reporting requirements of DMR, EPA expects this number to represent the minimum (DMR, 2018). EPA estimated 89,000 MP&M industrial sites in the in the US as an upper bounding estimate [OECD \(2011\)](#). The ESD does not provide total workers in the industry but cites a NIOSH study of 79 small machine shops, which observed an average of 46 machinists per site. The ESD also cites an EPA effluent limit guideline development for the MP&M industry, which estimated a single shift supervisor per shift, who could perform tasks such as transferring and diluting neat metalworking fluids, disposing spent metalworking fluids, and cleaning the machines and troughs [OECD \(2011\)](#).

Since the machinists perform the metal shaping operations, during which metalworking fluid mists are generated, EPA assesses the machinists as workers, as they have the highest potential exposure. EPA assessed the single shift supervisor per site as an ONU, as this employee is not expected to have as high an exposure as the machinists. Assuming two shifts per day (hence two

shift supervisors per day), EPA assesses 46 workers and two ONUs per site [OECD \(2011\)](#). Although it is possible the shift supervisors may perform some tasks that may lead to direct handling of the metalworking fluid as outlined in the ESD, EPA assesses these shift supervisors as ONUs as their exposures are expected to be less than that of the machinist. With the above distinction between machinists and supervisors, EPA used the worker-to-ONU ratio of 23-to-1. The number of establishments within this NAICS code that use metalworking fluids and the number of those establishments that use 1,4-dioxane-based metalworking fluids are unknown. EPA estimates three to 89,000 total sites per the ESD and estimates a total of 69 to 4,094,000 workers and three to 178,000 ONUs. Therefore, EPA provides the total number of establishments and potentially exposed workers and ONUs as bounding estimates, both high and low, of the number of establishments that use and the number of workers and ONUs that are potentially exposed to 1,4-dioxane-based metalworking fluids during metal shaping operations.

Worker and Occupational Non-Users Exposure Assessment

EPA assessed worker exposures *EPA AP-42 Loading Model* and the *EPA Mass Balance Inhalation Model* and varied the saturation factor (f), ventilation rate (Q), mixing factor (k) using a Monte Carlo simulation (see Appendix G.4) These models use default parameter values and assumptions to provide screening level assessments of inhalation exposures for container unloading operations. EPA estimated 77 containers per site per year using default values and equations provided in the ESD and assumes that one container is unloaded per day, resulting in an exposure duration of 3 minutes (0.054 hours). EPA presents these values, 0.17 and 0.61 mg/m³, as central tendency and high-end short-term exposures, respectively. The simulation also estimated 0.0011 and 0.0038 mg/m³ as 50th and 95th percentile 8-hour TWA exposures. EPA used these values to calculate acute and chronic inhalation exposures in the Monte Carlo simulation, varying working years (WY), using the equations in Appendix G.2. See Section 2.4.1.1.5 for a summary of the results.

A 1997 NIOSH HHE provided PBZ and area data for workers at the Dana Corporation, Spicer Axle Division facility in Fort Wayne, Indiana. NIOSH conducted PBZ and area measurements of water-soluble synthetic metalworking fluids and oil mists from conventional metalworking fluids. These data are of the total concentration of oil mists or synthetic metalworking fluid particulates in the air [Burton and Driscoll \(1997\)](#). The NIOSH HHE does not identify 1,4-dioxane as a component of the metalworking fluids used at the facility (although NIOSH did identify 1,4-dioxane as a component of a flow-coat paint used at the facility). To estimate potential 1,4-dioxane exposures, the concentration of the synthetic metalworking fluid or oil mist was multiplied by 0.1%, the high-end concentration of 1,4-dioxane in metalworking fluids identified by EPA [U.S. EPA \(2017d\)](#). These data are summarized in Table G-17.

Table G-17. 1997 NIOSH HHE PBZ and Area Sampling Data for Metalworking Fluids

Job Description/Area	Sample time (hr)	Sample Volume (L)	Concentration (mg/m ³) ^a	Concentration of 1,4-Dioxane (mg/m ³) ^{a, b}	Sample Type
Metalworking Fluids					
Several Operations at Transfer Lines/ Dept.	6.70	804	0.53	0.00053	Personal

661					
Roughing/ Dept. 661	6.77	812	0.43	0.00043	Personal
Four-Way/ Dept. 541	6.53	784	0.46	0.00046	Personal
Multiple/ Dept. 373	5.98	718	0.22	0.00022	Personal
Screw Machine– Lathing/ Dept. 171	6.28	754	0.24	0.00024	Personal
Apex Drill/ Dept. 151	6.22	746	0.24	0.00024	Personal
Threader/ Dept. 373	6.08	730	0.14	0.00014	Area
Broaching/ Dept. 375	5.82	698	0.17	0.00017	Area
Apex Drill/ Dept. 354	6.15	738	0.23	0.00023	Area
Lunch Tables/ Dept. 375	5.68	682	0.21	0.00021	Area
Oil Mists					
Lathing/H3	6.92	830	0.08	0.00008	Personal
Burr Drill/H6	6.63	796	0.1	0.0001	Personal
Gear Cutter/K6	6.50	780	0.23	0.00023	Personal
Burnisher/K6	6.48	778	0.13	0.00013	Personal
Screw Machine	6.32	758	0.13	0.00013	Personal
Gear Cutter/N9	6.37	764	0.3	0.0003	Personal
Gear Cutter/N7	6.40	768	0.25	0.00025	Personal
Gear Cutter/Grinder	6.03	724	0.26	0.00026	Personal
Gleason Cutting Machines/N5	6.10	732	0.33	0.00033	Area

^a The duration corresponds to the sample time listed for this concentration.

^b Calculated by multiplying concentration by 0.1%, the expected concentration of 1,4-dioxane.

Source: [Burton and Driscoll \(1997\)](#)

EPA compared the distribution of 8-hour TWA results produced by the Monte Carlo simulation with the 8-hour TWA values calculated from the NIOSH HHE sample measurements and observed that all of the NIOSH HHE results are less than the 10th percentile of the Monte Carlo distribution. This indicates that the NIOSH HHE sample results are insignificant compared to the distribution produced by the Monte Carlo simulation and contribute a minor effect on the overall final estimate.

EPA compiled the five area measurements from Table G-17 into a single dataset and calculated the 50th and 95th percentile to estimate central tendency and high-end ONU inhalation exposures. EPA used these values to calculate acute and chronic exposures using the equations in Appendix G.2. See Section 2.4.1.1.5 for a summary of the results.

The 2011 OECD ESD on the Use of Metalworking Fluids estimates typical and high-end exposures for different types of metalworking fluids. These estimates are provided in Table G-18

and are based on a NIOSH study of 79 small metalworking facilities. The concentrations for these estimates are for the solvent-extractable portion and do not include water contributions. EPA assumes the concentration data available is before dilution and is therefore already equal to the concentration of the dioxane in the mist.

Table G-18. 2011 ESD on Metalworking Fluids Inhalation Exposure Estimates

Type of Metalworking Fluid	Typical Mist Concentration (mg mist/m ³) ^a	Typical 1,4-Dioxane Concentration (mg/m ³) ^b	High-End Mist Concentration (mg mist/m ³) ^c	High-End 1,4-Dioxane Concentration (mg /m ³) ^b
Conventional Soluble	0.19	0.00019	0.87	0.00087
Semi-Synthetic	0.20	0.00020	0.88	0.00088
Synthetic	0.24	0.00024	1.10	0.0011
Straight Oil	0.39	0.00039	1.42	0.0014

^a Geometric Mean

^b Calculated by multiplying concentration by 0.1%, the expected concentration of 1,4-dioxane.

^c 90th Percentile

Source: [OECD \(2011\)](#)

G.6.5 Laboratory Chemical Use

The laboratory worker activities may include preparing the mobile phase by degassing with helium, nitrogen, or processing reactions in an ultrasonic bath [ECJRC \(2002\)](#). In addition to these applications and others listed in Section 2.4.1.1.7, EPA expects conditions of use could involve activities such as unloading small quantities of chemicals; applications/filling and emptying using small volumes for laboratory activities such as preparing samples, performing small scale reactions, or for quality control or calibration purposes; and loading waste 1,4-dioxane into containers for recycling or disposal. TWA exposures typically are small, as the majority of workers could only be exposed intermittently to 1,4-dioxane due to the infrequency of such applications and filling and emptying of the solvent reservoir is reportedly carried out in a fume cupboard. In addition to laboratory analysts/workers, ONUs may include supervisors, laboratory managers, and laboratory analysts and technicians that perform other tasks in a laboratory setting where 1,4-dioxane is used but do not directly handle the chemical and are therefore expected to have lower exposures.

Descriptions of the specific process for how 1,4-dioxane is used in each of these conditions of use are not available. In general, 1,4-dioxane could be received in small containers and used in small quantities on a lab bench under a fume cupboard or hood. After use, the waste 1,4-dioxane is collected and disposed of or recycled (see Figure G-6). Quantities used in laboratory use could be disposed of with other laboratory liquid waste and/or diluted under certain occasions, but quantities used by individual laboratories would be typically small.

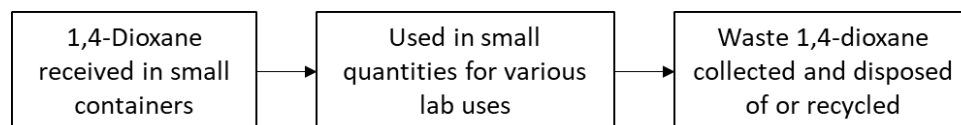


Figure G-6. General Laboratory Use Process Flow Diagram

Number of Potentially Exposed Workers and Occupational Non-Users

A single submitter to the 2016 CDR reported selling an unknown volume of 1,4-dioxane for use as a laboratory chemical. The submitter estimated selling 1,4-dioxane to fewer than 10 sites (through the use of wholesalers and retailers). The submitter further estimated that at least 50 but less than 100 laboratory workers could be potentially exposed [U.S. EPA \(2016c\)](#). EPA used U.S. Census and BLS data for the NAICS code 541380, Testing Laboratories, and relevant SOC codes to estimate a total of 6,844 sites, 6,610 workers, and 804 ONUs, which corresponds to an estimated average of one worker and 0.12 ONUs per site. EPA used these data to calculate a ratio of 8:1 workers to ONUs. EPA applied this ratio to the total number of workers reported in CDR to estimate total of 44 to 89 workers and 6 to 11 ONUs.

The number of establishments within this NAICS code that use 1,4-dioxane-based laboratory chemicals are unknown. Therefore, EPA used the total number of establishments and potentially exposed workers and ONUs in this NAICS code as bounding estimates for the number of establishments that use and the number of workers and ONUs that are potentially exposed to 1,4-dioxane-based laboratory chemicals in a laboratory setting. These bounding estimates likely overestimate the actual number of establishments and employees potentially exposed during the use of 1,4-dioxane as a laboratory chemical.

Worker and Occupational Non-User Exposure Assessment

The EU Risk Assessment [2002](#)) provides monitoring data for laboratory work activities from the Finnish Environmental Institute (FEI) and an unnamed company. Table G-19 summarizes the exposure levels. The assessment states that the first data point (laboratory work) is probably from the use of 1,4-dioxane as the mobile phase in HPLC and dilution ventilation was present but does not provide any context about specific worker activities for the rest of the data [ECJRC \(2002\)](#) reported: “[t]he Finnish Environmental Institute (FEI, 1996) provided some exposure data during the use of 1,4-dioxane in a cleaning agent, during the use in a laboratory (probably as the mobile phase in HPLC), and during medicine manufacturing (as an extractant). Company A (1997/1998) provided exposure data during the use of the substance in a laboratory, in the pharmaceutical industry ...”. The EU risk assessment grouped the laboratory use with pharmaceutical manufacturing; therefore, the risk assessment did not provide recommended central tendency or high-end values specific to laboratory use. The high concentrations in the monitoring data were considered outliers and the highest concentrations short-term peak exposures. An additional risk assessment report for 1,4-dioxane [NICNAS \(1998\)](#) did not provide occupational exposure data but cited a study where the highest 8-hour TWA value from personal monitoring was 1.8 ppm (approximately 6.5 mg/m³) [Rimatori et al. \(1994\)](#); [Hertlein \(1980\)](#).

Table G-19. Monitoring Data for Laboratory Chemicals

Industries or Task	Number of Samples	Exposure Levels (mg/m ³)		
		Range	Mean	90 th percentile
Laboratory Work (HPLC)	1	165 ^a		
Laboratory	305	0-166	0.11	0.58
Laboratory	29	<0.07-0.18	<0.07	0.15

^a Only a single measurement was provided for laboratory work associated with HPLC use.

Source: [ECJRC \(2002\)](#)

Based on the monitoring data available from the EU risk assessment [ECJRC \(2002\)](#), EPA used 0.11 mg/m³ and 5.7 mg/m³ to assess the central tendency and high-end exposures, respectively. EPA calculated the high-end value by calculating an 8-hour TWA of the 15-minute short-term peak exposure and the 90th percentile value of 0.58 mg/m³ per Equation G-11.

Equation G-11. High-End Inhalation Value for Laboratory Chemicals

$$\frac{\left(0.25 \text{ hr} \times 166 \frac{\text{mg}}{\text{m}^3}\right) + \left(7.75 \text{ hr} \times 0.58 \frac{\text{mg}}{\text{m}^3}\right)}{8 \text{ hours}} = 5.7 \frac{\text{mg}}{\text{m}^3}$$

This calculated, high-end value compares with the highest 8-hour TWA reported in the NICNAS report of 6.5 mg/m³. Acute and chronic inhalation exposures for laboratory uses are calculated using the equations in Appendix G.2 and sample calculations are found in Appendix G.3. Results of these calculations are summarized in Section 2.4.1.1.7.

G.6.6 Film Cement

The *Preliminary Information on Manufacturing, Processing, Distribution, Use, and Disposal: 1,4-Dioxane* lists one SDS for film cement, which contains 1,4-dioxane at a concentration of 45% to 50% [U.S. EPA \(2017d\)](#). Film cement is used in the film processing and archiving industries to splice celluloid movie film together. This splicing processing is typically done by hand in an open process. Film is cut using a special tool, then the cement is applied to the edges of the film by hand using a small brush. The pieces of film are joined together by closing the tool and heating to 35 °C to dry the cement. Film is also cleaned, which may be done using a sonic cleaner or as a manual operation. One site in Australia reports using 12 liters of the cement per year [NICNAS \(1998\)](#); [Okawa and Coye \(1982\)](#). A 1980 NIOSH HHE of two U.S. film laboratories observed upwards of 100 splices conducted by an employee per day and estimated less than 10 mL of cement used by an employee per shift [Okawa and Coye \(1982\)](#). See Figure G-7.

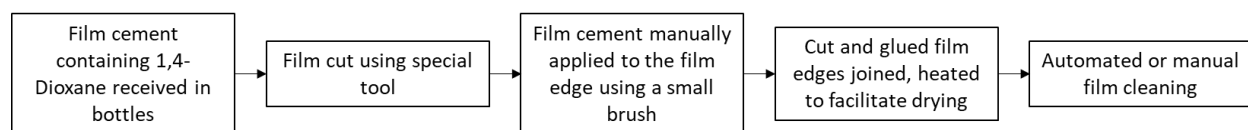


Figure G-7. Process Flow Diagram for Film Cement Application

The National Industrial Chemicals Notification and Assessment Scheme (NICNAS) reported that the splicing operation at a site in Australia was manual [NICNAS \(1998\)](#). Workers processed and cut the film, applied the cement, and joined the cut film pieces together using the heated tool. Workers would also manually clean the film using solvents. Two American film laboratories also used a similar process; therefore, EPA expects worker activities in the U.S. to be similar. These exposures are based on the activities shown in the process flow diagram in Figure G-7.

ONUs include employees that work at the film processing lab where 1,4-dioxane is used in a film cement, but they do not directly handle the chemical and are therefore expected to have lower exposures. ONUs for film laboratories include supervisors, laboratory managers, and laboratory workers that perform other tasks but do not directly handle 1,4-dioxane.

Number of Potentially Exposed Workers and Occupational Non-Users

NICNAS estimated up to 10 laboratories perform the film cement processing in Australia, with about three workers potentially exposed up to eight hours per day per site [NICNAS \(1998\)](#). The report also stated that an unknown additional number of workers could be exposed at these sites. The film laboratory could deploy up to four workers to handle duties related to film splicing [Okawa and Coye \(1982\)](#). EPA identified NAICS code 512199, Other Motion Picture and Video Industries, as the relevant NAICS code for this use. Data from the U.S. Census Bureau for the Statistics for U.S. Businesses (SUSB) for this code indicated 211 sites and 1,238 total employees. Due to the diversity of operations covered by this NAICS code, this could be an overestimate for the total number of sites and workers that perform this specific operation using film cement containing 1,4-dioxane. It is assumed that all U.S. film laboratories use a process similar to the one outlined in the NICNAS report and therefore have a similar number of workers per site. EPA estimated a total of 30 workers and 10 ONUs for all sites.

The number of establishments within this NAICS code that splice film and the number of those establishments that use 1,4-dioxane-based film cement are unknown. Therefore, EPA provides the total number of establishments and potentially exposed workers and ONUs in this NAICS code as bounding estimates of the number of establishments that use and the number of workers and ONUs that are potentially exposed to 1,4-dioxane-based film cement during film splicing operations. These bounding estimates could overestimate the actual number of establishments and employees potentially exposed to 1,4-dioxane during film splicing operations.

Worker and Occupational Non-User Exposure Assessment

The NICNAS report [NICNAS \(1998\)](#) did not have Australian air monitoring data but referenced a NIOSH HHE that collected data in 1980 from two U.S. film laboratories [Okawa and Coye \(1982\)](#). EPA noted that these are historic monitoring data and that processing technologies may have changed. The HHE identified 1,4-dioxane as a component in the film cement used in film

splicing. However, the HHE did not specify the concentration of 1,4-dioxane in the formulation. EPA calculated values for samples that were non-detects using the flow rate, and limit of detection from NIOSH Method 1602 [NIOSH \(1994\)](#). From the measured and calculated values, EPA calculated 8-hour TWA values (see Table G-20).

Table G-20. NIOSH HHE PBZ and Area Samples for Film Cement Use

Location	Job Title or Operation	Sample Type	Sample Duration (hr)	Concentration (mg/m ³) ^a	Calculated Concentration (mg/m ³) ^a	8-Hour TWA (mg/m ³)
Technicolor	Splicer (Behind glass doors)	PBZ	5.67	3.1	3.1	2.2
Technicolor	Splicer (Main Room)	PBZ	1.67	ND ^b	1.0 ^c	0.95 ^d
Technicolor	Splicer (Main Room)	PBZ	4.25	1.4	1.4	
Technicolor	Manual Film Cleaning	PBZ	6.42	3.5	3.5	2.81
MovieLab	Splicer	PBZ	5.58	ND ^b	0.30 ^c	0.21
MovieLab	Splicing General Area	Area	5.50	ND ^b	0.30 ^c	0.21

^a The duration corresponds to the sample time listed for this concentration.

^b ND – non-detect

^c EPA calculated a value for non-detects using limit of detection of 0.01 mg/sample [NIOSH \(1994\)](#).

^d These two samples are for the same operator; therefore, EPA averaged them together for the 8-hour TWA calculation.

Source: [Okawa and Coye \(1982\)](#)

Due to the small size of the data set (five data points), EPA calculated the 50th percentile to assess the central tendency exposure and presented the maximum as the high-end exposure. EPA used these values to calculate acute and chronic inhalation exposures using the equations in Appendix G.2. The results of these calculations are summarized in Section 2.4.1.1.8.

The one area sample result was a non-detect [Okawa and Coye \(1982\)](#), which means the concentration was lower than the level of detection for the method at that time. EPA calculated an upper bound for this value using half of the method detection limit. EPA considered this value as an 8-hour TWA exposure value for ONUs. This value is plausible, but EPA cannot determine the statistical representativeness of the value given the small sample size. This value was used to calculate acute and chronic inhalation exposures as per the equations in Appendix G.2. The results of these calculations are summarized in Section 2.4.1.1.8. Dermal exposures are not expected for ONUs.

G.6.7 Spray Foam Application

There are three main types of spray polyurethane foam (SPF): two-component high-pressure, two-component low-pressure, and one OCF. The low-pressure and OCF types are available for DIY-use, but the high-pressure type is only available for professional use. A safety data sheet

(SDS) identified in the *Preliminary Information on Manufacturing, Processing, Distribution, Use, and Disposal: 1,4-Dioxane* indicate that 1,4-dioxane is present in open- and closed-cell SPF, which are subsets of two-component high-pressure SPFs [U.S. EPA \(2017c, d\)](#). While one SDS has been identified where 1,4-dioxane was listed as an ingredient, it could also be an impurity/byproduct and the concentration could vary by the type of SPF.

This type of SPF is used for larger insulation applications, as an air sealant in hybrid insulations, and in roofing applications. The components are typically stored in 55-gallon drums. The operator pumps both components (sides A and B) through heated tubes from the supply tanks into a nozzle. 1,4-Dioxane is a component in Side B with concentrations typically around 0.1% [U.S. EPA \(2017c, d\)](#). Sides A and B begin to react in the nozzle and are sprayed at elevated pressures and temperatures (>150 °F and 1,200 psi). Closed-cell foam could be applied in layers. As the foam cures, it expands up to 120 times its original size. After curing, the foam could be trimmed or cut. Trimmings and waste foam are collected and disposed. See Figure G-8 for a typical process flow diagram for spray foam application.

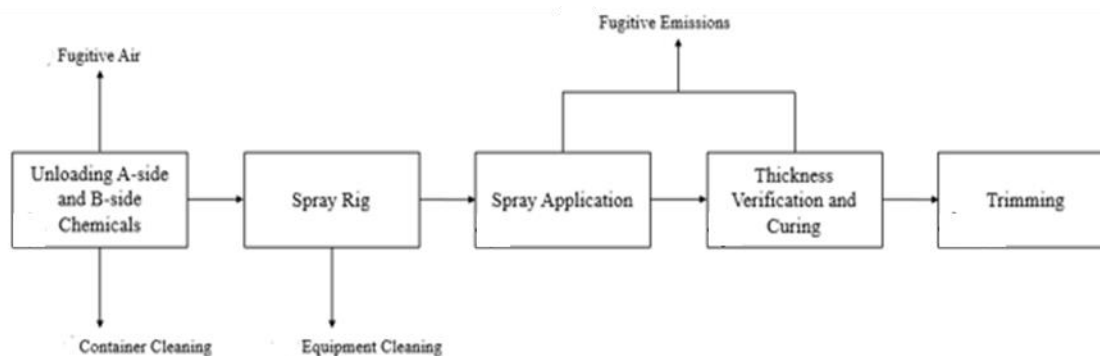


Figure G-8. Process Flow Diagram for Spray Application

Worker activities for the application of high-pressure SPF include transferring the component containing 1,4-dioxane from the drum to the supply tank, applying the spray foam mixture, trimming foam after it cures, and disposing of trimmings and waste that may contain 1,4-dioxane [U.S. EPA \(2018a, 2017c\)](#).

Non-sprayer workers include employees that work at the site where 1,4-dioxane is used during spray foam application, but do not directly handle the chemical and are therefore expected to have lower exposures. Non-sprayer workers for spray foam application include construction managers, engineers, drafters, supervisors, and workers performing other tasks that may be in the area where the spray foam is being applied, but do not perform tasks that result in the same level of exposures as workers. Non-sprayer workers may also perform trimming tasks after the insulation has cured.

Number of Potentially Exposed Workers and Non-Sprayer Workers

Data for the number of potentially exposed workers and non-sprayer workers are unknown. EPA reviewed BLS data for NAICS code 238310, Drywall and Insulation Contractors, along with relevant SOC codes, which estimated 17,857 establishments, 162,518 workers, and 15,627 non-sprayer workers. EPA estimated nine workers and one non-sprayer worker per establishment.

The number of establishments within this NAICS code that install spray polyurethane foam installation and the number of those establishments that use 1,4-dioxane-based spray polyurethane foam are unknown. Therefore, EPA considered the total number of establishments and potentially exposed workers and non-sprayer workers in this NAICS code as bounding estimates of the number of establishments that use and the number of workers and non-sprayer workers that are potentially exposed to 1,4-dioxane-based spray polyurethane foam during insulation installation. These bounding estimates are likely overestimates of the actual number of establishments and employees potentially exposed to 1,4-dioxane during spray polyurethane foam insulation installation, since only a single spray polyurethane foam product that contains 1,4-dioxane was identified.

Worker and Non-Sprayer Worker Exposure Assessment

Monitoring data for inhalation exposure to 1,4-dioxane from spray application of SPF is not known. EPA assumed that the spray foam containing 1,4-dioxane is only used for roofing applications, per the technical data sheet for the spray polyurethane foam identified in the *Preliminary Information on Manufacturing, Processing, Distribution, Use, and Disposal: 1,4-Dioxane* [U.S. EPA \(2017c\)](#). EPA used assumptions and values from the *2018 GS on the Application of Spray Polyurethane Foam Insulation* to calculate the use rate per site [U.S. EPA \(2018a\)](#). These values and relevant parameters are summarized in Table G-21.

Table G-21. Values Used for Daily Site Use Rate for SPF Application

Parameter	Symbol	Value	Unit
Operating days per site	OD_{site}	3 ^a	days/site
Roofing area	A	1500 ^b	ft ²
SPF density	ρ	3.2 ^c	lb/ft ³
SPF thickness	t	0.33 ^a	ft
Mass fraction of 1,4-dioxane in B-side	$F_{chem,B-Side}$	0.001 ^d	dimensionless
Mass fraction of B-side in mixed SPF	F_{B-Side}	0.5 ^c	dimensionless
Mass fraction of 1,4-dioxane in mixed SPF	$F_{chem,SPF}$	0.0005 ^a	dimensionless
Use rate of SPF per site	$Q_{SPF,site}$	718.5 ^a	kg spf/site
Daily Use Rate of 1,4-dioxane per site	$Q_{chem,site}$	0.12 ^a	kg chem/site-day
Number of drums B-side unloaded per site-job	N_{Drums}	1.7 ^a	drums/site-job
Unloading rate for drums	r	20 ^a	drums/hour

^a [U.S. EPA \(2018a\)](#)

^b [HomeAdvisor \(2018\)](#); [Huber \(2018\)](#)

^c [OMG Roofing Products \(2018\)](#)

^d [GAF \(2014\)](#)

Per the GS, EPA modeled inhalation exposures from unloading using the *EPA AP-42 Loading Model* and the *EPA Mass Balance Inhalation Model* and varied the saturation factor (f),

ventilation rate (Q), mixing factor (k) using a Monte Carlo simulation. See Appendix G.4 for more information about the Monte Carlo simulation. These models use default parameter values and assumptions to provide screening level assessments of inhalation exposures for container unloading operations. Assuming an unloading rate of 20 drums/hour and one drum/site, EPA estimates that workers will be exposed for less than two minutes during drum unloading.

EPA also used the *EPA Total PNOR PEL-Limiting Model* with the OSHA PEL for particulates (15 mg/m³) to estimate inhalation exposures to mists during application. EPA estimates an exposure of 0.0075 mg/m³ to mists during application. This estimate does not account for the potential evaporation of 1,4-dioxane from the mist particulates and the potential inhalation exposure of the evaporated vapors. 1,4-Dioxane has a high vapor pressure (40 mmHg at 25 °C); however, the weight % of 1,4-dioxane in the SPF particulates is very low (0.05 wt% in the mixed SPF). Therefore, the partial pressure of 1,4-dioxane is low enough so that inhalation might not be a significant route of exposure.

EPA estimated exposures from thickness verification using surrogate exposure data provided in the GS from a different chemical with similar properties. 1,2-Dichloroethane (1,2-DCE) has a vapor pressure of 61 mmHg and a molecular weight of 98.96 grams per mole, which is similar to the physical properties of 1,4-dioxane (VP = 40 mmHg at 25 °C, MW = 88.1 g/mol). The exposure data for the surrogate chemical showed a central tendency exposure of 0.044 mg/m³ and a high-end exposure of 0.077 mg/m³. EPA used Equation G-12 to estimate central tendency and high-end exposures to 1,4-dioxane during foam thickness verification. EPA assumes an exposure duration of one hour.

Equation G-12

$$C_{m_chem\ interest} = C_{m_surrogate} \times \frac{MW_{chem\ interest} \times VP_{chem\ interest} \times X_{chem\ interest}}{MW_{surrogate} \times VP_{surrogate} \times X_{surrogate}}$$

EPA calculated central tendency and high-end 8-hour TWA exposure assuming that the drum is unloaded at the beginning of the day and the remainder of the 8-hour shift is spent applying the spray foam insulation and verifying the thickness of the insulation. See Table G-22 for estimated exposure durations for each activity. EPA used these values to calculate acute and chronic inhalation exposures in the Monte Carlo simulation, varying working years (WY), using the equations in Appendix G.2. See Section 2.4.1.1.6 for a summary of the results.

Table G-22. Estimated Activity Exposure Durations

Activity	Exposure Duration (hours)
Drum Unloading	0.028
Spray Foam Application	6.97
Thickness Verification	1.0

Exposure data for non-sprayer workers were not available. Per the GS, EPA assumed that some non-sprayer workers may perform tasks related to trimming the cured spray foam insulation. EPA used the *EPA Total PNOR PEL-Limiting Model* with the OSHA PEL for particulates (15

mg/m³) to estimate inhalation exposures to particulates during trimming. An exposure of particulates at the rate of 0.0075 mg/m³ considered to occur during trimming. EPA averaged this exposure over an 8-hour shift, assuming this exposure occurs over one hour and that non-sprayer workers are not exposed to 1,4-dioxane during the rest of the shift. EPA presents this as an 8-hour TWA inhalation exposure value for non-sprayer workers. This value is plausible, but EPA cannot determine the statistical representativeness of the value given the small sample size. This value was used to calculate acute and chronic inhalation exposures as per the equations in Appendix G.2. Only inhalation exposures to vapors are expected, which could be less than worker exposures.

G.6.8 Printing Inks (3D)

The *Preliminary Information on Manufacturing, Processing, Distribution, Use, and Disposal: 1,4-Dioxane* identified one SDS for an inkjet printing cartridge used in standard inkjet printers that may contain 1,4-dioxane. However, the SDS does not indicate that 1,4-dioxane is an intended ingredient in this cartridge [U.S. EPA \(2017d\)](#). Recent articles identified 1,4-dioxane as a major component in inks used in additive manufacturing, also known as three-dimensional (3D) printing [He et al. \(2016\)](#); [Ryan and Hubbard \(2016\)](#); [Ruggiero et al. \(2015\)](#); [He et al. \(2013\)](#). Therefore, EPA assessed exposures related to the use of 1,4-dioxane as a component in printing inks in additive printing manufacturing.

1,4-Dioxane could be present in solvent-based inks that are used in a type of additive manufacturing known as material jetting. The concentration of 1,4-dioxane in these inks ranges from 75% to 99.5%, based on the solvent system [He et al. \(2016\)](#); [Ruggiero et al. \(2015\)](#); [He et al. \(2013\)](#). In this process, the ink could be made on site or received in cartridges or syringes (Figure G-9). The liquid ink is charged to a cartridge in the material printer. The printing head deposits the ink one drop at a time on the substrate. Each drop is cured to form a solid structure using an outside energy source, such as ultraviolet light or heat. The final product is cleaned in a bath of a concentrated, highly corrosive material to remove support structures [He et al. \(2016\)](#).

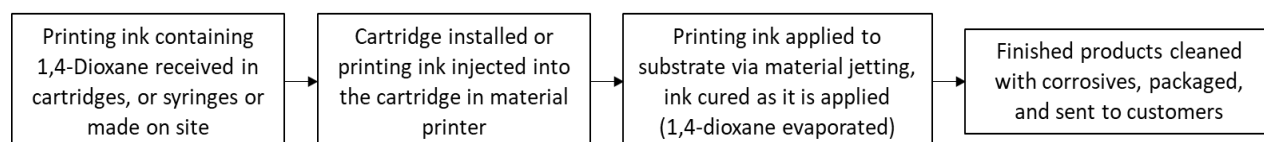


Figure G-9. Process Flow Diagram for Printing Inks (3D)

This type of 3D printing ink is used in research labs to print biomedical products, such as bioresorbable or biodegradable stents, implants, and scaffolds for tissue recovery. Making these devices using this method allows for lower production costs and increased customization [Ruggiero et al. \(2015\)](#); [He et al. \(2013\)](#). Workers could be exposed while charging the ink to the cartridges in the material printer, during the 3D printing process, and when disposing of spent cartridges and syringes. If the ink is made on site, workers could be exposed during this step in the process. ONUs include employees that work at the site where 1,4-dioxane is used in a laboratory setting, but they do not directly handle the chemical and are therefore expected to have lower exposures. ONUs for laboratory use include supervisors, laboratory managers, and laboratory workers that perform other tasks but do not directly handle 1,4-dioxane.

Number of Potentially Exposed Workers and Occupational Non-Users

EPA uses U.S. Census and BLS data for the NAICS code 339113, surgical appliance and supplies manufacturing, and relevant SOC codes to estimate a total of 10,767 sites, 59,970 workers, and 20,430 ONUs, which corresponds to an estimated average of six workers and two ONUs per site. The number of establishments within this NAICS code that print biomedical products and the number of those establishments that use 1,4-dioxane-based 3D printing inks are unknown. Therefore, EPA provided the total number of establishments and potentially exposed workers and ONUs in this NAICS code as bounding estimates of the number of establishments that use and the number of workers and ONUs that are potentially exposed to 1,4-dioxane-based 3D printing ink in biomedical product 3D printing. These bounding estimates could overestimate the actual number of establishments and employees potentially exposed to 1,4-dioxane during biomedical product 3D printing.

Worker and Occupational Non-User Exposure Assessment

A literature review and hazard assessment for material jetting identified exposure data for a number of chemicals, including 1,4-dioxane, during additive manufacturing. A piece of tubing was placed inside the unventilated 3D printer enclosure and attached to a 1.4-L Toxic Organic-15 (TO-15) canister, which was placed directly adjacent to the printer. Air Method, Toxic Organics-15 (TO-15) is an EPA method for sampling and analyzing volatile organic compounds (VOCs) using specially prepared canisters and gas chromatography/mass spectrometry. The air was sampled for an 8-hour period while the printer ran continuously. Since there was only a single sample run, only a single data point is available. 1,4-Dioxane was present inside the printer enclosure at a level of 27 ppb (0.097 mg/m³). The printer did not have local exhaust ventilation and relied on general ventilation. 1,4-dioxane levels could be higher if more printers were operating in the same area without local exhaust ventilation and could reach the NIOSH REL of 1 ppm. However, Ryan and Hubbard (2016) indicated that the results were based on a preliminary study and acknowledged that more statistically defensible sampling could be performed to better understand exposures during this process.

EPA presented this value as an 8-hour TWA exposure for workers. This value is plausible, but EPA cannot determine the statistical representativeness of the value given the small sample size. Additionally, this sample was taken inside the 3D printing enclosure and likely represents a higher exposure than what workers operating the 3D printer would typically experience. EPA used this value to calculate acute and chronic inhalation exposures as per the equations in Appendix G.2. Results of these calculations are summarized in Section 2.4.1.1.10.

Exposure data for ONUs were not available. EPA expects that ONU exposures are expected to be lower than worker exposures, since ONUs do not typically directly handle the chemical. Only inhalation exposures to vapors are expected, which could be less than worker exposures.

G.6.9 Dry Film Lubricant

The DOE's KCNSC indicated use of 1,4-dioxane as a carrier in the manufacture and application of a dry film lubricant. The KCNSC is one of eight sites that comprise the DOE's NNSA, which manufacture 85% of non-nuclear components of nuclear weapons (KCNSC (2018)).

The facility stated that the dry film lubricant was used on non-nuclear components for nuclear weapons. The manufacture of the dry film typically initiated by mixing 1,4-dioxane and other

solvents to create a solvent blend, which generally contained 16% 1,4-dioxane. The solvent blend was used to manufacture concentrated dry film lubricant with a final 1,4-dioxane concentration of 4% to 5%. Twelve half-pint containers of concentrated dry film lubricant were produced in each run [DOE \(2018a\)](#).

Prior to spray application of the dry film lubricant, the facility mixed about 1.5 pints of pure 1,4-dioxane with a half-pint container of concentrated dry film lubricant. The dry film lubricant and dioxane mixture was sprayed in a vented paint booth either by hand or an automated system onto the applicable parts. If the dry film lubricant needed to be removed from a part immediately after spraying, it was cleaned in an ultrasonic bath filled with one gallon of dioxane for three to five minutes and then rinsed in alcohol. The dioxane from the ultrasonic cleaner was disposed of in chemical waste containers. After application, parts were cured in an oven for one hour during which the 1,4-dioxane was evaporated and vented from the oven stack [DOE \(2018a\)](#).

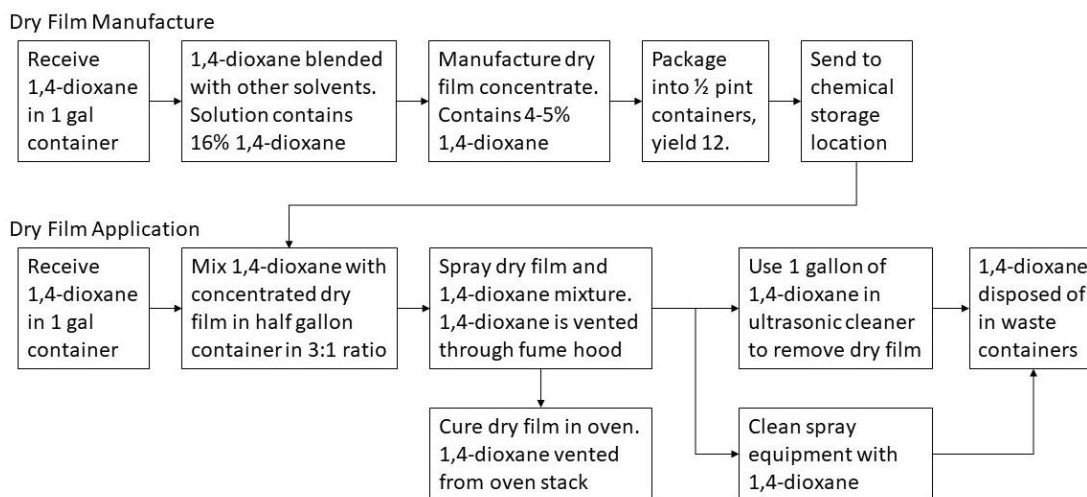


Figure G-10. Process Flow Diagram for Dry Film Lubricant in Nuclear Weapon Applications

Process flow diagram for dry film lubricant at the KCNSC is shown in Figure G-10. Workers activities included mixing, packaging, pouring, and spraying the dry film lubricant. If any part needed to have the dry film lubricant removed soon after spraying, the worker could use a small ultrasonic bath containing 1,4-dioxane. In addition, workers routinely cleaned the spray gun with 1,4-dioxane. KCNSC estimated that the dry film lubricant was manufactured six to eight times per year in one-gallon batches and each batch could take about an hour to manufacture. According to KCNSC, the dry film lubricant was applied, on average, once per week for a minimum of two hours and a maximum of six hours. These estimates included the mixing, application, and clean-up steps as described in Figure G-10. Factoring in holidays and down time, KCNSC estimated dry film lubricant application to be about 48 times per year [DOE \(2018a\)](#). It was assumed this process and these worker activities could be similar to other sites that produce and use 1,4-dioxane-based dry film lubricants.

ONUs include employees that work at the site where 1,4-dioxane is used in dry film lubricants, but they do not directly handle the chemical and are therefore expected to have lower exposures.

ONUs for dry film lubricant manufacture and use include supervisors, managers, and workers that perform other tasks but do not directly handle 1,4-dioxane.

Number of Potentially Exposed Workers and Occupational Non-Users

KCNCS provided an estimate of ten exposed or potentially exposed workers at the facility. This estimate includes three to four employees in the chemical material area where the dry film lubricant is formulated and another five to six employees who work in the paint shop where the dry film lubricant is spray applied [DOE \(2018b\)](#). KCNCS estimated that only one employee in each area is exposed as a worker with the rest considered ONUs.

The KCNCS is one of eight facilities in DOE’s NNSA [KCNCS \(2018\)](#). EPA believes that the operations at different DOE/NNSA facilities vary substantially and that it is unlikely that the operations at the KCNCS are similar to any of the other facilities. However, the KCNCS [2018](#)) does not have additional information on operations at the other DOE facilities, so it is unknown if other DOE NNSA sites use 1,4-dioxane in a similar way. As conservative, EPA assumed all eight facilities could use 1,4-dioxane for this application and therefore, EPA assessed a total of 16 workers and 64 ONUs potentially exposed to 1,4-dioxane across all NNSA sites. This may be an overestimate of workers and ONUs.

Worker and Occupational Non-User Exposure Assessment Methodology and Results

KCNCS provided the results of 20 area samples and 12 PBZ monitoring sample measurements to EPA [DOE \(2018a\)](#). EPA used these data to assess inhalation exposures to 1,4-dioxane for this condition of use. The PBZ samples included two full shift 8-hour TWA samples and five 8-hour TWAs that are derived from same-day task-based TWA samples, for a total of seven 8-hour TWA results, which are included below in Table G-23.

The 20 area samples KCNCS provided were gathered using a direct reading method. Direct reading instruments provide real-time monitoring using calibrated devices that record multiple single point readings. These readings do not provide time-weighted average results. Therefore, EPA did not use the area measurements.

Table G-23. PBZ Task and TWA Monitoring Data for Dry Film Lubricant Manufacture and Spray Application at KCNCS

Process	Task	Sample Collection Date	Sample Duration (min)	Sample Result (mg/m ³)	Calculated 8-hour TWA (mg/m ³)
Manufacture	Weighing material, mixing material using a paint shaker, pouring material into cans for packaging	10/16/2018	85	NP	0.035
Application	Mixing material, hand spray application, cleaning spray gun	2/11/2005	62	NP	0.11

Application	Material mixing, spray application	9/14/2010	30	2.1	0.47
Application	Spray application	9/14/2010	17	3.2	
Application	Equipment cleaning, pour material into step can	9/14/2010	62	1.6	
Application	Material preparation inside hood or closed mixing	9/21/2010	60	1.8	0.68
Application	Spray application	9/21/2010	60	1.8	
Application	All cleaning steps with exception of pouring material into equipment reservoir; opening step can (step can is mixed VOCs)	9/21/2010	50	2.2	
Application	Material preparation inside hood or closed mixing, pouring material into equipment container inside the hood, and spray application	10/11/2010	60	1.1	0.25
Application	All cleaning steps	10/11/2010	23	2.5	
Application	Material preparation and spray application	12/1/2011	395	np	1.9
Application	Material preparation, spray application, and cleanup	5/16/2013	425	np	0.97

NP: not provided.

EPA estimated the 95th percentile and 50th percentile of the calculated 8-hour TWA results to assess the high-end and central tendency exposures, respectively. These values were used to calculate acute and chronic inhalation exposures as per the equations in Appendix G.2. As referenced in Section 2.4.1.1.11, KCNSC indicated that the facility manufactured the dry film lubricant six to eight days per year and applied it about 48 days per year for a total exposure frequency of 56 days per year. This value was used in place of the standard 250 days per year assumption outlined in Appendix G.2. Results of these calculations are summarized in Section 2.4.1.1.11.

G.6.10 Disposal

Each of the conditions of use of 1,4-dioxane may generate waste streams of the chemical that are

collected and transported to third-party sites for disposal, treatment, or recycling. Industrial sites that treat or dispose onsite wastes that they themselves generate are assessed in each condition of use assessment in Sections 2.4.1.1.1 through 2.4.1.1.12. Wastes containing 1,4-dioxane that are generated during a condition of use and sent to a third-party site for treatment, disposal, or recycling could include the following:

Wastewater: 1,4-Dioxane may be contained in wastewater discharged to POTW or other, non-public treatment works for treatment. Industrial wastewater containing 1,4-dioxane discharged to a POTW may be subject to EPA or authorized NPDES state pretreatment programs. The assessment of wastewater discharges to POTWs and non-public treatment works of 1,4-dioxane is included in each of the condition of use assessments in Sections 2.4.1.1.1 through 2.4.1.1.12.

Solid Wastes: Solid wastes are defined under RCRA as any material that is discarded by being: abandoned; inherently waste-like; a discarded military munition; or recycled in certain ways (certain instances of the generation and legitimate reclamation of secondary materials are exempted as solid wastes under RCRA). Solid wastes may subsequently meet RCRA's definition of hazardous waste by either being listed as a waste at 40 CFR § 261.30 to § 261.35 or by meeting waste-like characteristics as defined at 40 CFR § 261.20 to 261.24. Solid wastes that are hazardous wastes are regulated under the more stringent requirements of Subtitle C of RCRA, whereas non-hazardous solid wastes are regulated under the less stringent requirements of Subtitle D of RCRA.

1,4-Dioxane is listed as a hazardous waste on the U list at 40 CFR § 261.30. This list designates specific unused commercial chemical products (CCP) that are pure or a commercial grade formulation as hazardous waste. The hazardous waste code for 1,4-dioxane is U108.

Wastes Exempted as Solid Wastes under RCRA: Certain conditions of use of 1,4-dioxane may generate wastes of 1,4-dioxane that are exempted as solid wastes under 40 CFR § 261.4(a). For example, the generation and legitimate reclamation of hazardous secondary materials of 1,4-dioxane may be exempt as a solid waste.

2018 TRI data lists off-site transfers of 1,4-dioxane to land disposal, wastewater treatment, incineration, and recycling facilities (see Figure G-11). About 69% of off-site transfers were incinerated, 19% sent to land disposal, and less than 1% is recycled off-site U.S. [U.S. EPA \(2016c\)](#).

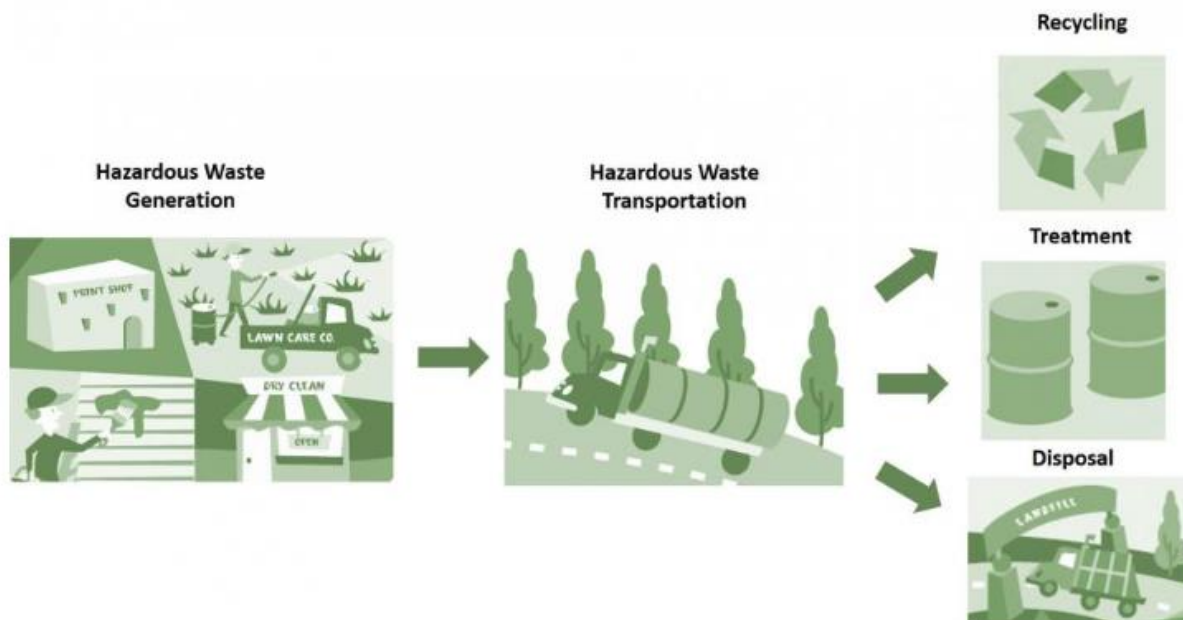


Figure G-11. Typical Waste Disposal Process

Source: [U.S. EPA \(2017d\)](#)

Municipal Waste Incineration

Municipal waste combustors (MWCs) that recover energy are generally located at large facilities comprising an enclosed tipping floor and a deep waste storage pit. Typical large MWCs may range in capacity from 250 to over 1,000 tons per day. Workers do not generally directly handle waste materials at the large facilities. Trucks may dump the waste directly into the pit, or waste may be tipped to the floor and later pushed into the pit by a worker operating a front-end loader. A large grapple from an overhead crane is used to grab waste from the pit and drop it into a hopper, where hydraulic rams feed the material continuously into the combustion unit at a controlled rate. The crane operator also uses the grapple to mix the waste within the pit, in order to provide a fuel consistent in composition and heating value, and to pick out hazardous or problematic waste.

Facilities burning refuse-derived fuel (RDF) conduct on-site sorting, shredding, and inspection of the waste prior to incineration to recover recyclables and remove hazardous waste or other unwanted materials. Sorting is usually an automated process that uses mechanical separation methods, such as trommel screens, disk screens, and magnetic separators. Once processed, the waste material could be transferred to a storage pit, or it could be conveyed directly to the hopper for combustion.

Tipping floor operations may generate dust. Air from the enclosed tipping floor, however, is continuously drawn into the combustion unit via one or more forced air fans to serve as the primary combustion air and minimize odors. Dust and lint present in the air is typically captured

in filters or other cleaning devices in order to prevent the clogging of steam coils, which are used to heat the combustion air and help dry higher-moisture inputs [Kitto \(1992\)](#).

Hazardous Waste Incineration

Commercial scale hazardous waste incinerators are generally two-chamber units, a rotary kiln followed by an afterburner, that accept both solid and liquid waste. Liquid wastes are pumped through pipes and are fed to the unit through nozzles that atomize the liquid for optimal combustion. Solids may be fed to the kiln as loose solids gravity fed to a hopper, or in drums or containers using a conveyor [ETC \(2018\)](#); [Heritage \(2018\)](#).

Incoming hazardous waste is usually received by truck or rail, and an inspection is required for the waste received. Receiving areas for liquid waste generally consist of a docking area, pumphouse, and storage facilities. For solids, conveyor devices are typically used to transport incoming waste [ETC \(2018\)](#); [Heritage \(2018\)](#).

Smaller scale units that burn municipal solid waste or hazardous waste (such as infectious and hazardous waste incinerators at hospitals) could require more direct handling of the materials by facility personnel. Units that are batch-loaded require the waste to be placed on the grate prior to operation and may involve manually dumping waste from a container or shoveling waste from a container onto the grate. See Figure G-12.

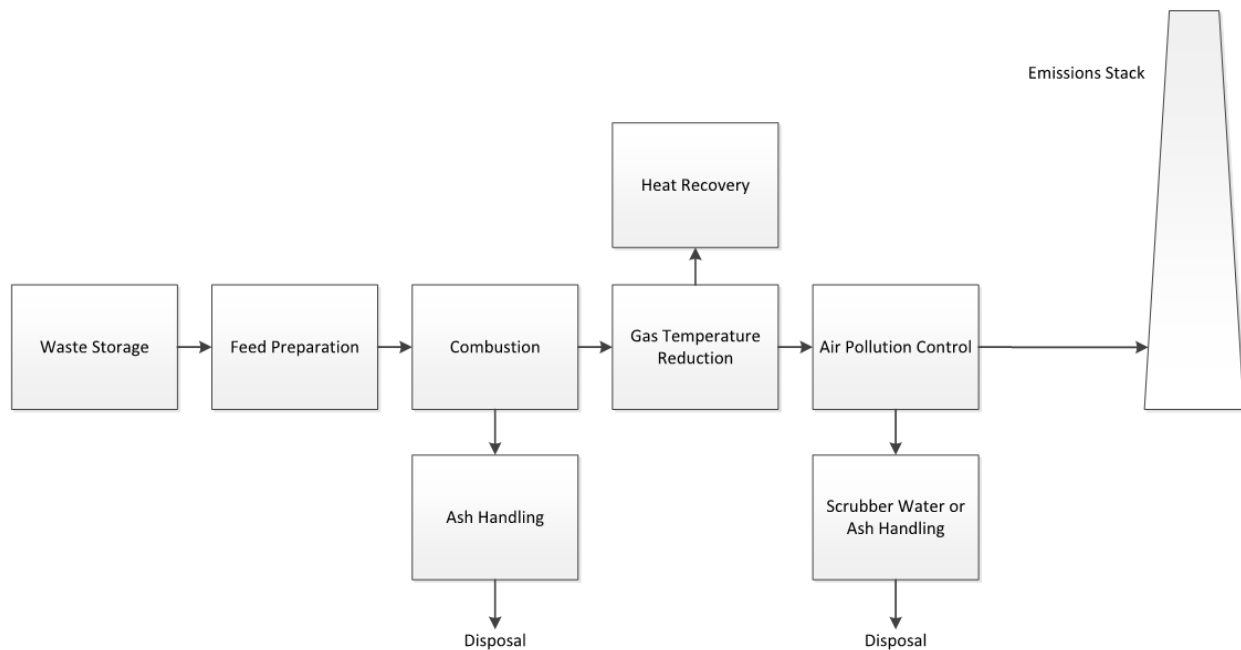


Figure G-12. Typical Industrial Incineration Process

Municipal Waste Landfill

Municipal solid waste landfills are discrete areas of land or excavated sites that receive household wastes and other types of non-hazardous wastes (*e.g.*, industrial and commercial solid wastes). Standards and requirements for municipal waste landfills include location restrictions, composite liner requirements, leachate collection and removal system, operating practices, groundwater monitoring requirements, closure-and post-closure care requirements, corrective

action provisions, and financial assurance. Non-hazardous solid wastes are regulated under RCRA Subtitle D, but states may impose more stringent requirements.

Municipal solid wastes may be first unloaded at waste transfer stations for temporary storage, prior to being transported to the landfill or other treatment or disposal facilities.

Hazardous Waste Landfill

Hazardous waste landfills are excavated or engineered sites specifically designed for the final disposal of non-liquid hazardous wastes. Design standards for these landfills require double liner, double leachate collection and removal systems, leak detection system, run on, runoff and wind dispersal controls, and construction quality assurance program [U.S. EPA \(2018a\)](#). There are also requirements for closure and post-closure of a landfill facility, such as the addition of a final cover over the landfill and continued monitoring and maintenance. These standards and requirements prevent potential contamination of groundwater and nearby surface water resources. Hazardous waste landfills are regulated under Part 264/265, Subpart N.

Solvent Recovery

Waste solvents are generated when it becomes contaminated with suspended and dissolved solids, organics, water, or other substances [U.S. EPA \(1980\)](#). Waste solvents could be restored to a condition that permits reuse via solvent reclamation/recycling [U.S. EPA \(1980\)](#). The recovery process could involve an initial vapor recovery (*e.g.*, condensation, adsorption and absorption) or mechanical separation (*e.g.*, decanting, filtering, draining, settling and centrifuging) step followed by distillation, purification and final packaging [U.S. EPA \(1980\)](#). Worker activities include unloading of waste solvents and loading of reclaimed solvents. Figure G-13 illustrates a typical solvent recovery process flow diagram [U.S. EPA \(1980\)](#).

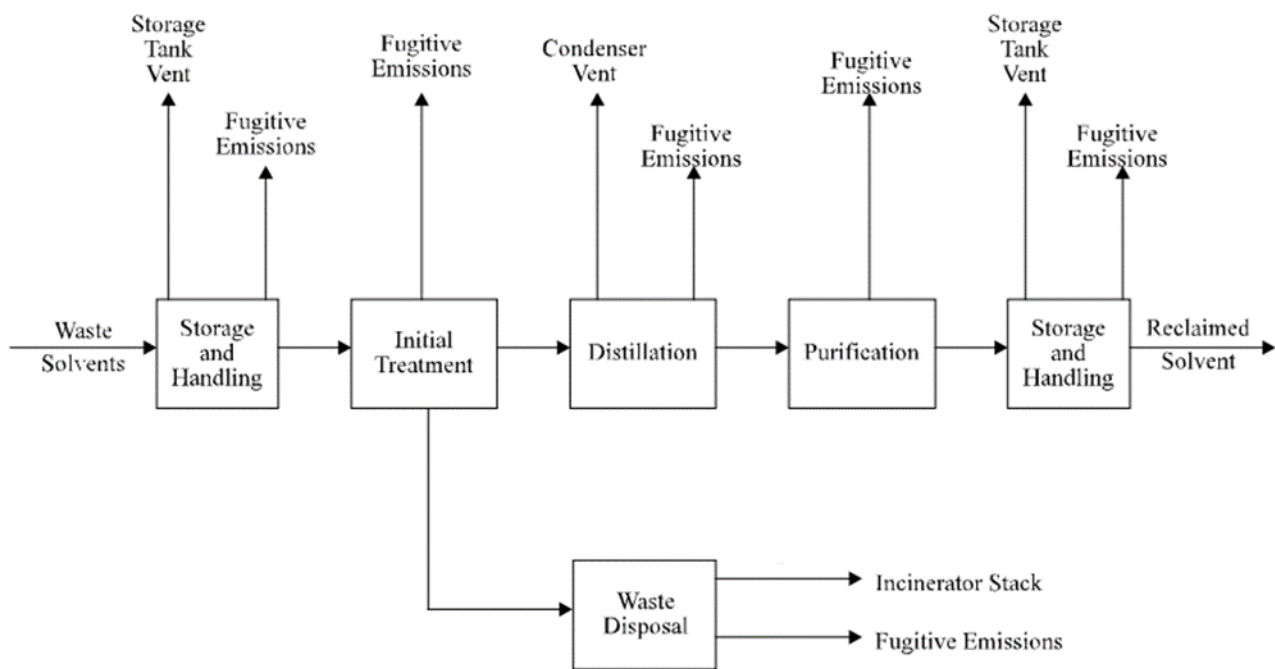


Figure G-13. General Process Flow Diagram for Solvent Recovery Processes

U.S. Source: [U.S. EPA \(1980\)](#)

Number of Potentially Exposed Workers and Occupational Non-Users

The total number of sites that treat and dispose wastes containing 1,4-dioxane is unknown. For reporting year 2018, six hazardous waste treatment and disposal facilities, one solid waste combustor and incinerator, four cement plants, and one facility listed under Ground or Treated Mineral Earth Manufacturing report released of 1,4-dioxane to the TRI [U.S. EPA \(2016c\)](#). Table G-24 presented the estimated number of workers and ONUs at these facilities based on EPA’s analysis of typical employment in those industry sectors. It is possible that additional hazardous waste treatment facilities treated and disposed 1,4-dioxane but did not meet the TRI reporting threshold for reporting year 2018. Therefore, the total number of workers and ONUs potentially exposed to 1,4-dioxane could be greater than 1177 workers and 53 ONUs.

Table G-24. NAICS Codes with Workers and ONUs for Disposal

NAICS Code	NAICS Description	Total Sites	Total Workers	Total ONUs	Number of Sites that Reported 1,4-Dioxane	Workers Potentially Exposed to 1,4-Dioxane	ONUs Potentially Exposed to 1,4-Dioxane
562211	Hazardous Waste Treatment and Disposal	892	8,054	4,836	6	54	30
562213	Solid Waste Combustors and Incinerators	102	1,356	814	1	13	8
327310	Cement Manufacturing	233	5,080	781	4	88	12

NAICS Code	NAICS Description	Total Sites	Total Workers	Total ONUs	Number of Sites that Reported 1,4-Dioxane	Workers Potentially Exposed to 1,4-Dioxane	ONUs Potentially Exposed to 1,4-Dioxane
327992	Ground or Treated Mineral Earth Manufacturing ^a	231	-	-	1	22	3
Grand Totals		3,052	19,820	9,631	12	177	53

^a BLS data are not available for the 327992 NAICS code and EPA assessed the number of workers and ONUs at cement manufacturing facilities as similar.

Worker and Occupational Non-User Activities

At waste disposal sites, workers are potentially exposed via dermal contact with wastes containing 1,4-dioxane or via inhalation of 1,4-dioxane vapor. Depending on the concentration of 1,4-dioxane in the waste stream, the route and level of exposure could be similar to that associated with container unloading activities. The assessments of worker exposure from chemical unloading activities are in the following sections.

Municipal Waste Incineration

At municipal waste incineration facilities, there could be one or more technicians present on the tipping floor to oversee operations, direct trucks, inspect incoming waste, or perform other tasks as warranted by individual facility practices. These workers may wear protective gear such as gloves, safety glasses, or dust masks. Specific worker protocols are largely up to individual companies, although state or local regulations may require certain worker safety standards be met. Federal operator training requirements pertain more to the operation of the regulated combustion unit rather than operator health and safety.

Workers are potentially exposed via inhalation to vapors while working on the tipping floor. Potentially-exposed workers include workers stationed on the tipping floor, including front-end loader and crane operators, as well as truck drivers. The potential for dermal exposures is minimized by the use of trucks and cranes to handle the wastes.

Hazardous Waste Incineration

More information is needed to determine the potential for worker exposures during hazardous waste incineration and any requirements for personal protective equipment. There is likely a greater potential for exposures while operating smaller scale incinerators that involve more direct handling of the wastes by the worker.

Municipal and Hazardous Waste Landfill

At landfills, typical worker activities may include operating refuse vehicles to weigh and unload the waste materials, operating bulldozers to spread and compact wastes, and monitoring, inspecting, and surveying and landfill site [CalRecycle \(2018\)](#).

Worker and Occupational Non-User Exposure Assessment

Bulk Shipments of Liquid Hazardous Waste

It is assumed that the 1,4-dioxane wastes that are generated, transported, and treated or disposed

as hazardous waste are done so via bulk liquid shipments. For example, a facility that uses 1,4-dioxane as a processing aid could generate and store the waste processing aid as relatively pure 1,4-dioxane and have it shipped to hazardous waste treatment, storage and disposal facilities (TSDFs).

Exposure data for this scenario are not known; therefore, the *EPA AP-42 Loading Model* and the *EPA Mass Balance Inhalation Model* were used to estimate inhalation exposures. These models use default parameter values and assumptions to provide screening level assessments of inhalation exposures for container loading and unloading operations. EPA used a Monte Carlo simulation to vary the saturation factor (f), ventilation rate (Q), mixing factor (k), and working years (WY). See Appendix G.4 for more information about the Monte Carlo simulation.

It is assumed that any exposures related to on-site waste treatment and disposal are addressed in the assessments for those uses in this report; therefore, this section assesses exposures to workers for wastes transferred from the use site to an off-site waste treatment and disposal facility. Table G-25 lists the off-site waste transfers reported in the 2018 TRI. EPA used the total value reported in this table as the PV for this assessment. It is assumed that the waste chemical is typically transported to the treatment and disposal sites in 55-gallon drums that estimated 2,427 drums per year. The 2018 TRI reported 12 waste treatment and disposal sites, resulting in an average of 388 drums per site per year. Facilities are only required to report to TRI if the facility has 10 or more full-time employees, is included in an applicable NAICS code, and manufactures, processes, or uses the chemical in quantities greater than a certain threshold (25,000 lb/yr for the manufacture or processing of the chemical, or 10,000 lb/yr for otherwise use of the chemical). Some sites that use 1,4-dioxane in this Industrial Uses category may not meet these qualifications and therefore are not required to report to TRI.

Table G-25. 2018 TRI Off-Site Transfers for 1,4-Dioxane

Off-Site Transfer	Total Quantity Reported (lb)
Land Disposal	543,252
Incineration	1,941,760
Recycled	8,043
Other	1,896
Total	2,494,951

U.S. Source: [U.S. EPA \(2016c\)](#)

EPA assumed that 1.75 drums are unloaded per site per day. Assuming a default unloading rate of 20 drums per hour, it would take an estimated 5.4 minutes (0.09 hours) for each site to a single drum each day. EPA estimated this exposure using the equations and parameters in Appendix G.2 and averaged the 5.4-minute exposures over an 8-hour shift, assuming the workers are exposed to 1,4-dioxane while unloading and then not exposed for the rest of the shift. The central tendency and high-end 8-hour TWA exposures for unloading drums are 1.87 and 6.64 mg/m³, respectively. EPA also presents the 5.4-minute exposures as central tendency and high-end short-term exposures EPA used these values to calculate acute and chronic inhalation exposures in the Monte Carlo simulation, varying working years (WY), using the equations in Appendix G.2.

Results of these calculations are summarized in Section 2.4.1.1.12.

Modeling was not performed to estimate exposures for ONUs. ONU exposures would be lower than worker exposures, since ONUs do not typically directly handle the chemical. Only inhalation exposures to vapors are expected, which would be less than worker exposures.

Municipal Solid Wastes

Certain commercial conditions of use of 1,4-dioxane could generate solid wastes that might be sent to municipal waste combustors or landfills. For example, spent spray polyurethane foam insulation containers or spray foam trimmings containing residual 1,4-dioxane used by contractors and technicians could be disposed as household hazardous waste as it is exempted as a hazardous waste under RCRA. While some municipalities may have collections of household hazardous wastes to prevent the comingling of household hazardous wastes with municipal waste streams, some users could inappropriately dispose of household hazardous wastes in the municipal waste stream.

EPA was not able to quantitatively assess worker or ONU exposures to 1,4-dioxane within municipal solid waste streams. The quantities of 1,4-dioxane could be diluted among the comingled municipal solid waste stream.

G.7 Dermal Exposure Assessment Method

This proposed method was developed through review of relevant literature and consideration of existing exposure models, such as EPA models and the European Centre for Ecotoxicology and Toxicology of Chemicals Targeted Risk Assessment (ECETOC TRA).

G.7.1 Incorporating the Effects of Evaporation

Current EPA dermal models do not incorporate the evaporation of material from the dermis. The dermal potential dose rate, D_{exp} (mg/day), is calculated as [U.S. EPA \(2013b\)](#):

Equation G-13

$$D_{exp} = S \times Q_u \times Y_{derm} \times FT$$

Where:

S is the surface area of contact (cm²; defaults: 535 cm² (Central tendency); 1,070 cm² (high end)). These values represent the surface area of one side of both hands (central tendency) and the full surface area of both sides of both hands (high end)), respectively, for the average adult male [U.S. EPA \(2013b\)](#).

Q_u is the quantity remaining on the skin (mg/cm²-event; defaults: 1.4 mg/cm²-event (central tendency); 2.1 mg/cm²-event (high end)).

Y_{derm} is the weight fraction of the chemical of interest in the liquid ($0 \leq Y_{derm} \leq 1$).

FT is the frequency of events (integer number per day).

Here Q_u does not represent the quantity remaining after evaporation, but represents the quantity remaining after the bulk liquid has fallen from the hand that cannot be removed by wiping the skin (*e.g.*, the film that remains on the skin).

One way to account for evaporation of a volatile solvent would be to add a multiplicative factor to the EPA model to represent the proportion of chemical that remains on the skin after evaporation, f_{abs} ($0 \leq f_{abs} \leq 1$):

Equation G-14

$$D_{exp} = S \times (Q_u \times f_{abs}) \times Y_{derm} \times FT$$

This approach simply removes the evaporated mass from the calculation of dermal uptake. Evaporation is not instantaneous, but the EPA model already has a simplified representation of the kinetics of dermal uptake.

G.7.2 Calculation of f_{abs}

Kasting and Miller (2006) developed a diffusion model to describe the absorption of volatile compounds applied to the skin. As part of the model, Kasting and Miller define a ratio of the liquid evaporation to absorption, χ . They derive the following definition of χ (which is dimensionless) at steady-state:

Equation G-15

$$\chi = 3.4 \times 10^{-3} u^{0.78} \frac{P_{vp} MW^{3.4}}{K_{oct}^{0.76} S_w}$$

Where:

u is the air velocity (m/s)

K_{oct} is the octanol:water partition coefficient

MW is the molecular weight

S_w is the water solubility ($\mu\text{g}/\text{cm}^3$)

P_{vp} is the vapor pressure (torr)

Chemicals for which $\chi \gg 1$ will largely evaporate from the skin surface, while chemicals for which $\chi \ll 1$ will be largely absorbed; $\chi = 1$ represents a balance between evaporation and absorption. Equation G-15 is applicable to chemicals having a log octanol/water partition coefficient less than or equal to three ($\text{Log } K_{ow} = -0.27$)²⁷. The equations that describe the fraction of the initial mass that is absorbed (or evaporated) are rather complex (Equations 20 and 21 of Kasting and Miller, 2006) but can be solved.

Small Doses (Case 1: $M_0 \leq M_{sat}$)

In the small dose scenario, the initial dose (M_0) is less than that required to saturate the upper layers of the *stratum corneum* ($M_0 \leq M_{sat}$), and the chemical is assumed to evaporate from the skin surface at a rate proportional to its local concentration.

²⁷ For simplification, Kasting and Miller (2006) does not consider the resistance of viable tissue layers underlying the stratum corneum, and the analysis is applicable to hydrophilic-to-moderately lipophilic chemicals. For small molecules, this limitation is equivalent to restricting the analysis to compounds where $\text{Log } K_{ow} \leq 3$ (in the current assessment $\text{Log } K_{ow} = -0.27$).

For this scenario, Frasch (2012) calculated the fraction of applied mass that is absorbed, based on the infinite limit of time (*i.e.*, infinite amount of time available for absorption after exposure):

Equation G-16

$$f_{abs} = \frac{m_{abs}(\infty)}{M_0} = \frac{2 + f\chi}{2 + 2\chi}$$

Where:

M_{abs} is the mass absorbed

M_0 is the initial mass applied

f is the relative depth of penetration in the *stratum corneum* ($f = 0.1$ can be assumed)

c is as previously defined

Note the simple algebraic solution in Equation G-16 provides a theoretical framework for the total mass that is systemically absorbed after exposure to a small finite dose (mass/area) of chemical, which depends on the relative rates of evaporation, permeation, and the initial load. At “infinite time”, the applied dose is either absorbed or evaporated (Frasch (2012)). The finite dose is a good model for *splash-type exposure in the workplace* (Frasch and Bunge (2015)).

The fraction of the applied mass that evaporates is simply the complement of that absorbed:

Equation G-17

$$\frac{m_{evap}(\infty)}{M_0} = 1 - f_{abs} = \frac{2\chi - f\chi}{2 + 2\chi}$$

Where:

m_{evap} is the mass evaporated

The fraction absorbed can also be represented as a function of dimensionless time τ (Dt/h^2), as shown in Equation G-18.

Equation G-18

$$f_{abs} = \frac{m_{abs}}{M_0} = 2 \sum_{n=1}^{\infty} \frac{1}{\lambda_n} (1 - e^{-\lambda_n^2 \tau}) \left(\frac{\chi^2 + \lambda_n^2}{\chi^2 + \lambda_n^2 + \chi} \right) \cdot \left(\frac{\cos(1-f)\lambda_n - \cos\lambda_n}{f \cdot \lambda_n} \right)$$

where the eigenvalues λ_n are the positive roots of the equation:

Equation G-19

$$\lambda_n \cdot \cot(\lambda_n) + \chi = 0$$

Equation G-18 and Equation G-19 must be solved analytically. It should be noted that the dimensionless time τ is not a representation of exposure duration for a work activity; rather, it represents the amount of time available for absorption after the initial exposure dose is applied. Since most dermal risk assessments are typically more concerned with the quantity absorbed, rather than the time course of absorption, the simple algebraic solution is recommended over the

analytical solution.

Large Doses (Case 2: $M_0 > M_{sat}$)

For large doses ($M_0 > M_{sat}$), the chemical saturates the upper layers of the stratum corneum, and any remaining amount forms a residual layer (or pool) on top of the skin. The pool acts as a reservoir to replenish the top layers of the membrane as the chemical permeates into the lower layer. In this case, absorption and evaporation approach steady-state values as the dose is increased, similar to an infinite dose scenario.

The steady-state fraction absorbed can be approximated by Equation G-20:

Equation G-20

$$f_{abs}(\infty) = \frac{1}{\chi + 1}$$

Table G-26 presents the estimated absorbed fraction calculated using the steady-state approximation for large doses (Equation G-20) for 1,4-dioxane.

Table G-26. Estimated Fraction Evaporated and Absorbed (fabs) using Equation G-20

Chemical Name	1,4-Dioxane
CASRN	123-91-1
Molecular Formula	C ₄ H ₈ O ₂
Molecular Weight (g/mol)	88.1
P _{Vp} (torr)	40
Universal gas constant, R (L*atm/K*mol)	0.0821
Temperature, T (K)	303
Log K _{ow}	-0.27
K _{oct}	0.5
S _w (g/L)	800
S _w (µg/cm ³)	800,000
<i>Industrial Setting</i>	
u (m/s) ^a	0.1674
Evaporative Flux, χ	0.28
<i>Fraction Evaporated</i>	0.22
<i>Fraction Absorbed</i>	0.78
<i>Commercial Setting</i>	
u (m/s) ^a	0.0878
Evaporative Flux, χ	0.17
<i>Fraction Evaporated</i>	0.14
<i>Fraction Absorbed</i>	0.86

^a EPA used air speeds from Baldwin and Maynard (1998): the 50th percentile of industrial occupational environments of 16.74 cm/s is used for industrial settings and the 50th percentile of commercial occupational environments of 8.78 cm/s is used for commercial settings.

G.7.3 Potential for Occlusion

Occlusion refers to skin covered directly or indirectly by impermeable films or substances. Chemical protective gloves are one of the most widely used forms of PPE intended to prevent skin exposure to chemicals. Gloves can prevent the evaporation of volatile chemicals from the skin. Chemicals trapped in the glove may be broadly distributed over the skin (increasing S in Equation G-13), or if not distributed within the glove, the chemical mass concentration on the skin at the site of contamination may be maintained for prolonged periods of time (increasing Q_u in Equation G-13). Conceptually, occlusion is similar to the “infinite dose” study design used in *in vitro* and *ex vivo* dermal penetration studies, in which the dermis is exposed to a large, continuous reservoir of chemical.

The protective measures could produce negative events due to the nature of occlusion, which

often causes stratum corneum hyper-hydration and reduces the protective barrier properties of the skin. Many gloves do not resist the penetration of low molecular weight chemicals: those chemicals may enter the glove and become trapped on the skin under occlusion for many hours. Breakthrough times for glove materials are often underestimates of the true breakthrough times, because the measurements do not consider increased temperature and flexing of the material during use, which is not accounted for in tests to determine breakthrough times. Occlusion by gloves raises skin temperature and hydration leading to a reduction in its natural barrier properties. The impact of occlusion on dermal uptake is complex: continuous contact with the chemical may degrade skin tissues, increasing the rate of uptake, but continuous contact may also saturate the skin, slowing uptake [Dancik et al. \(2015\)](#). Wearing gloves which are internally contaminated can lead to increased systemic absorption due to increased area of contact and reduced skin barrier properties, and repeated skin contact with chemicals can give higher than expected exposure if evaporation of the carrier occurs and the concentration in contact with the skin increases. These phenomena are dependent upon the chemical, the conditions of use and environmental conditions. It is probably not feasible to incorporate these sources of variability in a screening-level population model of dermal exposure without chemical-specific studies.

EPA does not expect occlusion scenarios to be a reasonable occurrence for all conditions of use. Specifically, occlusion is not expected at sites using chemicals in closed systems where the only potential of dermal exposure is during the connecting/disconnecting of hoses used for unloading/loading of bulk containers (*e.g.*, tank trucks or rail cars) or while collecting quality control samples including manufacturing sites, repackaging sites, sites processing the chemical as a reactant, formulation sites, and other similar industrial sites. Occlusion is also not expected to occur at highly controlled sites, such as pharmaceuticals manufacturing sites, where, due to purity requirements, the use of engineering controls is expected to limit potential dermal exposures. EPA also does not expect occlusion at sites where contact with bulk liquid chemical is not expected such as research laboratories where workers are only expected to handle the small quantities of the chemical in controlled environments and not the actual bulk liquid chemical.

G.7.4 Incorporating Glove Protection

Data about the frequency of effective glove use – that is, the proper use of effective gloves – is very limited in industrial settings. Initial literature review suggests that there is unlikely to be sufficient data to justify a specific probability distribution for effective glove use for a chemical or industry. Instead, the impact of effective glove use should be explored by considering different percentages of effectiveness (*e.g.*, 25% vs. 50% effectiveness).

Gloves only offer barrier protection until the chemical breaks through the glove material. Using a conceptual model, [Cherrie et al. \(2004\)](#) proposed a glove workplace protection factor – the ratio of estimated uptake through the hands without gloves to the estimated uptake through the hands while wearing gloves: this protection factor is driven by flux, and thus varies with time. The ECETOC TRA model represents the protection factor of gloves as a fixed, assigned protection factor equal to 5, 10, or 20 [Marquart et al. \(2017\)](#). Where, similar to the APR for respiratory protection, the inverse of the protection factor is the fraction of the chemical that penetrates the glove.

The protection afforded by gloves can be incorporated into the EPA model (Equation G-13) by modification of Q_u with a protection factor, PF (unitless, $PF \geq 1$):

Equation G-21

$$D_{exp} = S \times \frac{Q_u}{PF} \times Y_{derm} \times FT$$

Given the limited state of knowledge about the protection afforded by gloves in the workplace, it is reasonable to utilize the PF values of the ECETOC TRA model [Marquart et al. \(2017\)](#), rather than attempt to derive new values. Table G-27 presents the PF values from ECETOC TRA model (version 3). In the exposure data used to evaluate the ECETOC TRA model, Marquart et al. [2017](#)) reported that the observed glove protection factor was 34, compared to PF values of 5 or 10 used in the model.

Table G-27. Exposure Control Efficiencies and Protection Factors for Different Dermal Protection Strategies from ECETOC TRA v3

Dermal Protection Characteristics	Affected User Group	Indicated Efficiency (%)	Protection Factor, PF
a. Any glove / gauntlet without permeation data and without employee training	Both industrial and professional users	0	1
b. Gloves with available permeation data indicating that the material of construction offers good protection for the substance		80	5
c. Chemically resistant gloves (<i>i.e.</i> , as “b” above) with “basic” employee training		90	10
d. Chemically resistant gloves in combination with specific activity training (<i>e.g.</i> , procedure for glove removal and disposal) for tasks where dermal exposure can be expected to occur	Industrial users only	95	20

G.7.5 Proposed Dermal Dose Equation

Accounting for all parameters above, the proposed, overall equation for estimating dermal exposure is:

Equation G-22

$$D_{exp} = S \times \frac{(Q_u \times f_{abs})}{PF} \times Y_{derm} \times FT$$

EPA proposes to present exposure estimates for the following deterministic dermal exposure scenarios:

Dermal exposure without the use of protective gloves (Equation G-22, $PF = 1$)

Dermal exposure with the use of protective gloves (Equation G-22, $PF = 5$)

Dermal exposure with the use of protective gloves and employee training (Equation G-22, $PF = 20$ for industrial users and $PF = 10$ for professional users)

EPA assumes the following parameter values for Equation G-22 in addition to the parameter values presented in Table G-26:

S, the surface area of contact (cm²): 535 cm² (central tendency) and 1,070 cm² (high end), representing the total surface area of both hands.

Q_u, the quantity remaining on the skin: 1.4 mg/cm²-event (central tendency) and 2.1 mg/cm²-event (high end). These are the midpoint value and high-end of range value, respectively, used in the EPA/OPPT dermal contact with liquids models [U.S. EPA \(2013b\)](#).

Y_{derm}, the weight fraction of the chemical of interest in the liquid: EPA will assess a unique value of this parameter for each occupational scenario or group of similar occupational scenarios.

FT, the frequency of events: 1 event per day. Equation G-22 shows a linear relationship between FT and D_{exp}; however, this fails to account for time between contact events. Since the chemical simultaneously evaporates from and absorbs into the skin, the dermal exposure is a function of both the number of contact events per day and the time between contact events. EPA did not identify information on how many contact events may occur and the time between contact events. Therefore, EPA assumes a single contact event per day for estimating dermal exposures.

G.7.6 Equations for Calculating Acute and Chronic (Non-Cancer and Cancer) Dermal Doses

Equation E-12 estimates dermal potential dose rates (mg/day) to workers in occupational settings. The potential dose rates are then used to calculate acute retained doses (ARD), and chronic retained doses (CRD) for non-cancer and cancer risks.

Acute retained doses are calculated using Equation G

Equation G-23

$$ARD = \frac{D_{exp}}{BW}$$

Where:

ARD = acute retained dose (mg/kg-day)
D_{exp} = dermal potential dose rate (mg/kg)
BW = body weight (kg)

CRD is used to estimate exposures for non-cancer and cancer risks. CRD is calculated as follows:

Equation G-24

$$CRD = \frac{D_{exp} \times EF \times WY}{BW \times (AT \text{ or } AT_c)}$$

Equation G-25

$$AT = WY \times 365 \frac{\text{day}}{\text{yr}}$$

Equation G-26

$$AT_c = LT \times 365 \frac{\text{day}}{\text{yr}}$$

Where:

- CRD = Chronic retained dose used for chronic non-cancer or cancer risk calculations
- EF = Exposure frequency (day/yr)
- WY = Working years per lifetime (yr)
- AT = Averaging time (day) for chronic, non-cancer risk
- AT_c = Averaging time (day) for cancer risk
- LT = Lifetime years (yr) for cancer risk

Table XX summarizes the default parameter values used to calculate each of the above acute or chronic exposure estimates. Where multiple values are provided for EF, it indicates that EPA may have used different values for different conditions of use. The rationales for these differences are described below in this section.

Table G-28: Worker Exposure Parameters

Parameter Name	Symbol	Value	Unit
Exposure Frequency	EF	250 258 (50 th percentile) to 293 (95 th percentile) (dry cleaning only) 125 to 150 (DoD – oil analysis only) 30 to 36 (DoD – water pipe repair only)	days/yr
Working years	WY	31 (50 th percentile) 40 (95 th percentile)	years
Lifetime Years, cancer	LT	78	years
Body Weight	BW	80 (average adult worker) 72.4 (woman of childbearing age)	kg
Averaging Time, non-cancer	AT	11,315 (central tendency) ^a 14,600 (high-end) ^b	day
Averaging Time, cancer	AT _c	28,470	day

^a Calculated using the 50th percentile value for working years (WY)

^b Calculated using the 95th percentile value for working years (WY)

Exposure Frequency (EF)

EPA generally uses an exposure frequency of 250 days per year with two notable exceptions: dry cleaning and DoD uses. EPA assumed dry cleaners may operate between five and six days per week and 50 to 52 weeks per year resulting in a range of 250 to 312 annual working days per year (AWD). Taking into account fractional days exposed (*f*) resulted in an exposure frequency (EF) of 258 at the 50th percentile and 293 at the 95th percentile. For the two DoD uses, information was provided indicating process frequencies of two to three times per week (oil analysis) and two to three times per month (water pipe repair). EPA used the maximum frequency for high-end estimates and the midpoint frequency for central tendency estimates. For the oil analysis use this resulted in 125 days/yr at the central tendency and 150 days/yr at the high-end. For the water pipe repair, this resulted in 30 days/yr at the central tendency and 36 days/yr at the high-end.

EF is expressed as the number of days per year a worker is exposed to the chemical being assessed. In some cases, it may be reasonable to assume a worker is exposed to the chemical on each working day. In other cases, it may be more appropriate to estimate a worker's exposure to the chemical occurs during a subset of the worker's annual working days. The relationship between exposure frequency and annual working days can be described mathematically as follows:

Equation G-27

$$EF = f \times AWD$$

Where:

EF = exposure frequency, the number of days per year a worker is exposed to the chemical (day/yr)

f = fractional number of annual working days during which a worker is exposed to the chemical (unitless)

AWD = annual working days, the number of days per year a worker works (day/yr)

BLS [2016](#)) provides data on the total number of hours worked and total number of employees by each industry NAICS code. These data are available from the 3- to 6-digit NAICS level (where 3-digit NAICS are less granular and 6-digit NAICS are the most granular). Dividing the total, annual hours worked by the number of employees yields the average number of hours worked per employee per year for each NAICS.

EPA has identified approximately 140 NAICS codes applicable to the multiple conditions of use for the ten chemicals undergoing risk evaluation. For each NAICS code of interest, EPA looked up the average hours worked per employee per year at the most granular NAICS level available (*i.e.*, 4-digit, 5-digit, or 6-digit). EPA converted the working hours per employee to working days per year per employee assuming employees work an average of eight hours per day. The average number of days per year worked, or AWD, ranges from 169 to 282 days per year, with a 50th percentile value of 250 days per year. EPA repeated this analysis for all NAICS codes at the 4-digit level. The average AWD for all 4-digit NAICS codes ranges from 111 to 282 days per year, with a 50th percentile value of 228 days per year. 250 days per year is approximately the 75th percentile. In the absence of industry- and PCE-specific data, EPA assumes the parameter *f* is equal to one for all conditions of use except dry cleaning. Dry cleaning used a uniform

distribution from 0.8 to 1 for f . The 0.8 value was derived from the observation that the weighted average of 200 day/yr worked (from BLS/Census) is 80% of the standard assumption that a full-time worker works 250 day/yr. The maximum of 1 is appropriate as dry cleaners may be family owned and operated and some workers may work as much as every operating day.

Working Years (WY)

EPA has developed a triangular distribution for working years. EPA has defined the parameters of the triangular distribution as follows:

Minimum value: BLS CPS tenure data with current employer as a low-end estimate of the number of lifetime working years: 10.4 years;

Mode value: The 50th percentile tenure data with all employers from SIPP as a mode value for the number of lifetime working years: 36 years; and

Maximum value: The maximum average tenure data with all employers from SIPP as a high-end estimate on the number of lifetime working years: 44 years.

This triangular distribution has a 50th percentile value of 31 years and a 95th percentile value of 40 years. EPA uses these values for central tendency and high-end ADC and LADC calculations, respectively.

The BLS [2014](#)) provides information on employee tenure with *current employer* obtained from the Current Population Survey (CPS). CPS is a monthly sample survey of about 60,000 households that provides information on the labor force status of the civilian non-institutional population age 16 and over; CPS data are released every two years. The data are available by demographics and by generic industry sectors but are not available by NAICS codes.

The U.S. Census' [2016a](#)) Survey of Income and Program Participation (SIPP) provides information on *lifetime tenure with all employers*. SIPP is a household survey that collects data on income, labor force participation, social program participation and eligibility, and general demographic characteristics through a continuous series of national panel surveys of between 14,000 and 52,000 households [U.S. Census Bureau \(2016b\)](#). EPA analyzed the 2008 SIPP Panel Wave 1, a panel that began in 2008 and covers the interview months of September 2008 through December 2008 [U.S. Census Bureau \(2016a, b\)](#). For this panel, lifetime tenure data are available by Census Industry Codes, which can be cross-walked with NAICS codes.

SIPP data include fields for the industry in which each surveyed, employed individual works (TJBIND1), worker age (TAGE), and years of work experience *with all employers* over the surveyed individual's lifetime.²⁸ Census household surveys use different industry codes than the NAICS codes used in its firm surveys, so these were converted to NAICS using a published crosswalk [U.S. Census Bureau \(2016b\)](#). EPA calculated the average tenure for the following age

²⁸ To calculate the number of years of work experience EPA took the difference between the year first worked (TMAKMNYR) and the current data year (*i.e.*, 2008). EPA then subtracted any intervening months when not working (ETIMEOFF).

groups: 1) workers age 50 and older; 2) workers age 60 and older; and 3) workers of all ages employed at time of survey. EPA used tenure data for age group “50 and older” to determine the high-end lifetime working years, because the sample size in this age group is often substantially higher than the sample size for age group “60 and older”. For some industries, the number of workers surveyed, or the *sample size*, was too small to provide a reliable representation of the worker tenure in that industry. Therefore, EPA excluded data where the sample size is less than five from our analysis.

Table G-29 summarizes the average tenure for workers age 50 and older from SIPP data. Although the tenure may differ for any given industry sector, there is no significant variability between the 50th and 95th percentile values of average tenure across manufacturing and non-manufacturing sectors.

Table G-29: Overview of Average Worker Tenure from U.S. Census SIPP (Age Group 50+)

Industry Sectors	Working Years			
	Average	50 th Percentile	95 th Percentile	Maximum
All industry sectors relevant to the 10 chemicals undergoing risk evaluation	35.9	36	39	44
Manufacturing sectors (NAICS 31-33)	35.7	36	39	40
Non-manufacturing sectors (NAICS 42-81)	36.1	36	39	44

Source: Census Bureau, 2016a.

Note: Industries where sample size is less than five are excluded from this analysis.

BLS CPS data provides the median years of tenure that wage and salary workers had been with their current employer. **Table G-30** presents CPS data for all demographics (men and women) by age group from 2008 to 2012. To estimate the low-end value on number of working years, EPA uses the most recent (2014) CPS data for workers age 55 to 64 years, which indicates a median tenure of 10.4 years with their current employer. The use of this low-end value represents a scenario where workers are only exposed to the chemical of interest for a portion of their lifetime working years, as they may change jobs or move from one industry to another throughout their career.

Table G-30: Median Years of Tenure with Current Employer by Age Group

Age	January 2008	January 2010	January 2012	January 2014
16 years and over	4.1	4.4	4.6	4.6
16 to 17 years	0.7	0.7	0.7	0.7
18 to 19 years	0.8	1.0	0.8	0.8
20 to 24 years	1.3	1.5	1.3	1.3

25 years and over	5.1	5.2	5.4	5.5
25 to 34 years	2.7	3.1	3.2	3.0
35 to 44 years	4.9	5.1	5.3	5.2
45 to 54 years	7.6	7.8	7.8	7.9
55 to 64 years	9.9	10.0	10.3	10.4
65 years and over	10.2	9.9	10.3	10.3

Source: BLS, 2014b.

Lifetime Years (LT)

EPA assumes a lifetime of 78 years for all worker demographics.

Body Weight (BW)

EPA assumes a body weight of 80 kg for all average worker demographics and 72.4 kg for women of childbearing age.

Appendix H CONSUMER EXPOSURES

For additional consumer modeling support files, please see the following supplemental documents: *Supplemental Analysis to the Draft Risk Evaluation for 1,4-Dioxane - Consumer Exposure Assessment Model Input Parameters*; *Supplemental Analysis to the Draft Risk Evaluation for 1,4-Dioxane - Exposure Modeling Results and Risk Estimates for Consumer Exposures*.

H.1 Consumer Inhalation Exposure

H.1.1 CEM 2.1 and CEM

The Consumer Exposure Models ([CEM 2.1](#) and [CEM within E-FAST 2014](#)) predict indoor air concentrations from consumer product use by implementing a deterministic, mass-balance calculation utilizing an emission profile determined by implementing appropriate emission scenarios. The model uses a two-zone representation of the building of use (*e.g.*, residence, school, office), with Zone 1 representing the room where the consumer product is used (*e.g.*, a utility room) and Zone 2 being the remainder of the building. The product user is placed within Zone 1 for the duration of use, while a bystander is placed in Zone 2 during product use. Otherwise, product users and bystanders follow prescribed activity patterns throughout the simulated period. Each zone is considered well-mixed. Product users are exposed to airborne concentrations estimated within the near-field during the time of use and otherwise follow their prescribed activity pattern. Bystanders follow their prescribed activity pattern and are exposed to far-field concentrations when they are in Zone 1. Background concentrations can be set to a non-zero concentration if desired.

The general steps of the calculation engine within the CEM models include:

- Introduction of the chemical (*i.e.*, 1,4-dioxane) into the room of use (Zone 1) through two possible pathways: (1) overspray of the product or (2) evaporation from a thin film;
- Transfer of the chemical to the rest of the house (Zone 2) due to exchange of air between the different rooms;
- Exchange of the house air with outdoor air; and
- Compilation of estimated air concentrations in each zone as the modeled occupant (*i.e.*, user or bystander) moves about the house per prescribed activity patterns.

For acute exposure scenarios, emissions from each incidence of product usage are estimated over a period of 72 hours using the following approach that accounts for how a product is used or applied, the total applied mass of the product, the weight fraction of the chemical in the product, and the molecular weight and vapor pressure of the chemical. Time weighted averages (TWAs) were then computed based on these user and bystander concentration time series per available human health hazard data. For 1,4-dioxane, 8-hour TWAs were quantified for use in risk evaluation based on alignment of relevant acute human health hazard endpoints. For additional details on CEM 2.1's underlying emission models, assumptions, and algorithms, please see the User Guide Section 3: Detailed Descriptions of Models within CEM 2.1 [U.S. EPA \(2019a\)](#). The emission models used have been compared to other model results and measured data; see Appendix D: Model Corroboration of the User Guide Appendices for the results of these analyses [U.S. EPA \(2019b\)](#).

For chronic exposure scenarios, CEM within E-FAST 2014 was used to obtain lifetime average daily concentrations (LADCs) for the scenarios involving chronic exposures. Emissions are estimated over a period of 60 days. For cases where the evaporation time estimated exceeds 60 days, the model will truncate the emissions at 60 days. Conversely, for cases where the evaporation time is less than 60 days, emissions will be set to zero between the end of the evaporation time and 60 days. For more information on this version of CEM and its chronic inhalation estimates, refer to the [E-FAST 2014 Documentation Manual \(U.S. EPA, 2007\)](#).

Emission Models in CEM 2.1

Based on the suite of product scenarios developed to evaluate the 1,4-dioxane consumer conditions of use, the specific emission models applied for the purposes of this evaluation include: E1: Emission from Product Applied to a Surface Indoors Incremental Source Model and E4: Emission from Product Added to Water.

Product Scenarios in CEM

Based on the suite of product scenarios developed to evaluate the 1,4-dioxane consumer conditions of use, the specific models applied for the purposes of this evaluation include: Product Applied to Surface – Incremental Source Model and Product Added to Water – Constant Rate Model.

CEM 2.1's E1 model and CEM's Product Applied to Surface – Incremental Source Model are analogous and are generally applicable for liquid products applied to a surface such as cleaners. These emission models assume a constant application rate over a user-specified duration of use and an emission rate that declines exponentially over time, at a rate that depends on the chemical molecular weight and vapor pressure.

CEM 2.1's E4 model and CENM's Product Added to Water – Constant Rate Model assume emission at a constant rate over a duration that depends on the chemical's molecular weight and vapor pressure. If this estimated duration is longer than the user-specified duration of use, chemical emissions are truncated at the end of the product use period and the remaining chemical mass is assumed to go down the drain. These emission models are applied for use scenarios such as laundry and dishwashing detergent, dish soap, and textile dye.

H.1.2 MCCEM

The Multi-Chamber Concentration and Exposure Model (MCCEM) estimates indoor air concentrations of chemicals released from household products [EPA \(2010\)](#). It uses air infiltration and interzonal air flow rates with user-input emission rates to calculate time-varying concentrations in several zones or chambers within a residence. Four types of source models are available in MCCEM – constant, single exponential, incremental, and data entry. For additional details, see the MCCEM User Guide [EPA \(2019c\)](#).

Within MCCEM, the incremental source model is specifically designed for products that are applied to a surface (as SPF is) rather than products that are placed in an environment (*e.g.*, an air freshener). This distinction is important because the incremental source model considers the time or duration of application or use in its calculations of emissions and concentrations, while

the single exponential source model does not. The incremental model assumes a constant application rate over time, coupled with an emission rate for each instantaneously applied segment that declines exponentially. The equation for the time-varying emission rate resulting from the combination of constant application and exponentially declining emissions ([Evans, 1996](#)) utilized in the single exponential incremental model is shown below. This is a simplification of the overall incremental model in MCCEM that considers two emission decay constants and rates to capture emissions from both the evaporation and diffusion phases. However, the SPF scenario is better modeled by a single decay constant after application.

$$ER(t) = \frac{M \times WF \times CF}{t_a} \times \left[(1 - e^{-k(t-t_{start})}) - \left((1 - e^{-k(t-(t_{start}+t_a))}) \times H(t) \right) \right]$$

Where:

$ER(t)$	=	Emission rate at time t (mg/min)
M	=	Mass of product used (g)
WF	=	Weight fraction of chemical in product (unitless)
CF	=	Conversion factor (1000 mg/g)
t_{start}	=	Time of start of application (min)
t_a	=	Application time (min)
k	=	First-order rate constant for emissions decline (min^{-1})
t	=	Time (min)
$H(t)$	=	0/1 value used to indicate if product is actively in use
	=	0 if $t - (t_{start} + t_a) < 0$
	=	1 if $t - (t_{start} + t_a) > 0$

The incremental model can be populated using experimental data and proposed model of emission rates in [Karlovich et al. 2011b](#)). In this study, the authors measured air concentrations of 1,4-dioxane after taking samples from an open-cell SPF product applied to a cardboard box and placed in a small-scale environmental chamber. These concentrations were used to develop a mathematical relationship between the emission factor and loading factor based on the volume and airflow of the chamber.

$$EF = \frac{C_{chamber}}{LF \times ACH}$$

Where:

EF	=	Emission Factor ($\mu\text{g}/\text{m}^2\text{-hr}$)
$C_{chamber}$	=	Chamber concentration ($\mu\text{g}/\text{m}^3$)
LF	=	Loading factor (m^2/m^3)
ACH	=	air changes per hour

Based on the chamber air flow rate, foam sample surface area, and indoor air assumptions, the above equation can be reworked to find predicted air concentrations:

$$C_{air, predicted} = \frac{EF \times 0.5}{0.3}$$

The concentration data can be used to determine decay rates by fitting the data to a time series concentration function associated with MCCEM's incremental model. The general mass-balance equation for a test chamber can be integrated assuming an initial concentration of zero to the following:

$$C(t) = \frac{E_0}{V \left(\frac{Q}{V} - k \right)} \times (e^{-kt} - e^{-\frac{Q}{V}t})$$

Where:

$C(t)$	=	Concentration ($\mu\text{g}/\text{m}^3$)
E_0	=	Initial emission rate ($\mu\text{g}/\text{hr}$)
V	=	Volume of the chamber (m^3)
Q	=	Airflow rate into and out of the chamber (m^3/hr)
k	=	First-order rate constant (hr^{-1})
t	=	Time (hr)

Karlovich et al. [2011b](#)) collected air samples 4, 12, 24, and 48 hours after placing the sample in the chamber. Predicted indoor air concentrations (1,479, 663, 201, and 40 $\mu\text{g}/\text{m}^3$, respectively) were fitted to the concentration equation above to identify the initial emission rate and decay constant, 73.868 $\mu\text{g}/\text{hr}$ and 0.1 hr^{-1} , respectively. The emission rate was normalized to the applied surface area of SPF in the study (25 square inches) to find an emission rate per square inch of SPF applied, 2.955 $\mu\text{g}/\text{in}^2/\text{hr}$. This initial emission rate and decay constant can then be scaled appropriately to find the total mass applied in each application setting (attic, basement, and garage).

H.1.2.1 MCCEM Inputs for SPF Scenario

Product and Exposure Settings

The suggested values for house volume (492 m^3) and air exchange rate (0.45 ACH) are central values from the Exposure Factors Handbook ([EPA, 2011](#)). A two-story house is assumed for all cases. The attic volume is assumed to be half the volume of one story, or 123 m^3 . The basement volume is assumed to be the volume of one story, or 246 m^3 . The assumed garage volume (118 m^3) is the average volume of one- and two-car garages in 15 single-family homes with attached garages, as reported by [Batterman et al. 2007](#). The attic and garage are assumed to be outside of the standard house volume as they are not modeled to be conditioned or finished.

- For the attic scenario, interzonal airflow rates were applied based on measured air change rates at a variety of temperatures and wind speeds for vented and unvented attics ([Walker et al. 2005](#)). The central measured value at wind speeds of 2-3 m/s was about 1.5 air changes per hour (ACH) for the unvented attic and about 6.0 ACH for the vented. The latter case is used in this scenario as most US homes are assumed to have vented attics. When multiplied by the volume of the attic, this 6.0 ACH rate corresponds to an interzonal airflow rate of 738 m^3/hr between the attic and outdoors. Walker et al. also considered the airflow between unconditioned attics and the remainder of the houses, measuring an average of about 0.125 ACH at standard temperatures of 20-25°C. This corresponds to an interzonal airflow rate of 61.5 m^3/hr between the attic and the rest of the house (ROH). The suggested value of 0.45

ACH was applied for the rest of the house and outdoors, corresponding to an interzonal airflow rate of 221.4 m³/hr.

- For the basement scenario, interzonal airflow rates were applied using an algorithm developed in a study estimating the distributions for residential air exchange rates ([Koontz and Rector, 2005](#)). The estimated interzonal airflow rate between both basements and garages is estimated at 109 m³/hr. The suggested value of 0.45 ACH was applied for the rest of the house and outdoors, corresponding to an interzonal airflow rate of 110.7 m³/hr.
- For the garage scenario, interzonal airflow rates were informed by the results of a study measuring the airtightness of garages on a variety of homes under induced pressurized conditions ([Emmerich et al. 2003](#)). The average airtightness measured with the blower door was 48 ACH at 50 Pa, which corresponds to an air exchange rate of about 2.5 ACH and 295 m³/hr under normal conditions. The suggested value of 0.45 ACH was applied for the rest of the house and outdoors, corresponding to an interzonal airflow rate of 221.4 m³/hr.

A typical floor or ceiling loading ratio of 0.41 m²/ m³ (*i.e.*, for a ceiling height of 2.44 m; EPA, 2011), when multiplied by the upstairs volume of 246 m³, gives an estimated attic floor area of 100.9 m² (1086 sq. feet or 156,384 sq. inches). The same ratio applies to the garage ceiling, giving an estimated area of 48.4 m² (521 sq. feet or 75,024 sq. inches) when multiplied by the garage volume of 118 m³. The basement volume (246 m³) and ceiling height (2.44 m) indicate a floor area of 100.8 m², corresponding to dimensions of 7.9 m by 12.8 m. The wall area is 2.44 m x (7.9 m x 2 + 12.8 m x 2) = 101 m² or 1087 sq. ft. or 156,528 sq. inches. These areas of application surface were multiplied by the emission rate per square inch over the decay rate per hour to determine the total mass of 1,4-dioxane released in each setting: 4523.752659 mg in the attic, 4527.918177 mg in the basement, and 2170.234931 mg in the garage.

Use Patterns and Exposure Factors

An installation rate of 3 sq. ft./min or 180 sq. ft./hour is assumed, based on an [instructional video for DIY spray foam insulation installation](#). Corresponding estimates for the duration of installation are 6 hours for the attic floor, 6 hours for basement walls, and 3 hours for the garage ceiling. Each application was modeled to start at 9 AM. It is assumed that the user would be in the room of use during the time of application and in the rest of the house for the remainder of the model run. This assumption of staying at home produces a conservative estimate of exposure. Bystander exposure is based on the assumption that the bystander is home during the application period but spends the entire time in the rest of the house and no time in the room of use. In MCCEM, a breathing rate of 15.083 m³/day was estimated based on the recommended mean long-term exposure inhalation values in the 2011 Exposure Factors Handbook ([EPA, 2011](#)).

H.2 Consumer Dermal Exposure

Two models were used to evaluate consumer dermal exposures, the Fraction Absorbed model (P_DE2a within CEM) and the Permeability model (P_DER2b within CEM). A brief comparison of these two dermal models through the calculation of acute dose rates (ADRs) is provided below. They have been applied to distinct exposure conditions, with the permeability model applied to scenarios likely to involve occluded dermal contact where evaporation may be inhibited and the fraction absorbed model applied to scenarios less likely to involve occluded dermal contact.

The dermal models described below were run for all consumer conditions of use to provide a comparison between the two results while recognizing each model is unique in its approach to estimating dermal exposure and may not be directly comparable. Keeping these limitations in mind, the full suite of exposure results from both models is shown for all conditions of use in *Supplemental Analysis to the Draft Risk Evaluation for 1,4-Dioxane - Exposure Modeling Results and Risk Estimates for Consumer Exposures.xlsx*.

Because neither model considers the mass of chemical as an input in the absorbed dose equations, both have the potential to overestimate the dermal absorption by modeling a mass which is larger than the mass used in a scenario. Therefore, when utilizing either of the CEM models for dermal exposure estimations, a mass check is necessary outside of the CEM model to make sure the mass absorbed does not exceed the typical mass used for a given scenario.

CEM Absorption Fraction Model (P_DER2a)

The fraction absorbed model estimates the mass of a chemical absorbed through the application of a fractional absorption factor to the mass of chemical present on or in the skin following a use event. The initial dose or amount retained on the skin is determined using a film thickness approach. A fractional absorption factor is then applied to estimate the absorbed dose from the initial dose. The fraction absorbed is essentially the measure of two competing processes, evaporation of the chemical from the skin surface and penetration deeper into the skin. It can be estimated using an empirical relationship based on Frasch and Bunge (2015). Due to the model's consideration of evaporative processes, dermal exposure under unimpeded exposure conditions was considered to be more representative. For additional details on this model, please see Appendix H and the CEM User Guide Section 3: Detailed Descriptions of Models within CEM (U.S. EPA, 2019a).

The acute form of the absorption fraction model is given below:

$$ADR = \frac{AR \times F_{abs} \times \frac{SA}{BW} \times FQ_{ac} \times Dil \times WF \times ED_{ac} \times CF_1}{AT_{ac}}$$

Where:

- ADR = Acute daily dose rate (mg/kg-day)
- AR = Amount retained in the skin (g/cm², film thickness [cm] multiplied by product density)
- F_{abs} = Absorption fraction (see below)
- D_{ac} = Duration of use (min/event)
- SA/BW = Surface area to body weight ratio (cm²/kg)
- FQ_{ac} = Frequency of use (events/day, 1 for acute exposure scenarios)
- Dil = Product dilution fraction (unitless)
- WF = Weight fraction of chemical in product (unitless)
- ED_{ac} = Exposure duration (1 day for acute exposure scenarios)
- CF1 = Conversion factor (1,000 mg/g)
- AT_{cr} = Averaging time (1 day for acute exposure scenarios)

The fraction absorbed (F_{abs}) term is estimated using the ratio of evaporation from the stratum corneum to the dermal absorption rate through the stratum corneum, as informed by gas phase

mass transfer coefficient, vapor pressure, molecular weight, water solubility, real gas constant, and permeability coefficient.

$$FR_{abs} = \frac{3 + \chi \left[1 - \exp\left(-a \frac{D_{ac}}{t_{lag} \times CF_1}\right) \right]}{3(1 + \chi)}$$

Where:

- χ = Ratio of the evaporation rate from the stratum corneum (SC) to the dermal absorption rate
- a = Constant (2.906)
- D_{ac} = Duration of use (min/event)
- t_{lag} = Lag time for chemical transport through SC (hr)
- CF_1 = Conversion factor (60 min/hr)

The chronic form of the dermal absorption fraction model is given below:

$$LADD = \frac{AR \times F_{abs} \times \frac{SA}{BW} \times FQ_{cr} \times Dil \times WF \times ED_{cr} \times CF_1}{AT_{cr} \times CF_2}$$

Where:

- LADD = Lifetime average daily dose (mg/kg-day)
- D_{cr} = Duration of use (min/event)
- FQ_{cr} = Frequency of use (events or days/year)
- ED_{cr} = Exposure duration (57 years)
- CF_2 = Conversion factor (365 days/yr)
- AT_{cr} = Averaging time (78 years)

CEM Permeability Model (P_DER2b)

The permeability model estimates the mass of a chemical absorbed and dermal flux based on a permeability coefficient (K_p) and is based on the ability of a chemical to penetrate the skin layer once contact occurs. It assumes a constant supply of chemical directly in contact with the skin throughout the exposure duration. K_p is a measure of the rate of chemical flux through the skin. The parameter can either be specified by the user (if measured data are reasonably available) or be estimated within CEM using a chemical's molecular weight and octanol-water partition coefficient (K_{OW}). The permeability model does not inherently account for evaporative losses (unless the available flux or K_p values are based on non-occluded, evaporative conditions), which can be considerable for volatile chemicals in scenarios where evaporation is not impeded. While the permeability model does not explicitly represent exposures involving such impeded evaporation, the model assumptions make it the preferred model for an such a scenario. For additional details on this model, please see Appendix H and the CEM User Guide Section 3: Detailed Descriptions of Models within CEM ([U.S. EPA, 2019a](#)).

The acute form of the dermal permeability model is given below:

$$ADR = \frac{K_p \times D_{ac} \times \rho \times \frac{SA}{BW} \times FQ_{ac} \times Dil \times WF \times ED_{ac} \times CF_1}{AT_{ac} \times CF_2}$$

Where:

ADR	= Potential acute dose rate (mg/kg-day)
K_p	= Permeability coefficient (cm/hr)
D_{ac}	= Duration of use (min/event)
ρ	= Density of formulation (g/cm ³)
SA/BW	= Surface area to body weight ratio (cm ² /kg)
FQ_{ac}	= Frequency of use (events/day, 1 for acute exposure scenarios)
Dil	= Product dilution fraction (unitless)
WF	= Weight fraction of chemical in product (unitless)
ED_{ac}	= Exposure duration (1 day for acute exposure scenarios)
CF1	= Conversion factor (1,000 mg/g)
CF2	= Conversion factor (60 min/hr)
AT_{ac}	= Averaging time (1 day for acute exposure scenarios)

The chronic form of the dermal permeability model is given below:

$$LADD = \frac{K_p \times D_{cr} \times \rho \times \frac{SA}{BW} \times FQ_{cr} \times Dil \times WF \times ED_{cr} \times CF_1}{AT_{cr} \times CF_2 \times CF_3}$$

Where:

LADD	= Lifetime average daily dose (mg/kg-day)
D_{cr}	= Duration of use (min/event)
FQ_{cr}	= Frequency of use (events or days/year)
ED_{cr}	= Exposure duration (57 years)
CF3	= Conversion factor (365 days/yr)
AT_{cr}	= Averaging time (78 years)

H.3 Measured Emission Data

Systematic review identified several studies reporting emission rates or chamber emission concentrations of 1,4-dioxane from spray foam and paint samples. These emission data are summarized below. These data are not directly comparable to the predicted 8-hr TWAs presented for consumer exposure scenarios, as the 8-hr TWAs are zone-integrated to account for the activity patterns of the user or bystander (*i.e.*, the presented TWAs account for a user or bystander's movement throughout the house – Zones 1 and 2 – for the 8-hr period).

As described above, Karlovich et al. [2011b](#)) identified 1,4-dioxane in emissions from a two-component open-cell SPF hours and days after application. Chamber concentrations and emission factors were calculated from these sampling results. The emission factors were then used to predict indoor air concentrations (1,479, 663, 201, and 40 µg/m³ for samples measured at 4, 12, 24, and 48 hours, respectively).

Naldzhiev et al. [2019](#)) analyzed volatile organic compound presence in and emissions from three spray foam insulation products. Authors measured 1,4-dioxane in a two-component closed-cell SPF product, both in the raw material (*i.e.*, mixed spray foam, pre-application) and in the headspace from the cured foam. Air concentrations were not reported, but findings confirm 1,4-dioxane's presence in closed-cell SPF products. 1,4-Dioxane was not detected in the other two products tested including a commercially available, two-component closed-cell spray foam and a commercially available, one-component spray foam.

Poppendieck et al. [2017](#)) reported concentrations of 1,4-dioxane in micro-chamber air sampling of a high-pressure closed-cell spray foam. Initial concentrations (*i.e.*, at sampling time 0) were just above $100 \mu\text{g}/\text{m}^3$ and fell below $50 \mu\text{g}/\text{m}^3$ after roughly 48 hours of sampling. In the authors' related final report [Poppendieck \(2017\)](#), additional 1,4-dioxane chamber concentrations were reported for a "non-ideal" closed-cell spray foam. The non-ideal foam samples were submitted by the Consumer Product Safety Commission (CPSC) to reflect non-ideal preparation or application conditions such as off-ratio mixing of two-component foams, low substrate temperature, and incorrect nozzle pressure or temperature. Chamber concentrations measured from the non-ideal closed-cell foam were higher, falling between 500 and $1,000 \mu\text{g}/\text{m}^3$ at sampling time 0, $\sim 500 \mu\text{g}/\text{m}^3$ at 48 hours, and falling below $250 \mu\text{g}/\text{m}^3$ around 175 hours.

Won et al. [2014](#)) tested 30 building materials for 121 VOCs and reported measured chamber concentrations and emission factors for 1,4-dioxane in two of the product types covered in this consumer evaluation: foam insulation and paint. Chamber concentrations of 1,4-dioxane from various insulation products ranged from 0.25 to $44.68 \mu\text{g}/\text{m}^3$ at six hours, with the highest level measured from a two-component, closed-cell foam. Chamber concentrations of 1,4-dioxane from various paint products ranged from 0.80 to $1.74 \mu\text{g}/\text{m}^3$ at six hours, with the highest level measured from an interior latex paint. Study authors cite mean emission rates of $15.72 \mu\text{g}/\text{m}^2/\text{hr}$ and $1.97 \mu\text{g}/\text{m}^2/\text{hr}$ for insulation and paint, respectively.

The Danish EPA's 2018 Survey and Risk Assessment of Chemical Substances in Chemical Products Used for "Do-It-Yourself" Projects in the Home [EPA \(2018a\)](#) measured respiratory zone concentrations during a realistic use of specific products in a test room and then measured subsequent emissions in a climate chamber after five hours, three days, and 28 days. During application of water-based, two-component epoxy floor paint, respiratory zone levels of 1,4-dioxane were $220 \mu\text{g}/\text{m}^3$. At five hours, levels decreased to $21 \mu\text{g}/\text{m}^3$. In a 2020 follow-up survey, the Danish EPA [2019a](#)) tested additional products and reported chamber concentrations of 1,4-dioxane from two-component paint and lacquer ranging from 7 to $460 \mu\text{g}/\text{m}^3$ at five hours. Following application of floor polish, levels of 1,4-dioxane were measured at $68\text{-}70 \mu\text{g}/\text{m}^3$ at five hours.

Although measured chamber or test room concentrations are not directly comparable to the 8-hr TWAs estimated for the various consumer exposure scenarios, on the whole, these emission studies bolster confidence in the predicted air concentrations for the SPF and paint and floor lacquer conditions of use.

The predicted 8-hr TWAs for SPF range from 160 to $890 \mu\text{g}/\text{m}^3$ for users. These predicted estimates fall within the range predicted in Karlovich et al., [2011b](#)) for samples measured at four and 12 hours. Poppendieck et al. [2017](#)) also reported measured air concentrations that encompass the modeled consumer exposure estimates, with concentrations from non-ideal closed-cell spray foam ranging from 500 to $1,000 \mu\text{g}/\text{m}^3$ over the first 48 hours. Won et al. [2014](#)) reported levels of 1,4-dioxane well below the CEM 2.1 predictions, from 0.25 to $44.68 \mu\text{g}/\text{m}^3$ at six hours for various insulation products including foam board and two-component open- and closed-cell spray foams.

The predicted 8-hr TWA for paint and floor lacquer is 20 $\mu\text{g}/\text{m}^3$ for users, which is roughly one order of magnitude greater than concentrations measured in Won et al. (2014) (0.8 – 1.74 $\mu\text{g}/\text{m}^3$ at six hours), but aligns with the Danish EPA’s measured air concentration five hours after application of the two-component epoxy floor paint (21 $\mu\text{g}/\text{m}^3$) (EPA (2018a)). The predicted TWA also falls within the range of air concentrations taken five hours after application in the Danish EPA’s 2020 Follow-Up study, which reported levels from 7 to 460 $\mu\text{g}/\text{m}^3$ at five hours.

H.4 CEM Model Sensitivity Analysis Summary

The CEM 2.1 developers conducted a detailed sensitivity analysis for CEM, as described in Appendix C of the CEM User Guide (U.S. EPA (2019b)). The CEM developers included results of model corroboration analysis in Appendix D of the CEM User Guide (U.S. EPA (2019b)).

In brief, the analysis was conducted on continuous variables and categorical variables that were used in CEM emission or dermal models. A base run of different CEM models using various product or article categories, along with CEM defaults, was used. Individual variables were modified, one at a time, and the resulting Acute Dose Rate (ADR) and Chronic Average Daily Dose (CADD) were compared to the corresponding results for the base run. Benzyl alcohol, a VOC, was used as an example for product models such as those applied in this evaluation of 1,4-dioxane.

The tested model parameters were increased by 10%. The measure of sensitivity for continuous variables such as mass of product used, weight fraction, and air exchange rate was “elasticity,” defined as the ratio of percent change in each result to the corresponding percent change in model input. A positive elasticity indicates that an increase in the model parameter resulted in an increase in the model output, whereas a parameter with negative elasticity is associated with a decrease in the model output. For categorical variables such as receptor activity pattern (*i.e.*, work schedule) and room of use, the percent difference in model outputs for different category pairs was used as the measure of sensitivity.

The results are summarized below for the inhalation and dermal models used to evaluate consumer exposures to 1,4-dioxane (*i.e.*, emission models E1 and E3 and the dermal permeability model P_DER2b). For full results and additional background, refer to Appendix C of the CEM User Guide (U.S. EPA (2017b)).

H.4.1 Continuous Variables

For acute exposures generated from emission model E1, WF (weight fraction) and M_acute (mass of product used) have the greatest positive elasticities of the tested parameters. The next most sensitive parameters demonstrate negative elasticity and include: Vol_Building (building volume); AER_Zone2 (air exchange rate in Zone 2); AER_Zone1 (air exchange rate in Zone 1); Vol_Zone1 (room of use, or Zone 1 volume). Inhalation exposures from liquid products applied to surface such as surface cleaner were modeled using E1.

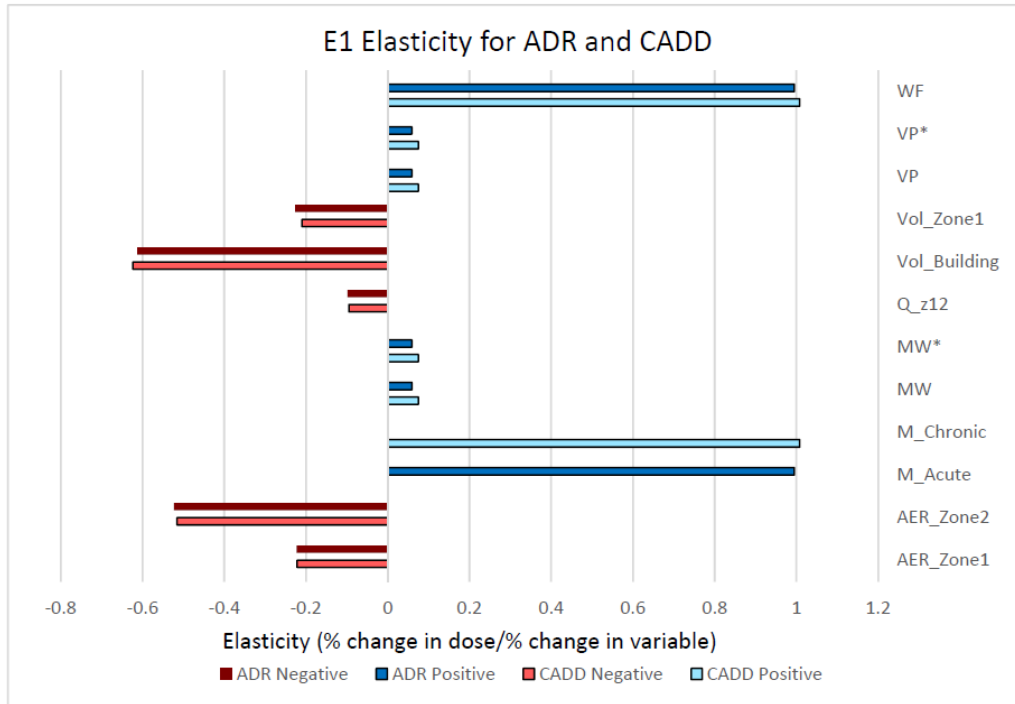


Figure H-1. Elasticities (≥ 0.05) for Parameters Applied in E1

For acute exposures generated from emission model E4, WF (weight fraction), M_acute (mass of product used), VP (vapor pressure), and MW (molecular weight) have the greatest positive elasticities of the tested parameters. The next most sensitive parameters demonstrate negative elasticity and include: Vol_Zone1 (room of use volume); Qz12 (interzonal ventilation rate); Vol_Building (building volume); AER_Zone2 (air exchange rate in Zone 2); AER_Zone1 (air exchange rate in Zone 1). Inhalation exposures from products added to water such as laundry detergent and dish soap were modeled using E4.

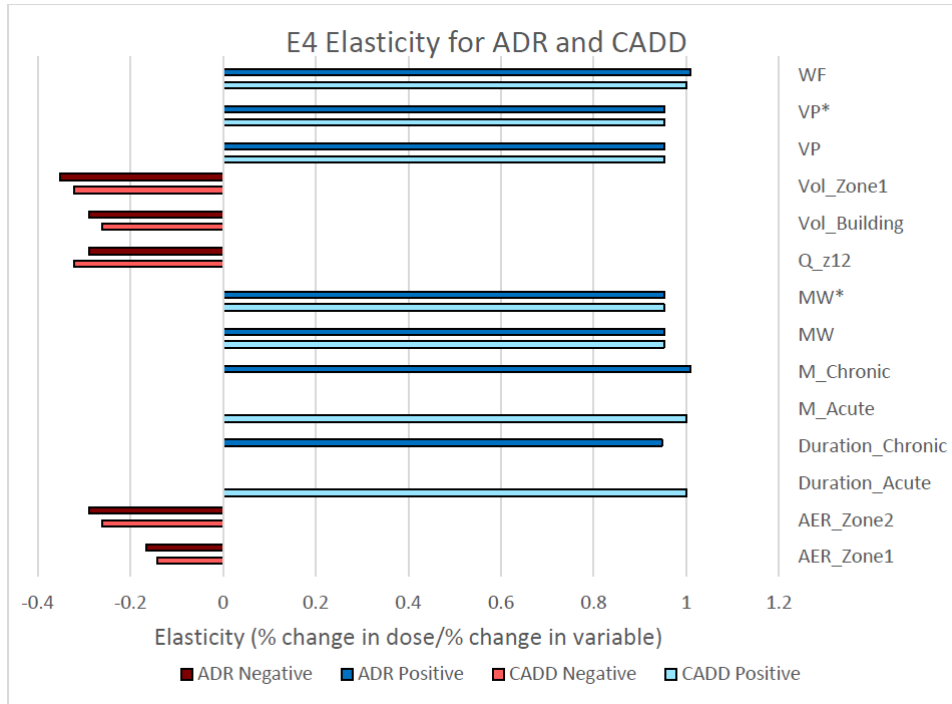


Figure H-2. Elasticities (≥ 0.05) for Parameters Applied in E4

For acute exposures generated from the dermal permeability model, the chemical properties that inform absorption rate, or absorption rate estimates, have the greatest elasticities. For 1,4-dioxane, dermal exposures from consumer product formulations were modeled using a measured Kp (permeability coefficient). Therefore, LogK_{OW} (octanol/water partition coefficient) and MW (molecular weight) were not used to estimate skin penetration.

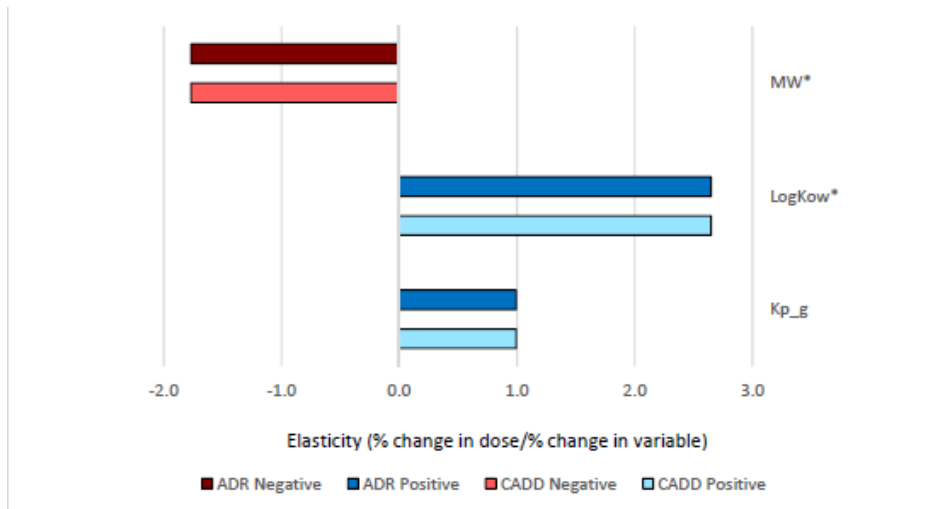


Figure H-3. Elasticities (≥ 0.05) for Parameters Applied in P_DER2b

H.4.2 Categorical Variables

For categorical variables there were multiple parameters that affected other model inputs. For example, varying the room type changed the ventilation rates, volume size and the amount of time per day that a person spent in the room. Thus, each modeling result was calculated as the percent difference from the base run. Among the categorical variables, the most sensitive parameters included receptor type (adult vs. child), room of use (Zone 1) selection, and application of the near-field bubble within Zone 1. However, these types of variables were held constant within a given product modeling scenario and were applied using consistent assumptions across all modeling scenarios.

Appendix I HUMAN HEALTH HAZARDS

I.1 Hazard and Data Quality Summary Tables by study duration/endpoint

I.1.1 Hazard and Data Evaluation Summary for Human Studies

Target Organ/System	Outcome/ Endpoint	Study Population	Exposure	Results	Reference	Data Quality Evaluation
ADME/PBPK	Half-lives of 1,4-dioxane determined in plasma and urine	4 Caucasian males, ages 40-49, scientists and businessmen at Dow Chemical, Freeport, Texas	Subjects exposed to 50ppm 1,4-dioxane in air for 6 hrs	Half-life determined for 1,4-D in plasma, statistical significance relative to an unexposed population is not applicable	Young et al. (1977)	Medium
Cancer	Breast cancer incidence	Participants in the California Teacher Study cohort, 1995-2011, (n=112,378 women)	National-Scale Air Toxics Assessment Modeled air concentrations	No significant association between breast cancer incidence and 1,4-D exposure	Garcia et al. (2015)	High

I.1.2 Hazard and Data Quality Evaluation Summary for Acute and Short-Term Studies

The acute, short-term table focuses on a single NOAEL or LOAEL per study with footnotes related to other effects measured/observed.

Target Organ/System ¹	Study Type	Species/ Strain/Sex (Number/group)	Exposure Route	Doses/ Concentrations ^a	Duration	Effect Dose or Concentration (NOAEL, LOAEL, LC ₅₀) (mg/m ³ or mg/kg-bw/day) (Sex)	Effect	Reference	Data Quality Evaluation
Hepatic	Acute	Rat, CD-1, M (n= unknown treated and controls)	Inhalation, vapor, whole-body	3603 or 7207 mg/m ³ (1000 or 2000 ppm)	4 hours	LOAEC = 3603 mg/m ³ (M)	Increased serum liver enzymes	Drew et al. (1978)	Medium

Target Organ/System ¹	Study Type	Species/Strain/Sex (Number/group)	Exposure Route	Doses/Concentrations ^a	Duration	Effect Dose or Concentration (NOAEL, LOAEL, LC ₅₀) (mg/m ³ or mg/kg-bw/day) (Sex)	Effect	Reference	Data Quality Evaluation
Respiratory ^{b,c}	Acute	Rat, F344/DuCrI (n = 10/sex/conc.)	Inhalation, vapor, whole-body	0, 429, 1013, 2875, 7920, 21,630 mg/m ³ (0, 119, 281, 798, 2198, 6002 ppm)	6 hours	NOAEC = 2875 mg/m ³	Vacuolar change in olfactory and respiratory epithelium (2 rats at two days but not 2 weeks after exposure)	Mattie et al. (2012)	Medium
Hepatic, renal, respiratory ^{b,c}	Short-term	Rat, Fischer 344 rats (n= 64 treated and controls)	Inhalation, vapor, whole-body	0, 378, 5599, 11,690 mg/m ³ (0, 105, 1554, 3245 ppm)	6h/d, 5 d/wk for 2 wk, assessed 1d and 2wk post exposure	LOAEC = 378 mg/m ³	Lesions in nasal cavity, liver, and kidney; hepatic single cell necrosis	Mattie et al. (2012)	High
Neurological ^d	Short-term	Rat, CFE, ^e F (n = 8)	Inhalation, vapor, whole-body	5405, 10,810, 21,620 mg/m ³ (1500, 3000, 6000 ppm)	4 hrs/day, 5 days a week for 10 exposures	NOAEC = 5405 mg/m ³	Decreased avoidance response	Goldberg et al. (1964)	Medium

^a Concentrations in ppm were converted to mg/m³ using the following equation: ppm*mw (88.1)/24.45. 24.45 is the gas constant at 760 mm Hg (101 kPa) atmospheric pressure and at 25 °C.

^b The neurological/behavioral endpoints from these studies received an unacceptable rating and therefore, were not included in the above table and body weight changes not reported.

^c No effects on hepatic, renal, hematology, clinical chemistry endpoints.

^d Body weight changes were observed at the highest concentration.

^e Presumed to be Sprague-Dawley rats.

I.1.3 Hazard and Data Evaluation Summary for the Developmental Toxicity Study

Target Organ/System	Study Type	Species/Strain/Sex (Number/group)	Exposure Route	Doses/Concentrations	Duration	Effect Dose or Concentration (NOAEL, LOAEL, LC ₅₀) (mg/m ³ or mg/kg-bw/day) (Sex)	Effect	Reference	Data Quality Evaluation
Reproductive toxicity (adverse effects on development of the offspring)	Developmental	Rat, Sprague Dawley, F (n=18-20/group)	Oral, gavage	0, 250, 500 or 1000 mg/kg-bw/day	GDs 6-15	NOAEL=500 mg/kg-bw/day (F) LOAEL= 1,000 mg/kg-bw/day (F)	Delayed ossification of the sternbrae and reduced fetal body weight	Giavini et al. (1985)	High

I.1.4 Hazard and Data Evaluation Summary for Subchronic and Chronic Non-Cancer Studies

The endpoints in the tables below focus on hepatic, renal and respiratory endpoints, the critical endpoints for 1,4-dioxane. NOAELs (or LOAELs) are provided for each critical endpoint; BMD modeling has also been conducted for some studies (as presented elsewhere). Although additional endpoints may have been reported or examined in these studies, they are observed less often or are less sensitive and have not been included in this table.

INHALATION

Target Organ/System	Study Type	Species/Strain/Sex (Number/group)	Exposure Route	Doses/Concentrations ^a	Duration	Effect Dose or Concentration (NOAEL, LOAEL, LC ₅₀) (mg/m ³ or mg/kg-bw/day) (Sex)	Effect	Reference	Data Quality Evaluation
Respiratory	Subchronic	Rat, F344/DuCrj, M/F (n=20/group)	Inhalation, vapor, whole body	0, 360, 721, 1441, 2883, 5765, 11,530 or 23,060 mg/m ³ (0, 100, 200, 400, 800, 1600, 3200 or 6400 ppm)	6 hours/day, 5 days/week for 13 weeks	NOAEC= 360 (M/F) mg/m ³	Increased relative lung weight	Kasai et al. (2008)	High
Respiratory	Chronic	Rat, F344/DuCrj, M (n=50/group)	Inhalation, vapor, whole body	0, 180, 900 or 4500 mg/m ³ (0, 50, 250 or 1250 ppm)	6 hours/day, 5 days/week for 2 years	LOAEC= 180 mg/m ³ (M)	Nasal cavity: atrophy and metaplasia in olfactory epithelium	Kasai et al. (2009)	High
Hepatic	Subchronic	Rat, F344/DuCrj, M/F (n=20/group)	Inhalation, vapor, whole body	0, 360, 721, 1441, 2883, 5765, 11,530 or 23,060 mg/m ³ (0, 100, 200, 400, 800, 1600, 3200 or 6400 ppm)	6 hours/day, 5 days/week for 13 weeks	NOAEC (F) = 2883 mg/m ³	Liver foci ^b	Kasai et al. (2008)	High
Hepatic	Chronic	Rat, F344/DuCrj, M (n=50/group)	Inhalation, vapor, whole body	0, 180, 900 or 4500 mg/m ³ (0, 50, 250 or 1250 ppm)	6 hours/day, 5 days/week for 2 years	NOAEC = 901 mg/m ³	Liver foci, spongiosis hepatis, necrosis, increased enzymes and liver weight	Kasai et al. (2009)	High
Renal	Subchronic	Rat, F344/DuCrj, M/F (n=20/group)	Inhalation, vapor, whole body	0, 360, 721, 1441, 2883, 5765, 11,530 or 23,060 mg/m ³ (0, 100, 200, 400, 800, 1600, 3200 or 6400 ppm)	6 hours/day, 5 days/week for 13 weeks	NOAEC (F) = 5765 mg/m ³	Hydropic change in proximal tubule	Kasai et al. (2008)	High

Target Organ/System	Study Type	Species/Strain/Sex (Number/group)	Exposure Route	Doses/Concentrations ^a	Duration	Effect Dose or Concentration (NOAEL, LOAEL, LC ₅₀) (mg/m ³ or mg/kg-bw/day) (Sex)	Effect	Reference	Data Quality Evaluation
Renal	Chronic	Rat, F344/DuCr j, M (n=50/group)	Inhalation, vapor, whole body	0, 180, 900 or 4500 mg/m ³ (0, 50, 250 or 1250 ppm)	6 hours/day, 5 days/week for 2 years	NOAEC = 901 mg/m ³ ^c	hydropic change and decreased urine pH	Kasai et al. (2009)	High

^a Concentrations in ppm were converted to mg/m³ using the following equation: ppm*mw (88.1)/24.45. 24.45 is the gas constant at 760 mm Hg (101 kPa) atmospheric pressure and at 25 °C.

^b Liver weights were increased at ≥ 2912 mg/mg³ (800 ppm); single cell necrosis, centrilobular swelling and increased liver enzymes seen at 11,650 mg/m³

^c Nuclear enlargement of proximal tubule observed at 910 mg/m³

ORAL

Target Organ/System ¹	Study Type	Species/Strain/Sex (Number/group) ²	Exposure Route	Doses/Concentrations ³	Duration ⁴	Effect Dose or Concentration (NOAEL, LOAEL, LC ₅₀) ⁵ (mg/m ³ or mg/kg-bw/day) (Sex)	Effect ⁶	Reference ⁷	Data Quality Evaluation ⁸
Hepatic	Chronic	Rat, Wistar, M (n=26 treated, 9 controls)	Oral, drinking water	0 or 640 mg/kg-bw/day	63 weeks	LOAEL= 640 mg/kg-bw/day (M)	Hepatocytes with enlarged hyperchromic nuclei	Argus et al. (1965)	Medium
Hepatic	Chronic	Rat, Sprague Dawley, M (n=30/group)	Oral, drinking water	0, 430, 574, 803 or 1032 mg/kg-bw/day	13 months	LOAEL= 430 mg/kg-bw/day (M)	Hepatocytomegaly	Argus et al. (1973)	Low
Hepatic	Chronic	Rat, Sherman, M/F (n=120/group)	Oral, drinking water	0, 9.6, 94 or 1015 mg/kg-bw/day (M); 0, 19, 148 or 1599 mg/kg-bw/day (F)	2 years	NOAEL= 9.6 mg/kg-bw/day (M) LOAEL = 94 mg/kg-bw/day (M)	Degeneration and necrosis of hepatocytes	Kociba et al. (1974)	High

Target Organ/System ¹	Study Type	Species/Strain/Sex (Number/group) ²	Exposure Route	Doses/Concentrations ³	Duration ⁴	Effect Dose or Concentration (NOAEL, LOAEL, LC ₅₀) ⁵ (mg/m ³ or mg/kg-bw/day) (Sex)	Effect ⁶	Reference ⁷	Data Quality Evaluation ⁸
Hepatic	Sub chronic	Rat, F344/DuCrj, M/F (n=20/group)	Oral, drinking water	0, 52, 126, 274, 657 or 1554 mg/kg-bw/day (M); 0, 83, 185, 427, 756 or 1614 mg/kg-bw/day (F)	13 weeks	NOAEL= 52 mg/kg-bw/day (M) LOAEL= 126 mg/kg-bw/day (M)	Hepatocyte swelling	Kano et al. (2008)	Medium
Hepatic	Chronic	Rat, F344/DuCrj, M/F (n=100/group)	Oral, drinking water	0, 11, 55 or 274 mg/kg-bw/day (M); 0, 18, 83 or 429 mg/kg-bw/day (F)	2 years	NOAEL= 11 mg/kg-bw/day (M) LOAEL= 55 mg/kg-bw/day (M)	Mixed cell liver foci	Kano et al. (2009); JBRC (1998)	High/High
Hepatic	Chronic	Rat, F344/DuCrj, M/F (n=100/group)	Oral, drinking water	0, 11, 55 or 274 mg/kg-bw/day (M); 0, 18, 83 or 429 mg/kg-bw/day (F)	2 years	NOAEL= 55 mg/kg-bw/day (M) LOAEL= 274 mg/kg-bw/day (M)	Increases in serum liver enzymes (GOT, GPT, LDH and ALP)	Kano et al. (2009); JBRC (1998)	High/High
Hepatic	Chronic	Mouse, Crj:BDF1, M/F (n=100/group)	Oral, drinking water	0, 49, 191 or 677 mg/kg-bw/day (M); 0, 66, 278 or 964 mg/kg-bw/day (F)	2 years	NOAEL= 49 mg/kg-bw/day (M) LOAEL= 191 mg/kg-bw/day (M)	Increases in serum liver enzymes (GOT, GPT, LDH and ALP)	Kano et al. (2009); JBRC (1998)	High/High
Renal	Chronic	Rat, Wistar, M (n=26 treated, 9 controls)	Oral, drinking water	0 or 640 mg/kg-bw/day	63 weeks	LOAEL= 640 mg/kg-bw/day (M)	Glomerulonephritis	Argus et al. (1965)	Medium
Renal	Chronic	Rat, Sprague Dawley, M (n=30/group)	Oral, drinking water	0, 430, 574, 803 or 1032 mg/kg-bw/day	13 months	LOAEL= 430 mg/kg-bw/day (M)	Glomerulonephritis	Argus et al. (1973)	Low

Target Organ/System ¹	Study Type	Species/Strain/Sex (Number/group) ²	Exposure Route	Doses/Concentrations ³	Duration ⁴	Effect Dose or Concentration (NOAEL, LOAEL, LC ₅₀) ⁵ (mg/m ³ or mg/kg-bw/day) (Sex)	Effect ⁶	Reference ⁷	Data Quality Evaluation ⁸
Renal	Chronic	Rat, Sherman, M/F (n=120/group)	Oral, drinking water	0, 9.6, 94 or 1015 mg/kg-bw/day (M); 0, 19, 148 or 1599 mg/kg-bw/day (F)	2 years	NOAEL= 9.6 mg/kg-bw/day (M) LOAEL= 94 mg/kg-bw/day (M)	Degeneration and necrosis of renal tubular cells	Kociba et al. (1974)	High
Respiratory	Chronic	Rat, F344/DuCrj, M/F (n=20/group)	Oral, drinking water	0, 52, 126, 274, 657 or 1554 mg/kg-bw/day (M); 0, 83, 185, 427, 756 or 1614 mg/kg-bw/day (F)	13 weeks	NOAEL= 52 mg/kg-bw/day (M) LOAEL= 126 mg/kg-bw/day (M)		Kano et al. (2008)	Medium
Respiratory	Chronic	Rat, F344/DuCrj, M/F (n=100/group)	Oral, drinking water	0, 11, 55 or 274 mg/kg-bw/day (M); 0, 18, 83 or 429 mg/kg-bw/day (F)	2 years	NOAEL= 55 mg/kg-bw/day (M) LOAEL= 274 mg/kg-bw/day (M)	Atrophy of nasal olfactory epithelium; nasal adhesion and inflammation	Kano et al. (2009); JBRC (1998)	High; High
Respiratory	Sub chronic	Mouse, Crj:BDF1, M/F (n=20/group)	Oral, drinking water	0, 86, 231, 585, 882 or 1570 mg/kg-bw/day (M); 0, 170, 387, 898, 1620 or 2669 mg/kg-bw/day (F)	13 weeks	NOAEL= 170 mg/kg-bw/day (F) LOAEL= 387 mg/kg-bw/day (F)		Kano et al. (2008)	Medium
Respiratory	Chronic	Mouse, B6C3F1, M/F (n=100/group)	Oral, drinking water	0, 720 or 830 mg/kg-bw/day (M); 0, 380 or 860 mg/kg-bw/day (F)	90 weeks	LOAEL= 380 mg/kg-bw/day (F)	Pneumonia and rhinitis	NCI (1978)	Low

Target Organ/System ¹	Study Type	Species/Strain/Sex (Number/group) ²	Exposure Route	Doses/Concentrations ³	Duration ⁴	Effect Dose or Concentration (NOAEL, LOAEL, LC ₅₀) ⁵ (mg/m ³ or mg/kg-bw/day) (Sex)	Effect ⁶	Reference ⁷	Data Quality Evaluation ⁸
Respiratory	Chronic	Mouse, Crj:BDF1, M/F (n=100/group)	Oral, drinking water	0, 49, 191 or 677 mg/kg-bw/day (M); 0, 66, 278 or 964 mg/kg-bw/day (F)	2 years	NOAEL= 66 mg/kg-bw/day (F) LOAEL= 278 mg/kg-bw/day (F)	Nasal inflammation	Kano et al. (2009); JBRC (1998)	High

I.1.5 Hazard and Data Evaluation Summary for Genotoxicity Studies

Target Organ/System	Study Type	Species/Strain/Cell type (Number/Group if relevant)	Exposure Route	Doses/Concentrations	Duration	Effect Concentration/Result	Effect measured	Reference	Data Quality Evaluation
Genotoxicity	Short Term	<i>S. typhimurium</i> strains TA98, TA100, TA1535, TA1537	<i>In vitro</i>	0, 10,000 ug/plate	1 week	Negative	Reverse Mutation	Haworth et al. (1983)	High
Genotoxicity	Short Term	<i>S. typhimurium</i> strains TA98, TA100, TA1530, TA1535, TA1537	<i>In vitro</i>	ND	NR	False-negative	Mutagenesis (Ames assay)	Khudoley et al. (1987)	Medium
Genotoxicity	Acute	<i>S. typhimurium</i> strains TA98, TA100, TA1535, TA1537	<i>In vitro</i>	0, 5,000 µg/plate	30 minutes	Negative	Reverse mutation	Morita and Hayashi (1998)	High
Genotoxicity	Acute	<i>S. typhimurium</i>	<i>In vitro</i>	0, 103 mg	24 hours	Negative	Reverse	Nestmann et	Medium

Target Organ/System	Study Type	Species/Strain/Cell type (Number/Group if relevant)	Exposure Route	Doses/Concentrations	Duration	Effect Concentration/Result	Effect measured	Reference	Data Quality Evaluation
		strains TA100, TA1535					mutation	al. (1984)	
Genotoxicity	Short Term	<i>S. typhimurium</i> strains TA98, TA100, TA1535, TA1537, TA1538	<i>In vitro</i>	0, 5.17, 15.5, 31.0, 62, 103 mg	48 hours	Negative	Reverse mutation	Stott et al. (1981) ; Dow Chemical (1989d)	High
Genotoxicity	Short Term	<i>E. coli</i> K-12 uvrB/recA	<i>In vitro</i>	1,150 mmol/L	1 day	Negative	DNA Repair	Hellmér and Bolcsfoldi (1992)	High
Genotoxicity	Acute	<i>E. coli</i> WP2/WP2uvrA	<i>In vitro</i>	0, 5,000 ug/plate	24 hours	Negative	Reverse Mutation	Morita and Hayashi (1998)	High
Genotoxicity	Acute	<i>P. phosphoreum</i> M169	<i>In vitro</i>	ND	18 hours	Negative	Mutagenicity, DNA damage	Kwan et al. (1990)	unacceptable
Genotoxicity	Short Term	<i>S. cerevisiae</i> D61.M	<i>In vitro</i>	0, 1.48, 1.96, 2.44, 2.91, 3.38, 4.31, 4.75%	7 days	Negative	Aneuploidy	Zimmerman et al. (1985)	unacceptable
Genotoxicity	Acute	<i>D. melanogaster</i>	<i>In vitro</i>	0, 1, 1.5, 2, 3, 3.5% in sucrose media	24 hours	LOAEL at 2%	Meiotic nondisjunction	Munoz and Barnett (2002)	High
Genotoxicity		<i>D. melanogaster</i>	<i>In vitro</i>	35,000 ppm in feed, 7 days or 50,000 ppm (5% in water) by injection			Sex-linked recessive lethal test	Yoon et al. (1985)	Medium
Genotoxicity	Acute	Male CDF Fischer 344 rat	<i>In vitro</i>	10 ⁰ to 10 ⁻⁸ Molar	18 hours	Negative	Unscheduled DNA synthesis	Stott et al. (1981) ; Dow	High

Target Organ/ System	Study Type	Species/ Strain/Cell type (Number/ Group if relevant)	Exposure Route	Doses/ Concentrations	Duration	Effect Concentration/ Result	Effect measured	Reference	Data Quality Evaluation
		hepatocytes						Chemical (1989d)	
Genotoxicity	Acute	Rat hepatocytes	<i>In vitro</i>	0, 0.03, 0.3, 3, 10, 30 mM	3 hours	LOAEL at 0.3 mM	DNA damage; single-strand breaks measured by alkaline elution	Sina et al. (1983)	High
Genotoxicity	Short Term	Primary hepatocyte culture from male F344 rats	<i>In vitro</i>	0, 0.001, 0.01, 0.1, 1 mM	5 days	Negative	DNA repair	Goldsworthy et al. (1991)	High
Genotoxicity	Short Term	L5178Y mouse lymphoma cells	<i>In vitro</i>	0, 5,000 ug/mL	48 hours	Negative	Forward mutation assay	Mcgregor et al. (1991)	High
Genotoxicity	Acute	L5178Y mouse lymphoma cells	<i>In vitro</i>	0, 5,000 ug/mL	24 hours	Negative	Forward mutation assay	Morita and Hayashi (1998)	High
Genotoxicity	Short Term	BALB/3T3 cells	<i>In vitro</i>	0, 0.25, 0.5, 1.0, 2.0 mg/mL	48 hours	LOAEL at 0.5 mg/mL	Cell transformation	Sheu et al. (1988)	High
Genotoxicity	Acute	CHO cells	<i>In vitro</i>	0, 1,050, 3,500, 10,500 ug/L	2 hours	Negative	SCE	Galloway et al. (1987)	High
Genotoxicity	Short Term	CHO cells	<i>In vitro</i>	0, 1,050, 3,500, 10,500 ug/L	26 hours	Negative	Chromosomal aberration	Galloway et al. (1987)	High
Genotoxicity	Short Term	CHO cells	<i>In vitro</i>	0, 5,000 ug/mL	26 hours	Negative	SCE	Morita and Hayashi (1998)	High
Genotoxicity	Short Term	CHO cells	<i>In vitro</i>	0, 5,000 ug/mL	44 hours	Negative	Chromosomal aberration	Morita and Hayashi (1998)	High

Target Organ/System	Study Type	Species/Strain/Cell type (Number/Group if relevant)	Exposure Route	Doses/Concentrations	Duration	Effect Concentration/Result	Effect measured	Reference	Data Quality Evaluation
Genotoxicity	Short Term	CHO cells	<i>In vitro</i>	0, 5,000 ug/mL	44 hours	Negative	Micronucleus formation	Morita and Hayashi (1998)	High
Genotoxicity	Acute	Calf thymus DNA	<i>In vitro</i>	0.04 pmol/mg/DNA	16 hours	Negative	Covalent binding to DNA	Woo et al. (1977c)	Unacceptable
Genotoxicity	Acute	Female Sprague Dawley Rat	<i>In vivo</i>	0, 168, 840, 2,550, 4,200 mg/kg	21 hours	LOAEL at 2,550 mg/kg	DNA damage; single-strand breaks measured by alkaline elution	Kitchin and Brown (1990)	Medium
Genotoxicity	Subchronic	Male Sprague Dawley Rat	<i>In vivo</i>	0, 10, 100, 1000 mg/kg	11 weeks	Negative	DNA alkylation in hepatocytes	Stott et al. (1981); Dow Chemical (1989d)	High
Genotoxicity	Short Term	Male B6C3F1 Mouse	<i>In vivo</i>	0, 500, 1,000, 2,000 mg/kg daily dose; 0, 2,000, 3,000, 4,000 mg/kg single injection	48 hours	Negative up to daily doses of 2,000, Single dose of 4,000 mg/kg	Micronucleus formation in bone marrow	McFee et al. (1994)	High
Genotoxicity	Short Term	Male and female C57BL6 Mouse; Male BALB/c Mouse	<i>In vivo</i>	0, 450, 900, 1,800, 3,600 mg/kg (C57BL6); 0, 5,000 mg/kg (BALB/c)	48 hours	LOAEL of 900 mg/kg (C57BL6); Negative up to 5,000 mg/kg (BALB/c)	Micronucleus formation in bone marrow	Mirkova (1994)	High
Genotoxicity	Short Term	Male CD1 Mouse	<i>In vivo</i>	0, 500, 1,000, 2,000, 3,200 mg/kg	72 hours	Negative up to 3,200 mg/kg	Micronucleus formation in peripheral blood	Morita (1994)	High
Genotoxicity	Short Term	Male CD1	<i>In vivo</i>	0, 1,000, 2,000,	7 days	LOAEL at	Micronucleus	Morita and	High

Target Organ/System	Study Type	Species/Strain/Cell type (Number/Group if relevant)	Exposure Route	Doses/Concentrations	Duration	Effect Concentration/Result	Effect measured	Reference	Data Quality Evaluation
		Mouse		or 3,000 mg/kg		2,000 mg/kg	formation in hepatocytes	Hayashi (1998)	
Genotoxicity	Short Term	Male CD1 Mouse	<i>In vivo</i>	0, 1,000, 2,000, or 3,000 mg/kg	7 days	Negative	Micronucleus formation in peripheral blood	Morita and Hayashi (1998)	High
Genotoxicity	Acute	Male CBA and C57BL6 Mouse	<i>In vivo</i>	0, 1,800, 3,600 mg/kg	24 hours	Negative	Micronucleus formation in bone marrow	Tinwell and Ashby (1994)	High
Genotoxicity	Short Term	Male CD1 Mouse	<i>In vivo</i>	0, 1,500, 2,500, 3,500 mg/kg per day for 5 days	6 days	LOAEL of 1,500 mg/kg-day for 5 days	Micronuclei formation in bone marrow	Roy et al. (2005)	High
Genotoxicity	Short Term	Male CD1 Mouse	<i>In vivo</i>	0, 1,500, 2,500, 3,500 mg/kg per day for 5 days	6 days	LOAEL of 2,500 mg/kg-day for 5 days	Micronuclei formation in hepatocytes	Roy et al. (2005)	High
Genotoxicity	Subchronic	Male Sprague Dawley Rat	<i>In vivo</i>	0, 10, 100, 1,000 mg/kg-day for 11 weeks	11 weeks	Negative	DNA repair in hepatocytes	Stott et al. (1981) ; Dow Chemical (1989d)	High
Genotoxicity	Acute	Male F344 Rat	<i>In vivo</i>	0, 10, 100, 1,000 gm/kg for 2 or 12 hours;	12 hours	Negative	DNA repair in hepatocytes (autoradiograph)	Goldsworthy et al. (1991)	High
Genotoxicity	Short Term	Male F344 Rat	<i>In vivo</i>	0, 1,500 mg/kg-day for 8 days + 1,000 mg/kg gavage dose 12 hours prior to sacrifice	8 days	Negative	DNA repair in nasal epithelial cells from the nasoturbinate or maxilloturbinate	Goldsworthy et al. (1991)	Unacceptable
Genotoxicity	Short Term	Male F344 Rat	<i>In vivo</i>	0, 1,000 mg/kg	2 weeks	LOAEL of	Replicative	Goldsworthy	High

Target Organ/System	Study Type	Species/Strain/Cell type (Number/Group if relevant)	Exposure Route	Doses/Concentrations	Duration	Effect Concentration/Result	Effect measured	Reference	Data Quality Evaluation
				for 24 or 48 hours; 1,500 mg/kg-day for 1 or 2 weeks		1,000 mg/kg for 24 or 48 hours; 1,500 mg/kg-day for 1 or 2 weeks	DNA synthesis (<i>i.e.</i> , cell proliferation) in hepatocytes	et al. (1991)	
Genotoxicity	Short Term	Male F344 Rat	<i>In vivo</i>	0, 1,500 mg/kg-day for 2 weeks	2 weeks	1,500 mg/kg-day for 2 weeks	Replicative DNA synthesis (<i>i.e.</i> , cell proliferation) in nasal epithelial cells	Goldsworthy et al. (1991)	Unacceptable
Genotoxicity	Acute	Male Sprague Dawley Rat	<i>In vivo</i>	0, 10, 100 mg/rat	24 hours	LOAEL of 10 mg/rat	RNA synthesis; inhibition of RNA polymerase A and B	Kurl et al. (1981)	Unacceptable
Genotoxicity	Short Term	Male F344 Rat	<i>In vivo</i>	0, 1,000, 1,500, 2,000, 4,000 mg/kg	48 hours	LOAEL of 1,000 mg/kg	DNA synthesis in hepatocytes	Miyagawa et al. (1999)	High
Genotoxicity	Short Term	Male F344 Rat	<i>In vivo</i>	0, 1,000, 2,000 mg/kg	48 hours	LOAEL of 2,000 mg/kg	DNA synthesis in hepatocytes	Uno et al. (1994)	Medium
Genotoxicity	Short Term	Male Sprague Dawley Rat	<i>In vivo</i>	0, 10, 100, or 1,000 mg/kg.	11 weeks	LOAEL of 1,000 mg/kg-day for 11 weeks	DNA synthesis in hepatocytes	Stott et al. (1981) ; Dow Chemical (1989d)	High
Genotoxicity	Short term	Male F344/DuCr1Cr1j rats	<i>In vivo</i>	1000, 2000, 3000 mg/kg	6 days	LOAEL of 1,000 mg/kg	Liver micronucleus test by juvenile rat method	Itoh and Hattori (2019)	High
Genotoxicity	Short term	Male F344/DuCr1Cr1j	<i>In vivo</i>	1000, 2000, 3000 mg/kg	24 or 48 hours	LOAEL of 3,000 mg/kg	Bone marrow micronucleus	Itoh and Hattori	High

Target Organ/System	Study Type	Species/Strain/Cell type (Number/Group if relevant)	Exposure Route	Doses/Concentrations	Duration	Effect Concentration/Result	Effect measured	Reference	Data Quality Evaluation
		rats					test	(2019)	
Genotoxicity	Short term	Male F344/DuCr1Cr1j rats	<i>In vivo</i>	1000, 2000, 3000 mg/kg	15 or 30 days	No effect at any doses tested	Mutagenicity by <i>Pig-a</i> gene mutation assay	Itoh and Hattori (2019)	High
Genotoxicity	Long Term	Male <i>gpt</i> delta transgenic F344 rats	<i>In vivo</i>	0, 200, 1,000, 5,000 ppm	16 weeks	Positive at 5,000 ppm	Increased relative mRNA expression levels	Gi et al. (2018)	High
Genotoxicity	Long Term	Male <i>gpt</i> delta transgenic F344 rats	<i>In vivo</i>	0, 0.2, 2, or 20 ppm	16 weeks	Negative up to 20 ppm	Mutagenesis	Gi et al. (2018)	High
Genotoxicity	Long Term	Male <i>gpt</i> delta transgenic F344 rats	<i>In vivo</i>	0, 2, 20, 200, 2,000, 5,000 ppm	16 weeks	Positive at 2,000 ppm	Increased GST-P-positive foci induction and cell proliferation	Gi et al. (2018)	High

NR- not reported; ND – not determined

I.1.6 Data Evaluation Summary for Chronic Cancer Studies

Cancer Incidence for 1,4-Dioxane Studies with Acceptable Data Quality Ratings¹

Study Type	Species/Strain/Sex (Number/group)	Exposure Route	Doses/Concentrations	Duration	Cancer Incidence	Effect	Reference	Data Quality Evaluation
Chronic	Rat, Wistar, M (n=26 treated, 9 controls)	Oral, drinking water	0 or 640 mg/kg-bw/day	63 weeks	6/26 treated rats	Hepatocellular carcinomas	Argus et al. (1965)	Medium

Study Type	Species/ Strain/Sex (Number/ group)	Exposure Route	Doses/ Concentrations	Duration	Cancer Incidence	Effect	Reference	Data Quality Evaluation
Chronic	Rat, Wistar, M (n=26 treated, 9 controls)	Oral, drinking water	0 or 640 mg/kg-bw/day	63 weeks	1/26 treated rats	Transitional cell carcinoma in kidney's pelvis	Argus et al. (1965)	Medium
Chronic	Rat, Wistar, M (n=26 treated, 9 controls)	Oral, drinking water	0 or 640 mg/kg-bw/day	63 weeks	1/26 treated rats	Leukemia	Argus et al. (1965)	Medium
Chronic	Rat, Sprague Dawley, M (n=30/group)	Oral, drinking water	0, 430, 574, 803 or 1032 mg/kg-bw/day	13 months	5/28-32 rats (dose not specified)	Liver	Argus et al. (1973)	Low
Chronic	Rat, F344/DuCrj , M/F, (n=100/group)	Oral, drinking water	0, 11, 55, or 274 mg/kg-bw/day (M) 0, 18, 83, or 429 mg/kg-bw/day (F)	2 years	3,4,7,32 (M, 50 rats/ dose) 3,1,6,48 (F, 50 rats/ dose)	Hepatocellular adenoma	Kano et al. (2009); JBRC (1998)	High
Chronic	Rat, F344/DuCrj , M/F, (n=100/group)	Oral, drinking water	0, 11, 55, or 274 mg/kg-bw/day (M) 0, 18, 83, or 429 mg/kg-bw/day (F)	2 years	0,0,0,14 (M, 50 rats/ dose) 0,0,0,10 (F, 50 rats/ dose)	Hepatocellular carcinoma	Kano et al. (2009); JBRC (1998)	High
Chronic	Rat, F344/DuCrj , M/F, (n=100/group)	Oral, drinking water	0, 11, 55, or 274 mg/kg-bw/day (M) 0, 18, 83, or 429 mg/kg-bw/day (F)	2 years	3,4,7,39 (M, 50 rats/ dose) 3,1,6,48 (F, 50 rats/ dose)	Either hepatocellular adenoma or carcinoma	Kano et al. (2009); JBRC (1998)	High

Study Type	Species/ Strain/Sex (Number/ group)	Exposure Route	Doses/ Concentrations	Duration	Cancer Incidence	Effect	Reference	Data Quality Evaluation
Chronic	Rat, F344/DuCrj , M/F, (n= 100/group)	Oral, drinking water	0, 11, 55, or 274 mg/kg- bw/day (M) 0, 18, 83, or 429 mg/kg-bw/day (F)	2 years	1,1,0,4 (M, 50 rats/ dose) 3,2,1,3 (F, 50 rats/ dose)	Mammary gland- Fibroadenoma	Kano et al. (2009); JBRC (1998)	High
Chronic	Rat, F344/DuCrj , M/F, (n= 100/group)	Oral, drinking water	0, 11, 55, or 274 mg/kg- bw/day (M) 0, 18, 83, or 429 mg/kg-bw/day (F)	2 years	0,1,2,2 (M, 50 rats/ dose) 6,7,10,16 (F, 50 rats/ dose)	Mammary gland- Adenoma	Kano et al. (2009); JBRC (1998)	High
Chronic	Rat, F344/DuCrj , M/F, (n= 100/group)	Oral, drinking water	0, 11, 55, or 274 mg/kg- bw/day (M) 0, 18, 83, or 429 mg/kg-bw/day (F)	2 years	1,2,2,6 (M, 50 rats/ dose) 8,8,11,18 (F, 50 rats/ dose)	Mammary gland- Either fibroadenoma or adenoma	Kano et al. (2009); JBRC (1998)	High
Chronic	Rat, F344/DuCrj , M/F, (n= 100/group)	Oral, drinking water	0, 11, 55, or 274 mg/kg- bw/day (M) 0, 18, 83, or 429 mg/kg-bw/day (F)	2 years	2,2,5,28 (M, 50 rats/ dose) 1,0,0,0 (F, 50 rats/ dose)	Peritoneum- Mesothelioma	Kano et al. (2009); JBRC (1998)	High
Chronic	Rat, F344/DuCrj , M/F, (n= 100/group)	Oral, drinking water	0, 11, 55, or 274 mg/kg- bw/day (M) 0, 18, 83, or 429 mg/kg-bw/day (F)	2 years	0,0,0,3 (M, 50 rats/ dose) 0,0,0,7 (F, 50 rats/ dose)	Nasal- Squamous cell carcinoma	Kano et al. (2009); JBRC (1998)	High

Study Type	Species/ Strain/Sex (Number/ group)	Exposure Route	Doses/ Concentrations	Duration	Cancer Incidence	Effect	Reference	Data Quality Evaluation
Chronic	Rat, F344/DuCrj , M/F, (n= 100/group)	Oral, drinking water	0, 11, 55, or 274 mg/kg- bw/day (M) 0, 18, 83, or 429 mg/kg-bw/day (F)	2 years	0,0,0,2 (M, 50 rats/ dose) 0,0,0,0 (F, 50 rats/ dose)	Nasal- Sarcoma	Kano et al. (2009); JBRC (1998)	High
Chronic	Rat, F344/DuCrj , M/F, (n= 100/group)	Oral, drinking water	0, 11, 55, or 274 mg/kg- bw/day (M) 0, 18, 83, or 429 mg/kg-bw/day (F)	2 years	0,0,0,1 (M, 50 rats/ dose) 0,0,0,0 (F, 50 rats/ dose)	Nasal- Rhabdomyosarcoma	Kano et al. (2009); JBRC (1998)	High
Chronic	Rat, F344/DuCrj , M/F, (n= 100/group)	Oral, drinking water	0, 11, 55, or 274 mg/kg- bw/day (M) 0, 18, 83, or 429 mg/kg-bw/day (F)	2 years	0,0,0,1 (M, 50 rats/ dose) 0,0,0,1 (F, 50 rats/ dose)	Nasal- Esthesioneuroepithelioma	Kano et al. (2009); JBRC (1998)	High
Chronic	Rat, F344/DuCrj, M (n= 50/group)	Inhalation, vapor, whole body	0, 180, 900, or 4500 mg/m3 (0, 50, 250, or 1250 ppm)	6 hours/dy, 5 days/wk, for 2 years	0,0,1,6 (50 rats per dose group)	Nasal squamous cell carcinoma	Kasai et al. (2009)	High
Chronic	Rat, F344/DuCrj, M (n= 50/group)	Inhalation, vapor, whole body	0, 180, 900, or 4500 mg/m3 (0, 50, 250, or 1250 ppm)	6 hours/dy, 5 days/wk, for 2 years	1,2,3,21 (50 rats per dose group)	Hepatocellular adenoma	Kasai et al. (2009)	High

Study Type	Species/ Strain/Sex (Number/ group)	Exposure Route	Doses/ Concentrations	Duration	Cancer Incidence	Effect	Reference	Data Quality Evaluation
Chronic	Rat, F344/DuCrj, M (n= 50/group)	Inhalation, vapor, whole body	0, 180, 900, or 4500 mg/m ³ (0, 50, 250, or 1250 ppm)	6 hours/dy, 5 days/wk, for 2 years	0,0,1,2 (50 rats per dose group)	Hepatocellular carcinoma	Kasai et al. (2009)	High
Chronic	Rat, F344/DuCrj, M (n= 50/group)	Inhalation, vapor, whole body	0, 180, 900, or 4500 mg/m ³ (0, 50, 250, or 1250 ppm)	6 hours/dy, 5 days/wk, for 2 years	0,0,0,4 (50 rats per dose group)	Renal cell carcinoma	Kasai et al. (2009)	High
Chronic	Rat, F344/DuCrj, M (n= 50/group)	Inhalation, vapor, whole body	0, 180, 900, or 4500 mg/m ³ (0, 50, 250, or 1250 ppm)	6 hours/dy, 5 days/wk, for 2 years	2,4,14,41 (50 rats per dose group)	Peritoneal mesothelioma	Kasai et al. (2009)	High
Chronic	Rat, F344/DuCrj, M (n= 50/group)	Inhalation, vapor, whole body	0, 180, 900, or 4500 mg/m ³ (0, 50, 250, or 1250 ppm)	6 hours/dy, 5 days/wk, for 2 years	1,2,3,5 (50 rats per dose group)	Mammary gland fibroadenoma	Kasai et al. (2009)	High
Chronic	Rat, F344/DuCrj, M (n= 50/group)	Inhalation, vapor, whole body	0, 180, 900, or 4500 mg/m ³ (0, 50, 250, or 1250 ppm)	6 hours/dy, 5 days/wk, for 2 years	0,0,0,1 (50 rats per dose group)	Mammary gland adenoma	Kasai et al. (2009)	High

Study Type	Species/ Strain/Sex (Number/ group)	Exposure Route	Doses/ Concentrations	Duration	Cancer Incidence	Effect	Reference	Data Quality Evaluation
Chronic	Rat, F344/DuCrj, M (n= 50/group)	Inhalation, vapor, whole body	0, 180, 900, or 4500 mg/m ³ (0, 50, 250, or 1250 ppm)	6 hours/dy, 5 days/wk, for 2 years	0,0,0,4 (50 rats per dose group)	Zymbal gland adenoma	Kasai et al. (2009)	High
Chronic	Rat, F344/DuCrj, M (n= 50/group)	Inhalation, vapor, whole body	0, 180, 900, or 4500 mg/m ³ (0, 50, 250, or 1250 ppm)	6 hours/dy, 5 days/wk, for 2 years	1,4,9,5 (50 rats per dose group)	Subcutis fibroma	Kasai et al. (2009)	High
Chronic	Rat, Sherman, M/F, (n=120/group)	Oral, drinking water	0, 9.6, 94, or 1015 mg/kg- bw/day (M) 0, 19, 148, or 1599 mg/kg- bw/day (F)	2 years	2/106, 0/110, 1/106, 12/66	Hepatic tumors (all types)	Kociba et al. (1974)	High
Chronic	Rat, Sherman, M/F, (n=120/group)	Oral, drinking water	0, 9.6, 94, or 1015 mg/kg- bw/day (M) 0, 19, 148, or 1599 mg/kg- bw/day(F)	2 years	1/106, 0/110, 1/106, 10/66	Hepatocellular carcinoma	Kociba et al. (1974)	High
Chronic	Rat, Sherman, M/F, (n=120/group)	Oral, drinking water	0, 9.6, 94, or 1015 mg/kg- bw/day (M) 0, 19, 148, or 1599 mg/kg- bw/day (F)	2 years	0/106, 0/110, 0/106, 3/66	Nasal carcinoma	Kociba et al. (1974)	High

Study Type	Species/ Strain/Sex (Number/ group)	Exposure Route	Doses/ Concentrations	Duration	Cancer Incidence	Effect	Reference	Data Quality Evaluation
Chronic	Mouse, B6C3F1, M/F (n=100/group)	Oral, drinking water	0, 720 or 830 mg/kg-bw/day (M); 0, 380 or 860 mg/kg-bw/day (F)	90 weeks	2/49, 18/50, 24/47 (M) 0/50, 12/48, 29/37 (F)	Hepatocellular carcinoma	NCI (1978)	Low
Chronic	Mouse, B6C3F1, M/F (n=100/group)	Oral, drinking water	0, 720 or 830 mg/kg-bw/day (M); 0, 380 or 860 mg/kg-bw/day (F)	90 weeks	8/49, 19/50, 28/47 (M) 0/50, 21/48, 35/37 (F)	Hepatocellular adenoma or carcinoma	NCI (1978)	Low
Chronic	Rat, Osborne- Mendel, F ² (n=70/group)	Oral, drinking water	0, 350 or 640 mg/kg-bw/day (F)	110 weeks	0/34, 10/35, 8/35 (F)	Nasal cavity squamous cell carcinoma	NCI (1978)	Low
Chronic	Rat, Osborne- Mendel, F ² (n=70/group)	Oral, drinking water	0, 350 or 640 mg/kg-bw/day (F)	110 weeks	0/31, 10/33, 11/32 (F)	Hepatocellular carcinoma	NCI (1978)	Low

¹ Unacceptable studies are not included in this table.

²The results for male rats were considered unacceptable and are not included in this table.

I.1.7 Data Evaluation Summary for Mechanistic Studies

Table I-1. Summary of Mechanistic Data for 1,4-Dioxane

Target Organ/System	Study Type	Species/Strain/Cell type (Number/Group if relevant)	Exposure Route	Doses/Concentrations	Duration	Effect Concentration/Result	Effect measured	Reference	Data Quality Evaluation
Genotoxicity	Short-term	Fly, Drosophila melanogaster, F (n=50/treatment group)	In vitro	1, 1.5, 2, 3 or 3.5% 1,4-dioxane (in 4% sucrose aqueous solution)	24 hrs	LOAEL = 1.5% solution (F)	Increased meiotic non-disjunction in oocytes	Munoz and Barnett (2002)	High
Genotoxicity	Acute	Male CDF Fischer 344 rat hepatocytes	In vitro	10 ⁰ to 10 ⁻⁸ Molar	18 hours	Negative for DNA damage	Unscheduled DNA synthesis	Dow Chemical (1989b)	Medium
Hepatic	Acute	Rat liver microsomes (n = 3 trials/dose)	In vitro	0, 0.1, 0.25, 0.5, 0.75 or 1% v/v	10 min	AC ₅₀ (MET) = 0.25% v/v; 29.4 mM AC ₅₀ (IMI) = 0.10% v/v; 11.7 mM	Decrease in CYP450 activity measured with metoprolol (MET) or imipramine (IMI) metabolism	Shah et al. (2015)	High
Hepatic	Not reported	Rat liver microsomes (n = 3 trials/dose)	In vitro	0, 0.1, 0.25, 0.5, 0.75 or 1% v/v	Not Reported	AC ₅₀ = <0.10% v/v; <11.7 mM	Decrease in p-nitrophenol hydroxylase activity measured with p-nitrophenol metabolism	Patil et al. (2015)	High

Target Organ/System	Study Type	Species/Strain/Cell type (Number/Group if relevant)	Exposure Route	Doses/Concentrations	Duration	Effect Concentration/Result	Effect measured	Reference	Data Quality Evaluation
Genotoxicity	Acute	Male CDF Fischer 344 rat hepatocytes	In vitro	10 ⁰ to 10 ⁻⁸ Molar	18 hours	Negative for DNA damage	Unscheduled DNA synthesis	Dow Chemical (1989d) (pg 248-261)	Medium
Genotoxicity	Short Term	<i>S. typhimurium</i> strains TA98, TA100, TA1535, TA1537	In vitro	0, 10,000 ug/plate	1 week	Negative up to 10,000 ug/plate	Reverse Mutation	Haworth et al. (1983)	High
Genotoxicity	Short Term	<i>S. typhimurium</i> strains TA98, TA100, TA1530, TA1535, TA1537	In vitro	ND	NR	False-negative	Mutagenesis (Ames assay)	Khudoley et al. (1987)	Medium
Genotoxicity	Acute	<i>S. typhimurium</i> strains TA98, TA100, TA1535, TA1537	In vitro	0, 5,000 µg/plate	30 minutes	Negative up to 5,000 µg/plate	Reverse mutation	Morita and Hayashi (1998)	High
Genotoxicity	Acute	<i>S. typhimurium</i> strains TA100, TA1535	In vitro	0, 103 mg	24 hours	Negative up to 103 mg	Reverse mutation	Nestmann et al. (1984)	Medium
Genotoxicity	Short Term	<i>S. typhimurium</i> strains TA98, TA100, TA1535, TA1537, TA1538	In vitro	0, 5.17, 15.5, 31.0, 62, 103 mg	NR	Negative up to 103 mg	Reverse mutation	Stott et al. (1981)	High
Genotoxicity	Short Term	<i>E. coli</i> K-12 uvrB/recA	In vitro	1,150 mmol/L	1 day	Negative up to 1,150 mmol/L	DNA Repair	Hellmér and Bolcsfoldi (1992)	High
Genotoxicity	Acute	<i>E. coli</i> WP2/WP2uvrA	In vitro	0, 5,000 ug/plate	24 hours	Negative up to 5,000 ug/plate	Reverse Mutation	Morita and Hayashi (1998)	High

Genotoxicity	Acute	P. phosphoreum M169	In vitro	ND	18 hours	Negative	Mutagenicity, DNA damage	Kwan et al. (1990)	Unacceptable
Genotoxicity	Short Term	S. cerevisiae D61.M	In vitro	0, 1.48, 1.96, 2.44, 2.91, 3.38, 4.31, 4.75%	7 days	Negative up to 4.75%	Aneuploidy	Zimmermann et al. (1985)	Unacceptable
Genotoxicity	Acute	<i>D. melanogaster</i>	In vitro	0, 1, 1.5, 2, 3, 3.5% in sucrose media	24 hours	LOAEL at 2%	Meiotic nondisjunction	Munoz and Barnett (2002)	High
Genotoxicity		<i>D. melanogaster</i>	In vitro	35,000 ppm in feed, 7 days or 50,000 ppm (5% in water) by injection			Sex-linked recessive lethal test	Yoon et al. (1985)	Medium
Genotoxicity	Acute	Rat hepatocytes	In vitro	0, 0.03, 0.3, 3, 10, 30 mM	3 hours	LOAEL at 0.3 mM	DNA damage; single-strand breaks measured by alkaline elution	Sina et al. (1983)	High
Genotoxicity	Short Term	Primary hepatocyte culture from male F344 rats	In vitro	0, 0.001, 0.01, 0.1, 1 mM	5 days	Negative up to 1mM	DNA repair	Goldsworthy et al. (1991)	High
Genotoxicity	Short Term	L5178Y mouse lymphoma cells	In vitro	0, 5,000 ug/mL	48 hours	Negative up to 5,000 ug/mL	Forward mutation assay	Mcgregor et al. (1991)	High
Genotoxicity	Acute	L5178Y mouse lymphoma cells	In vitro	0, 5,000 ug/mL	24 hours	Negative up to 5,000 ug/mL	Forward mutation assay	Morita and Hayashi (1998)	High
Genotoxicity	Short Term	BALB/3T3 cells	In vitro	0, 0.25, 0.5, 1.0, 2.0 mg/mL	48 hours	LOAEL at 0.5 mg/mL	Cell transformation	Sheu et al. (1988)	High
Genotoxicity	Acute	CHO cells	In vitro	0, 1,050, 3,500, 10,500 ug/L	2 hours	Negative up to 10,500 ug/mL	SCE	Galloway et al. (1987)	High
Genotoxicity	Short Term	CHO cells	In vitro	0, 1,050, 3,500, 10,500 ug/L	26 hours	Negative up to 10,500 ug/mL	Chromosomal aberration	Galloway et al. (1987)	High
Genotoxicity	Short Term	CHO cells	In vitro	0, 5,000 ug/mL	26 hours	Negative up to 5,000 ug/mL	SCE	Morita and Hayashi (1998)	High

Genotoxicity	Short Term	CHO cells	In vitro	0, 5,000 ug/mL	44 hours	Negative up to 5,000 ug/mL	Chromosomal aberration	Morita and Hayashi (1998)	High
Genotoxicity	Short Term	CHO cells	In vitro	0, 5,000 ug/mL	44 hours	Negative up to 5,000 ug/mL	Micronucleus formation	Morita and Hayashi (1998)	High
Genotoxicity	Acute	Calf thymus DNA	In vitro	0.04 pmol/mg/DNA	16 hours	Negative up to 0.04 pmol/mg/DNA (bound)	Covalent binding to DNA	Woo et al. (1977c)	Unacceptable
Genotoxicity	Acute	Female Sprague Dawley Rat	In vivo	0, 168, 840, 2,550, 4,200 mg/kg	21 hours	LOAEL at 2,550 mg/kg	DNA damage; single-strand breaks measured by alkaline elution	Kitchin and Brown (1990)	Medium
Genotoxicity	Subchronic	Male Sprague Dawley Rat	In vivo	0, 10, 100, 1000 mg/kg	11 weeks	Negative up to 1,000 mg/kg	DNA alkylation in hepatocytes	Stott et al. (1981)	High
Genotoxicity	Short Term	Male B6C3F1 Mouse	In vivo	0, 500, 1,000, 2,000 mg/kg daily dose; 0, 2,000, 3,000, 4,000 mg/kg single injection	48 hours	Negative up to daily doses of 2,000, Single dose of 4,000 mg/kg	Micronucleus formation in bone marrow	McFee et al. (1994)	High
Genotoxicity	Short Term	Male and female C57BL6 Mouse; Male BALB/c Mouse	In vivo	0, 450, 900, 1,800, 3,600 mg/kg (C57BL6); 0, 5,000 mg/kg (BALB/c)	48 hours	LOAEL of 900 mg/kg (C57BL6); Negative up to 5,000 mg/kg (BALB/c)	Micronucleus formation in bone marrow	Mirkova (1994)	High
Genotoxicity	Short Term	Male CD1 Mouse	In vivo	0, 500, 1,000, 2,000, 3,200 mg/kg	72 hours	Negative up to 3,200 mg/kg	Micronucleus formation in peripheral blood	Morita (1994)	High
Genotoxicity	Short Term	Male CD1 Mouse	In vivo	0, 1,000, 2,000, or 3,000 mg/kg	7 days	LOAEL at 2,000 mg/kg	Micronucleus formation in hepatocytes	Morita and Hayashi (1998)	High
Genotoxicity	Short Term	Male CD1 Mouse	In vivo	0, 1,000, 2,000, or 3,000 mg/kg	7 days	Negative up to 3,000 mg/kg	Micronucleus formation in peripheral blood	Morita and Hayashi (1998)	High

Genotoxicity	Acute	Male CBA and C57BL6 Mouse	In vivo	0, 1,800, 3,600 mg/kg	24 hours	Negative up to 3,600 mg/kg	Micronucleus formation in bone marrow	Tinwell and Ashby (1994)	High
Genotoxicity	Short Term	Male CD1 Mouse	In vivo	0, 1,500, 2,500, 3,500 mg/kg per day for 5 days	6 days	LOAEL of 1,500 mg/kg-day for 5 days	Micronuclei formation in bone marrow	Roy et al. (2005)	High
Genotoxicity	Short Term	Male CD1 Mouse	In vivo	0, 1,500, 2,500, 3,500 mg/kg per day for 5 days	6 days	LOAEL of 2,500 mg/kg-day for 5 days	Micronuclei formation in hepatocytes	Roy et al. (2005)	High
Genotoxicity	Subchronic	Male Sprague Dawley Rat	In vivo	0, 10, 100, 1,000 mg/kg-day for 11 weeks	11 weeks	Negative up to 1,000 mg/kg-day for 11 weeks	DNA repair in hepatocytes	Stott et al. (1981)	High
Genotoxicity	Acute	Male F344 Rat	In vivo	0, 10, 100, 1,000 gm/kg for 2 or 12 hours;	12 hours	Negative up to 1,000 mg/kg for 2 or 12 hours	DNA repair in hepatocytes (autoradiograph)	Goldsworthy et al. (1991)	High
Genotoxicity	Short Term	Male F344 Rat	In vivo	0, 1,500 mg/kg-day for 8 days + 1,000 mg/kg gavage dose 12 hours prior to sacrifice	8 days	Negative up to 1,500 mg/kg-day for 8 days + 1,000 mg/kg gavage dose 12 hours prior to sacrifice	DNA repair in nasal epithelial cells from the nasoturbinate or maxilloturbinate	Goldsworthy et al. (1991)	Unacceptable
Genotoxicity	Short Term	Male F344 Rat	In vivo	0, 1,000 mg/kg for 24 or 48 hours; 1,500 mg/kg-day for 1 or 2 weeks	2 weeks	LOAEL of 1,000 mg/kg for 24 or 48 hours; 1,500 mg/kg-day for 1 or 2 weeks	Replicative DNA synthesis (<i>i.e.</i> , cell proliferation) in hepatocytes	Goldsworthy et al. (1991)	High
Genotoxicity	Short Term	Male F344 Rat	In vivo	0, 1,500 mg/kg-day for 2 weeks	2 weeks	1,500 mg/kg-day for 2 weeks	Replicative DNA synthesis (<i>i.e.</i> , cell proliferation) in nasal epithelial cells	Goldsworthy et al. (1991)	Unacceptable
Genotoxicity	Acute	Male Sprague Dawley Rat	In vivo	0, 10, 100 mg/rat	24 hours	LOAEL of 10 mg/rat	RNA synthesis; inhibition of RNA polymerase A and B	Kurl et al. (1981)	Unacceptable

Genotoxicity	Short Term	Male F344 Rat	In vivo	0, 1,000, 1,500, 2,000, 4,000 mg/kg	48 hours	LOAEL of 1,000 mg/kg	DNA synthesis in hepatocytes	Miyagawa et al. (1999)	High
Genotoxicity	Short Term	Male F344 Rat	In vivo	0, 1,000, 2,000 mg/kg	48 hours	LOAEL of 2,000 mg/kg	DNA synthesis in hepatocytes	Uno et al. (1994)	Medium
Genotoxicity	Short Term	Male Sprague Dawley Rat	In vivo	0, 10, 100, or 1,000 mg/kg.	11 weeks	LOAEL of 1,000 mg/kg-day for 11 weeks	DNA synthesis in hepatocytes	Stott et al. (1981)	High
Genotoxicity	Long Term	Male <i>gpt</i> delta transgenic F344 rats	In vivo	0, 200, 1,000, 5,000 ppm	16 weeks	Positive at 5,000 ppm	Increased relative mRNA expression levels	Gi et al. (2018)	High
Genotoxicity	Long Term	Male <i>gpt</i> delta transgenic F344 rats	In vivo	0, 0.2, 2, or 20 ppm	16 weeks	Negative up to 20 ppm	Mutagenesis	Gi et al. (2018)	High
Genotoxicity	Long Term	Male <i>gpt</i> delta transgenic F344 rats	In vivo	0, 2, 20, 200, 2,000, 5,000 ppm	16 weeks	Positive at 2,000 ppm	Increased GST-P-positive foci induction and cell proliferation	Gi et al. (2018)	High

Table I-2. Cancer Incidence for 1,4-Dioxane Studies with Acceptable Data Quality Ratings¹

Study Type	Species/ Strain/Sex (Number/ group)	Exposure Route	Doses/ Concentrations	Duration	Cancer Incidence	Effect	Reference	Data Quality Evaluation
Chronic	Rat, Wistar, M (n=26 treated, 9 controls)	Oral, drinking water	0 or 640 mg/kg-bw/day	63 weeks	6/26 treated rats	Hepatocellular carcinomas	Argus et al. (1965)	Medium
Chronic	Rat, Wistar, M (n=26 treated, 9 controls)	Oral, drinking water	0 or 640 mg/kg-bw/day	63 weeks	1/26 treated rats	Transitional cell carcinoma in kidney's pelvis	Argus et al. (1965)	Medium
Chronic	Rat, Wistar, M (n=26 treated, 9 controls)	Oral, drinking water	0 or 640 mg/kg-bw/day	63 weeks	1/26 treated rats	Leukemia	Argus et al. (1965)	Medium
Chronic	Rat, Sprague Dawley, M (n=30/group)	Oral, drinking water	0, 430, 574, 803 or 1032 mg/kg-bw/day	13 months	5/28-32 rats (dose not specified)	Liver	Argus et al. (1973)	Low

Study Type	Species/ Strain/Sex (Number/ group)	Exposure Route	Doses/ Concentrations	Duration	Cancer Incidence	Effect	Reference	Data Quality Evaluation
Chronic	Rat, F344/DuCrj , M/F, (n= 100/group)	Oral, drinking water	0, 11, 55, or 274 mg/kg-bw/day (M) 0, 18, 83, or 429 mg/kg-bw/day (F)	2 years	3,4,7,32 (M, 50 rats/ dose) 3,1,6,48 (F, 50 rats/ dose)	Hepatocellular adenoma	Kano et al. (2009; JBRC (1998)	High
Chronic	Rat, F344/DuCrj , M/F, (n= 100/group)	Oral, drinking water	0, 11, 55, or 274 mg/kg-bw/day (M) 0, 18, 83, or 429 mg/kg-bw/day (F)	2 years	0,0,0,14 (M, 50 rats/ dose) 0,0,0,10 (F, 50 rats/ dose)	Hepatocellular carcinoma	Kano et al. (2009; JBRC (1998)	High
Chronic	Rat, F344/DuCrj , M/F, (n= 100/group)	Oral, drinking water	0, 11, 55, or 274 mg/kg-bw/day (M) 0, 18, 83, or 429 mg/kg-bw/day (F)	2 years	3,4,7,39 (M, 50 rats/ dose) 3,1,6,48 (F, 50 rats/ dose)	Either hepatocellular adenoma or carcinoma	Kano et al. (2009; JBRC (1998)	High
Chronic	Rat, F344/DuCrj , M/F, (n= 100/group)	Oral, drinking water	0, 11, 55, or 274 mg/kg-bw/day (M) 0, 18, 83, or 429 mg/kg-bw/day (F)	2 years	1,1,0,4 (M, 50 rats/ dose) 3,2,1,3 (F, 50 rats/ dose)	Mammary gland- Fibroadenoma	Kano et al. (2009; JBRC (1998)	High
Chronic	Rat, F344/DuCrj , M/F, (n= 100/group)	Oral, drinking water	0, 11, 55, or 274 mg/kg-bw/day (M) 0, 18, 83, or 429 mg/kg-bw/day (F)	2 years	0,1,2,2 (M, 50 rats/ dose) 6,7,10,16 (F, 50 rats/ dose)	Mammary gland- Adenoma	Kano et al. (2009; JBRC (1998)	High
Chronic	Rat, F344/DuCrj , M/F, (n= 100/group)	Oral, drinking water	0, 11, 55, or 274 mg/kg-bw/day (M) 0, 18, 83, or 429 mg/kg-bw/day (F)	2 years	1,2,2,6 (M, 50 rats/ dose) 8,8,11,18 (F, 50 rats/ dose)	Mammary gland- Either fibroadenoma or adenoma	Kano et al. (2009; JBRC (1998)	High
Chronic	Rat, F344/DuCrj , M/F, (n= 100/group)	Oral, drinking water	0, 11, 55, or 274 mg/kg-bw/day (M) 0, 18, 83, or 429 mg/kg-bw/day (F)	2 years	2,2,5,28 (M, 50 rats/ dose) 1,0,0,0 (F, 50 rats/ dose)	Peritoneum- Mesothelioma	Kano et al. (2009; JBRC (1998)	High
Chronic	Rat, F344/DuCrj , M/F, (n= 100/group)	Oral, drinking water	0, 11, 55, or 274 mg/kg-bw/day (M) 0, 18, 83, or 429 mg/kg-bw/day (F)	2 years	0,0,0,3 (M, 50 rats/ dose) 0,0,0,7 (F, 50 rats/ dose)	Nasal- Squamous cell carcinoma	Kano et al. (2009; JBRC (1998)	High

Study Type	Species/ Strain/Sex (Number/ group)	Exposure Route	Doses/ Concentrations	Duration	Cancer Incidence	Effect	Reference	Data Quality Evaluation
Chronic	Rat, F344/DuCrj , M/F, (n= 100/group)	Oral, drinking water	0, 11, 55, or 274 mg/kg-bw/day (M) 0, 18, 83, or 429 mg/kg-bw/day (F)	2 years	0,0,0,2 (M, 50 rats/ dose) 0,0,0,0 (F, 50 rats/ dose)	Nasal- Sarcoma	Kano et al. (2009); JBRC (1998)	High
Chronic	Rat, F344/DuCrj , M/F, (n= 100/group)	Oral, drinking water	0, 11, 55, or 274 mg/kg-bw/day (M) 0, 18, 83, or 429 mg/kg-bw/day (F)	2 years	0,0,0,1 (M, 50 rats/ dose) 0,0,0,0 (F, 50 rats/ dose)	Nasal- Rhabdomyosarcoma	Kano et al. (2009); JBRC (1998)	High
Chronic	Rat, F344/DuCrj , M/F, (n= 100/group)	Oral, drinking water	0, 11, 55, or 274 mg/kg-bw/day (M) 0, 18, 83, or 429 mg/kg-bw/day (F)	2 years	0,0,0,1 (M, 50 rats/ dose) 0,0,0,1 (F, 50 rats/ dose)	Nasal- Esthesioneuroepithelioma	Kano et al. (2009); JBRC (1998)	High
Chronic	Rat, F344/DuCrj, M (n= 50/group)	Inhalation, vapor, whole body	0, 180, 900, or 4500 mg/m3 (0, 50, 250, or 1250 ppm)	6 hours/dy, 5 days/wk, for 2 years	0,0,1,6 (50 rats per dose group)	Nasal squamous cell carcinoma	Kasai et al. (2009)	High
Chronic	Rat, F344/DuCrj, M (n= 50/group)	Inhalation, vapor, whole body	0, 180, 900, or 4500 mg/m3 (0, 50, 250, or 1250 ppm)	6 hours/dy, 5 days/wk, for 2 years	1,2,3,21 (50 rats per dose group)	Hepatocellular adenoma	Kasai et al. (2009)	High
Chronic	Rat, F344/DuCrj, M (n= 50/group)	Inhalation, vapor, whole body	0, 180, 900, or 4500 mg/m3 (0, 50, 250, or 1250 ppm)	6 hours/dy, 5 days/wk, for 2 years	0,0,1,2 (50 rats per dose group)	Hepatocellular carcinoma	Kasai et al. (2009)	High
Chronic	Rat, F344/DuCrj, M (n= 50/group)	Inhalation, vapor, whole body	0, 180, 900, or 4500 mg/m3 (0, 50, 250, or 1250 ppm)	6 hours/dy, 5 days/wk, for 2 years	0,0,0,4 (50 rats per dose group)	Renal cell carcinoma	Kasai et al. (2009)	High
Chronic	Rat, F344/DuCrj, M (n= 50/group)	Inhalation, vapor, whole body	0, 180, 900, or 4500 mg/m3 (0, 50, 250, or 1250 ppm)	6 hours/dy, 5 days/wk, for 2 years	2,4,14,41 (50 rats per dose group)	Peritoneal mesothelioma	Kasai et al. (2009)	High
Chronic	Rat, F344/DuCrj, M (n= 50/group)	Inhalation, vapor, whole body	0, 180, 900, or 4500 mg/m3 (0, 50, 250, or 1250 ppm)	6 hours/dy, 5 days/wk, for 2 years	1,2,3,5 (50 rats per dose group)	Mammary gland fibroadenoma	Kasai et al. (2009)	High
Chronic	Rat, F344/DuCrj, M (n= 50/group)	Inhalation, vapor, whole body	0, 180, 900, or 4500 mg/m3 (0, 50, 250, or 1250 ppm)	6 hours/dy, 5 days/wk, for 2 years	0,0,0,1 (50 rats per dose group)	Mammary gland adenoma	Kasai et al. (2009)	High

Study Type	Species/ Strain/Sex (Number/ group)	Exposure Route	Doses/ Concentrations	Duration	Cancer Incidence	Effect	Reference	Data Quality Evaluation
Chronic	Rat, F344/DuCrj, M (n= 50/group)	Inhalation, vapor, whole body	0, 180, 900, or 4500 mg/m ³ (0, 50, 250, or 1250 ppm)	6 hours/dy, 5 days/wk, for 2 years	0,0,0,4 (50 rats per dose group)	Zymbal gland adenoma	Kasai et al. (2009)	High
Chronic	Rat, F344/DuCrj, M (n= 50/group)	Inhalation, vapor, whole body	0, 180, 900, or 4500 mg/m ³ (0, 50, 250, or 1250 ppm)	6 hours/dy, 5 days/wk, for 2 years	1,4,9,5 (50 rats per dose group)	Subcutis fibroma	Kasai et al. (2009)	High
Chronic	Rat, Sherman, M/F, (n=120/group)	Oral, drinking water	0, 9.6, 94, or 1015 mg/kg-bw/day (M) 0, 19, 148, or 1599 mg/kg-bw/day (F)	2 years	2/106, 0/110, 1/106, 12/66	Hepatic tumors (all types)	Kociba et al. (1974)	High
Chronic	Rat, Sherman, M/F, (n=120/group)	Oral, drinking water	0, 9.6, 94, or 1015 mg/kg-bw/day (M) 0, 19, 148, or 1599 mg/kg-bw/day(F)	2 years	1/106, 0/110, 1/106, 10/66	Hepatocellular carcinoma	Kociba et al. (1974)	High
Chronic	Rat, Sherman, M/F, (n=120/group)	Oral, drinking water	0, 9.6, 94, or 1015 mg/kg-bw/day (M) 0, 19, 148, or 1599 mg/kg-bw/day (F)	2 years	0/106, 0/110, 0/106, 3/66	Nasal carcinoma	Kociba et al. (1974)	High
Chronic	Mouse, B6C3F1, M/F (n=100/group)	Oral, drinking water	0, 720 or 830 mg/kg-bw/day (M); 0, 380 or 860 mg/kg-bw/day (F)	90 weeks	2/49, 18/50, 24/47 (M) 0/50, 12/48, 29/37 (F)	Hepatocellular carcinoma	NCI (1978)	Low
Chronic	Mouse, B6C3F1, M/F (n=100/group)	Oral, drinking water	0, 720 or 830 mg/kg-bw/day (M); 0, 380 or 860 mg/kg-bw/day (F)	90 weeks	8/49, 19/50, 28/47 (M) 0/50, 21/48, 35/37 (F)	Hepatocellular adenoma or carcinoma	NCI (1978)	Low
Chronic	Rat, Osborne- Mendel, F ² (n=70/group)	Oral, drinking water	0, 350 or 640 mg/kg-bw/day (F)	110 weeks	0/34, 10/35, 8/35 (F)	Nasal cavity squamous cell carcinoma	NCI (1978)	Low
Chronic	Rat, Osborne- Mendel, F ² (n=70/group)	Oral, drinking water	0, 350 or 640 mg/kg-bw/day (F)	110 weeks	0/31, 10/33, 11/32 (F)	Hepatocellular carcinoma	NCI (1978)	Low

¹ Unacceptable studies are not included in this table.

²The results for male rats were considered unacceptable and are not included in this table.

I.1.8 Hazard Data Tables

Table I-3. Incidences of non-neoplastic lesions in male F344 rats exposed to 1,4-dioxane via inhalation for 2 years (6 hours/day, 5 days/week) [Kasai et al. \(2009\)](#)

Tissue	Endpoint	Concentration (ppm) and incidence			
		0 ppm	50 ppm	250 ppm	1250 ppm
Liver	Centrilobular necrosis	1	3	6	12
Nasal	Squamous cell metaplasia; respiratory epithelium	0	0	7	44
	Squamous cell hyperplasia; respiratory epithelium	0	0	1	10
	Respiratory metaplasia; olfactory epithelium	11	34	49	48
	Atrophy; olfactory epithelium	0	40	47	48
	Hydropic change; lamina propia	0	2	36	49
	Sclerosis, lamina propia	0	0	22	40

Data quality evaluations for this study were determined to high (see Appendix G)
N=50 for all data.

Table I-4. Altered hepatocellular foci data in F344/DuCrj rats exposed to 1,4-dioxane via drinking water for 2 years (ad libitum) [Kano et al. \(2009\)](#)

Endpoint	Male				Female			
	0 ppm	200 mg/kg-d	1000 mg/kg-d	5000 mg/kg-d	0 ppm	200 mg/kg-d	1000 mg/kg-d	5000 mg/kg-d
Mixed cell foci	2	8	14	13	1	1	3	11

Data quality evaluations for this study were determined to high (see Appendix G)
N=50 for all data.

Table I-5. Incidence of cortical tubule degeneration in female Osborne-Mendel rats exposed to 1,4-dioxane via drinking water for 2 years (ad libitum) [NCI \(1978\)](#)

Species and endpoint	Dose (mg/kg-d) and incidence		
Female Osborne-Mendel rats			
Dose (mg/kg-d)	0 mg/kg-d	350 mg/kg-d	640 mg/kg-d

<i>Kidney</i>			
Cortical tubule degeneration	0/31	0/34	10/32

Data quality evaluations for B6C3F1 mice (male and female) and OM rats (female) from this study were determined to be low (see Appendix G). Data in for male OM rats were determined to be unacceptable and are not included in this table.

Table I-6. Tumor incidence data in male F344 rats exposed to 1,4-dioxane via inhalation for 2 years (6 hours/day, 5 days/week) [Kasai et al. \(2009\)](#)

Endpoint	Concentration (ppm) and incidence (%)			
	0 ppm	50 ppm	250 ppm	1250 ppm
<i>Nasal cavity</i>				
Squamous cell carcinoma	0/50 (0%)	0/50 (0%)	1/50 (2%)	6/50 (12%)
<i>Liver</i>				
Hepatocellular adenoma	1/50 (2%)	2/50 (4%)	3/50 (6%)	21/50 (42%)
Hepatocellular carcinoma	0/50 (0%)	0/50 (0%)	1/50 (2%)	2/50 (4%)
Hepatocellular adenoma or carcinoma*	1/50 (2%)	2/50 (4%)	4/50 (8%)	22/50 (44%)
<i>Kidney</i>				
Renal cell carcinoma	0/50 (0%)	0/50 (0%)	0/50 (0%)	4/50 (8%)
<i>Peritoneum</i>				
Mesothelioma	2/50 (4%)	4/50 (8%)	14/50 (28%)	41/50 (82%)
<i>Mammary gland</i>				
Fibroadenoma	1/50 (2%)	2/50 (4%)	3/50 (6%)	5/50 (10%)
Adenoma	0/50 (0%)	0/50 (0%)	0/50 (0%)	1/50 (2%)
<i>Zymbal gland</i>				
Adenoma	0/50 (0%)	0/50 (0%)	0/50 (0%)	4/50 (8%)
<i>Subcutis</i>				
Fibroma	1/50 (2%)	4/50 (8%)	9/50 (18%)	5/50 (10%)

Data quality evaluations for this study were determined to high (see Appendix G).

*Incidences of hepatocellular adenomas or carcinomas were corrected to account for rats that exhibited both adenomas and carcinomas (data were provided to U.S. EPA by communication with the study author [Kasai \(2008\)](#))

Table I-7. Tumor Incidence data in male and female F344/DuCrj rats and Crj:BDF1 mice exposed to 1,4-dioxane via drinking water for 2 years (ad libitum) [Kano et al. \(2009\)](#)

Species and endpoint	Dose (mg/kg-d) and incidence (%)			
	0 mg/kg-d	11 mg/kg-d	55 mg/kg-d	274 mg/kg-d
Male F344/DuCrj rats				
Dose (mg/kg-d)	0 mg/kg-d	11 mg/kg-d	55 mg/kg-d	274 mg/kg-d
<i>Nasal cavity</i>				
Squamous cell carcinoma	0/50 (0%)	0/50 (0%)	0/50 (0%)	3/50 (6%)
<i>Liver</i>				
Hepatocellular adenoma	3/50 (6%)	4/50 (8%)	7/50 (14%)	32/50 (64%)
Hepatocellular carcinoma	0/50 (0%)	0/50 (0%)	0/50 (0%)	14/50 (28%)
Hepatocellular adenoma or carcinoma	3/50 (6%)	4/50 (8%)	7/50 (14%)	39/50 (78%)
<i>Subcutis</i>				
Fibroma	5/50 (10%)	3/50 (6%)	5/50 (10%)	12/50 (24%)
<i>Peritoneum</i>				
Mesothelioma	2/50 (4%)	2/50 (4%)	5/50 (10%)	28/50 (56%)
Female F344/DuCrj rats				
Dose (mg/kg-d)	0 mg/kg-d	18 mg/kg-d	83 mg/kg-d	429 mg/kg-d
<i>Nasal cavity</i>				
Squamous cell carcinoma	0/50 (0%)	0/50 (0%)	0/50 (0%)	7/50 (14%)
<i>Liver</i>				
Hepatocellular adenoma	3/50 (6%)	1/50 (2%)	6/50 (12%)	48/50 (96%)
Hepatocellular carcinoma	0/50 (0%)	0/50 (0%)	0/50 (0%)	10/50 (20%)
Hepatocellular adenoma or carcinoma	3/50 (6%)	1/50 (2%)	6/50 (12%)	48/50 (96%)
<i>Mammary gland</i>				
Adenoma	6/50 (12%)	7/50 (14%)	10/50 (20%)	16/50 (32%)
Female Crj:BDF1 mice				
Dose (mg/kg-d)	0 mg/kg-d	66 mg/kg-d	278 mg/kg-d	964 mg/kg-d
<i>Liver</i>				
Hepatocellular adenoma	5/50 (10%)	31/50 (62%)	20/50 (40%)	3/50 (6%)
Hepatocellular carcinoma	0/50 (0%)	6/50 (12%)	30/50 (60%)	45/50 (90%)
Hepatocellular adenoma or carcinoma	5/50 (10%)	35/50 (70%)	41/50 (82%)	46/50 (92%)
Male Crj:BDF1 mice				
Dose (mg/kg-d)	0 mg/kg-d	49 mg/kg-d	191 mg/kg-d	677 mg/kg-d
<i>Liver</i>				

Hepatocellular adenoma	9/50 (18%)	17/50 (34%)	23/50 (46%)	11/50 (22%)
Hepatocellular carcinoma	15/50 (30%)	20/50 (40%)	23/50 (46%)	36/50 (72%)
Hepatocellular adenoma or carcinoma	23/50 (46%)	31/50 (62%)	37/50 (74%)	40/50 (80%)

Data quality evaluations for this study were determined to high (see Appendix G).

Table I-8. Tumor Incidence data in in male and female Sherman rats (combined) exposed to 1,4-dioxane via drinking water for 2 years (ad libitum) [Kociba et al. \(1974\)](#)

Endpoint	Dose (mg/kg-d, average of male and female) and incidence (%)			
	0 mg/kg-d	14 mg/kg-d	121 mg/kg-d	1307 mg/kg-d
<i>Liver</i>				
Hepatic tumors (all types)	2/106 (2%)	0/110 (0%)	1/106 (0.9%)	12/66 (18%)
Hepatocellular carcinoma	1/106 (0.9%)	0/110 (0%)	1/106 (0.9%)	10/66 (15%)
Cholangiocarcinoma	1/106 (0.9%)	0/110 (0%)	0/106(0%)	0/66 (0%)
Cholangioma	0/106 (0%)	0/110 (0%)	0/106(0%)	2/66 (3%)
<i>Nasal turbinates</i>				
Squamous cell carcinoma	0/106 (0%)	0/110 (0%)	0/106 (0%)	3/66 (5%)

Data quality evaluations for this study were determined to high (see Appendix G).

Table I-9. Tumor Incidence data in male and female B6C3F1 mice, and female Osborne-Mendel rats exposed to 1,4-dioxane via drinking water for 2 years (ad libitum) [NCI \(1978\)](#)

Species and endpoint	Dose (mg/kg-d) and incidence (%)		
	0 mg/kg-d	720 mg/kg-d	830 mg/kg-d
Male B6C3F1 mice			
<i>Liver</i>			
Hepatocellular adenoma	6/49 (12%)	1/50 (2%)	4/47 (9%)
Hepatocellular carcinoma	2/49 (4%)	18/50 (36%)	24/47 (51%)
Hepatocellular adenoma or carcinoma	8/49 (16%)	19/50 (38%)	28/47 (60%)
Female B6C3F1 mice			

Dose (mg/kg-d)	0 mg/kg-d	380 mg/kg-d	860 mg/kg-d
<i>Liver</i>			
Hepatocellular adenoma	0/50 (0%)	9/48 (19%)	6/37 (16%)
Hepatocellular carcinoma	0/50 (0%)	12/48 (25%)	29/37 (78%)
Hepatocellular adenoma or carcinoma	0/50 (0%)	21/48 (44%)	35/37 (95%)
Female Osborne-Mendel rats			
Dose (mg/kg-d)	0 mg/kg-d	350 mg/kg-d	640 mg/kg-d
<i>Nasal turbinate</i>			
Squamous cell carcinoma	0/34 (0%)	10/35 (29%)	8/35 (23%)
<i>Liver</i>			
Hepatocellular adenoma	0/31 (0%)	10/33 (30%)	11/32 (34%)

Data quality evaluations for B6C3F1 mice (male and female) and OM rats (female) from this study were determined to be low (see Appendix G). Data in for male OM rats were determined to be unacceptable and are not included in this table.

Appendix J MODE OF ACTION ANALYSIS

J.1 Introduction

EPA evaluated proposed modes of action (MOAs) for 1,4-dioxane carcinogenicity using the MOA framework proposed in EPA's [Guidelines for Carcinogen Risk Assessment U.S. EPA \(2005a\)](#). The MOA framework is an analytic tool that applies modified Hill criteria for causality to evaluate whether available data support a hypothesized carcinogenic MOA. This MOA analysis for 1,4-dioxane considers evidence from animal cancer bioassays, genotoxicity studies, proposed key events, MOAs published in the peer-reviewed literature, and the analysis previously presented in EPA's IRIS Toxicological Review of 1,4 Dioxane [U.S. EPA \(2013d\)](#).

1,4-Dioxane is a multisite carcinogen associated with increased incidences of liver tumors, kidney tumors, nasal cavity tumors, and peritoneal mesothelioma in rats and increased incidences of liver tumors in mice. EPA does not have sufficient information to determine whether carcinogenic effects of 1,4-dioxane at each tumor site are mediated by the parent compound, metabolites, or both. The most well-developed MOAs for 1,4-dioxane carcinogenicity focus on the MOA for liver tumors. Therefore, this MOA analysis focuses on plausible MOAs of 1,4-dioxane liver carcinogenicity.

J.2 Potential MOAs of 1,4-Dioxane Liver Carcinogenicity

EPA considered four of the plausible MOAs for liver carcinogenicity of 1,4-dioxane, including metabolic saturation and cytotoxicity followed by regenerative proliferation, proliferation in the absence of cytotoxicity, mutagenic and other genotoxic mechanisms, and CAR/PXR-mediated effects:

- **MOA1: Metabolic saturation, cytotoxicity and proliferative regeneration.** In this hypothesized MOA, metabolic saturation leads to the accumulation of the parent compound 1,4-dioxane, which causes liver tumors through cytotoxicity and subsequent regenerative proliferation. Dourson et al. [2017](#); [2014](#)) proposed specific key events and compiled evidence from animal bioassays [McConnell \(2013\)](#); [Kociba et al. \(1974\)](#). EPA used the framework for MOA analysis described in EPA's [Guidelines for Carcinogen Risk Assessment U.S. EPA \(2005a\)](#) to further evaluate the current evidence for this proposed mode of action (MOA) for 1,4-dioxane carcinogenicity.
- **MOA2: Cell proliferation in the absence of cytotoxicity.** It is possible that 1,4-dioxane or a metabolite leads to cell proliferation in the absence of cytotoxicity. This potential MOA has not been articulated in the peer-reviewed literature and there is insufficient information to determine the specific key events through which 1,4-dioxane or its metabolites may lead to proliferation.

- **MOA3: Mutagenicity and other forms of genotoxicity.** As described in Section 4.2.3.2, EPA concluded that there is insufficient data to determine whether 1,4-dioxane is mutagenic or induces cancer through a mutagenic MOA. In the absence of other information about MOA, EPA often takes the health protective approach of assuming a linear no-threshold risk model consistent with a mutagenic MOA.
- **MOA4: CAR/PXR mediated effects.** The nuclear receptors CAR and PXR have been proposed as mediators of liver toxicity and carcinogenicity. Mechanistic evidence from other chemicals indicates that CAR agonists may lead to proliferation and liver tumors in the absence of cell death [Elcombe et al. \(2014\)](#). While this is a plausible MOA for 1,4-dioxane carcinogenicity, the key events in the MOA linking 1,4-dioxane to CAR-mediated carcinogenicity have not been clearly articulated in the literature, and 1,4-dioxane has not been identified as a CAR agonist. One 16-week drinking water exposure study in transgenic rats evaluated a panel of CYP enzymes that are induced by nuclear receptors CAR, PXR, PPAR α , or AhR and found no changes in mRNA expression of these CYPs in rat livers following 1,4-dioxane exposure [Gi et al. \(2018\)](#). No studies have evaluated this mechanism in the presence of tumor formation. EPA concluded that there is insufficient chemical-specific data to meaningfully evaluate this proposed MOA.

Of these potential MOAs, cytotoxicity and proliferative regeneration (MOA1) is the one most widely discussed in the literature. Therefore, the rest of this analysis focuses on evaluating the available evidence for MOA1.

J.3 MOA analysis for metabolic saturation, cytotoxicity and proliferative regeneration (MOA1) as the basis for 1,4-dioxane-induced liver carcinogenicity

J.3.1 Description of the hypothesized MOA

In this proposed MOA, metabolic saturation leads to accumulation of the parent compound 1,4-dioxane. Accumulated 1,4-dioxane then causes cytotoxicity by an undetermined mechanism. Cytotoxicity is followed by regenerative proliferation, leading to liver tumors. The proposed MOA and the strength of evidence for each key event is summarized in Figure 6-1. Evidence in support of each key event is summarized in Table J-1..

In a previous analysis, EPA determined that evidence in support of this MOA was inconclusive [U.S. EPA \(2005a\)](#). New supplemental data that were not available to EPA at the time of the previous review have since been published. Dourson et al. [2017](#); [2014](#)) proposed specific key events for this MOA and compiled supporting evidence from animal bioassays. Dourson et al. support this MOA hypothesis using previously unavailable liver histopathology data from translated Japanese Bioassay Research Center (JBRC) study reports (the data underlying [Kano et al. \(2008\)](#) and [Kano et al. \(2009\)](#)) and reanalyzed liver histopathology data from the 1978 NCI study [McConnell \(2013\)](#).

In addition, previously unpublished incidence data from Kociba (1974) and an unpublished 90 day ACC study were made available to EPA and the public through the public comment process for this risk evaluation. EPA reviewed these submissions and concluded that while they provide some information that is relevant to mechanism, they do not provide information in support of a specific MOA. The hepatic nuclear injury reported in unpublished Kociba data does not seem to coincide with other liver toxicity, and does not seem to be an early event or precondition for the other changes to occur. The 90-day ACC study reported liver toxicity and corresponding changes in gene expression, but these effects are not specific to carcinogenicity. The study did not contribute evidence that the events reported in the study were key events and necessary sufficient precursors to tumor formation

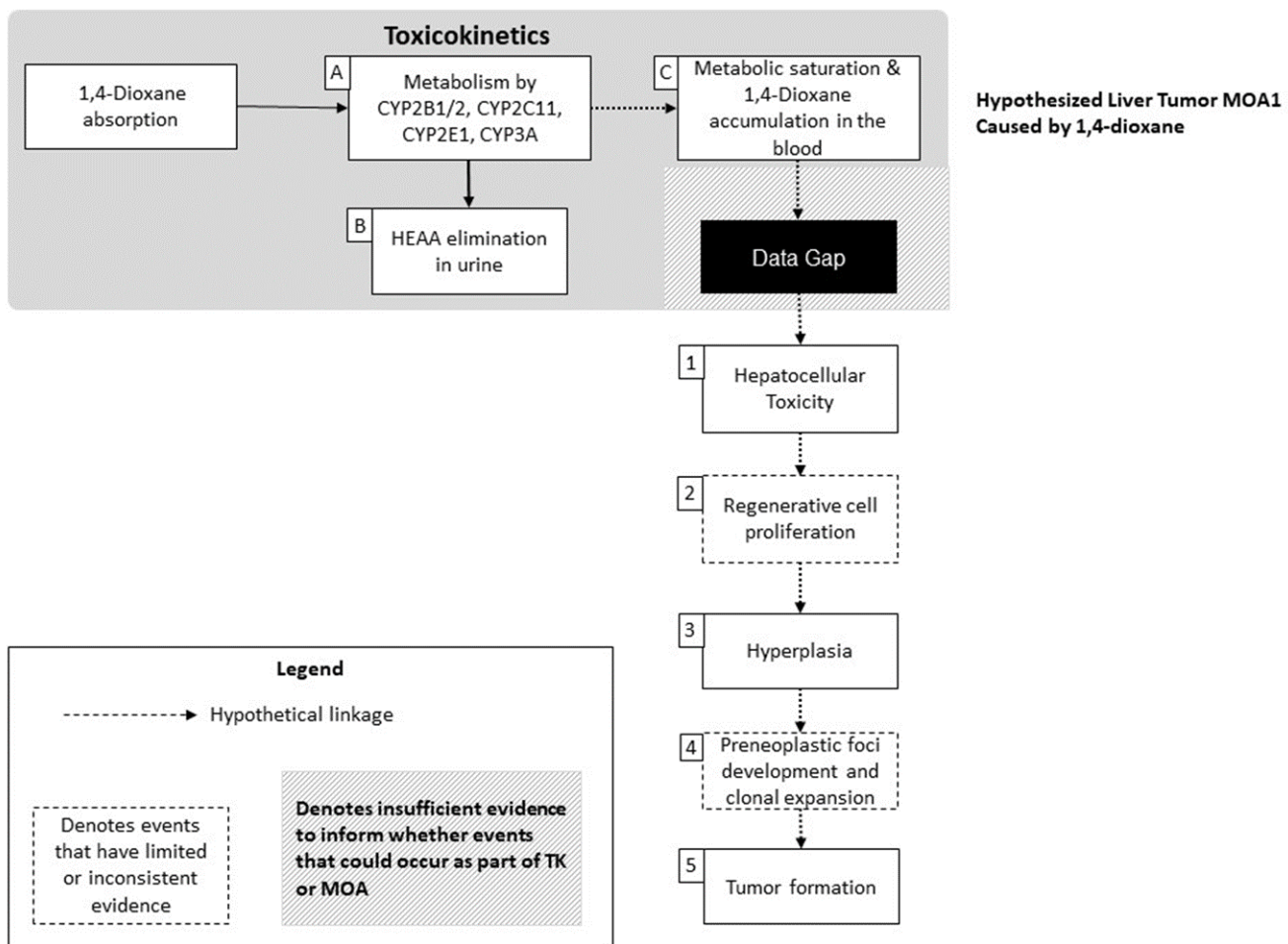


Figure 6-1. Hypothesized Liver Tumor MOA1 for 1,4-dioxane

Table J-1. Supporting Evidence for Hypothesized Liver Tumor MOA1 for 1,4-dioxane

Key Event	Event Description	Key Event Relationship/Supporting Data	Reference
Exposure & absorption Inhalation	1,4-dioxane exposure and absorption	1,4-dioxane exposure may occur via breathing of contaminated air or via dermal absorption	ATSDR (2012)
A. Metabolism	Metabolism by CYP2B1/2, CYP2C11, CYP2E1, CYP3A	Increased activity of CYP450 isozymes (<i>i.e.</i> , CYP2B1/2, CYP2C11, CYP2E1, CYP3A) metabolize 1,4-dioxane into β -hydroxyethoxy acetic acid (HEAA) and other metabolites possibly including diethylene glycol and diglycolic acid	Nannelli et al. (2005); Woo et al. (1977a)
B.	Excretion	1,4-dioxane metabolite, HEAA is excreted in urine	Nannelli et al. (2005); Young et al. (1978a, b); Woo et al. (1977a); Woo et al. (1977b); Young et al. (1977)
C	Metabolic saturation and accumulation of 1,4-dioxane	Metabolic capacity exceeded leading to accumulation of 1,4-dioxane	Nannelli et al. (2005); Goldsworthy et al. (1991); Kociba et al. (1975)
1	Hepatocellular Toxicity	Hepatocellular toxicity marked by the following: there were hepatotoxicity findings from two 2-year studies where male and female rats received oral doses of 1,4-dioxane in drinking water Kano et al. (2008); Kociba et al. (1974) . These findings included anisonucleosis, a morphological manifestation of nuclear injury characterized by variation in the size of the cell nuclei. This nuclear change was coincident with findings of hepatocyte swelling (vacuolar degeneration) and hepatocellular necrosis. Further support for liver toxicity were findings of increased serum levels of the enzymes ALT (GPT), AST (GOT), ALP, GGT, and LDH in male and female rats receiving oral 1,4-dioxane exposures in drinking water Kano et al. (2008); JBRC (1998) Lundberg et al. (1986); Kociba et al. (1975) and receiving 1,4-Dioxane inhalation exposures Kasai et al. (2009); Kasai et al. (2008); Drew et al. (1978) . While, serum levels, in general, were significantly increased by <2-fold, it is	Kasai et al. (2009); Kasai (2008); JBRC (1998); Stott et al. (1981); Drew et al. (1978)

		clear that the liver is affected because: 1) the liver is the only organ common to ALT, AST, ALP, GGT, and LDH Whalan (2000) ; and 2) there were concurrent histopathology findings (vacuolization, nuclear enlargement, and necrosis) supporting 1,4-Dioxane hepatotoxicity.	
2	Regenerative cell proliferation	Increases in cell proliferation in hepatocytes were reported using replicative DNA synthesis as a surrogate marker at doses observed to be tumorigenic. Inconsistency in characterization of histopathology.	McConnell (2013) ; Miyagawa et al. (1999) ; JBRC (1998) ; Goldsworthy et al. (1991) ; Stott et al. (1981) ; Kociba et al. (1975) ; Kociba et al. (1974)
3	Hyperplasia	Hepatocyte hyperplasia observed with clear and mixed foci development. Liver hyperplasia in rats and mice	McConnell (2013) ; Kano et al. (2008) ; JBRC (1998) ; Yamazaki et al. (1994) ; NCI (1978)
4	Preneoplastic foci development and clonal expansion	Evidence (limited, 1 study) of foci development and clonal expansion observed at high (1000 mg/kg/day) dose in a tumor promotion study. Additional evidence of foci development in rats includes acidophilic, mixed, and basophilic hepatocellular foci changes reported following inhalation or oral drinking water exposures. These findings were not dose-responsive, but were correlative with increased incidence of hepatocellular adenoma and/or carcinoma at the highest administered dose.	Kano et al. (2009) ; Kasai et al. (2009) ; Lundberg et al. (1987)
5	Tumor formation	Hepatic adenomas and carcinomas formed	McConnell (2013) ; Kano et al. (2009) ; JBRC (1998) ; Yamazaki et al. (1994) ; NCI (1978)

			Kociba et al. (1975); Kociba et al. (1974).
--	--	--	--

J.3.2 Description of experimental support for the hypothesized MOA

J.3.3 Strength, consistency, and specificity of association

As summarized in Table I-1, there is experimental evidence that is consistent with several of the key events in the proposed MOA. This section describes and evaluates the evidence in support of each key event, including the level of statistical and biological significance of the data, and the consistency and specificity of observations across studies.

Strength of evidence for 1,4-dioxane metabolism, excretion, and metabolic saturation (Key Events A, B, and C in Table J-1.)

Toxicokinetic studies indicate that while metabolism of 1,4-dioxane follows first-order kinetics at lower doses, higher oral doses exhibit nonlinear Michaelis-Menten kinetics [Young et al. \(1978a, b\)](#); [Kociba et al. \(1975\)](#). [Dourson et al. \(2017; 2014\)](#) concluded that this is an indication of metabolic saturation and that liver toxicity primarily occurs following metabolic saturation at high doses that are not relevant for human exposures. Conversely, there is no clear evidence for metabolic saturation in inhalation studies. In a 13-week inhalation study, metabolic saturation was not observed at plasma concentrations of up to 730 and 1,054 µg/mL in male and female rats, respectively [Kasai \(2008\)](#). Following inhalation exposure to 400-3200 ppm 1,4-dioxane, plasma concentrations increased linearly with dose, consistent with first-order kinetics. The lack of metabolic saturation following inhalation exposure may be due to enzyme induction and/or due to toxicokinetic differences between inhalation and oral exposures related to first-pass metabolism. Increased incidence of liver tumors in male rats was reported following inhalation exposure to 1250 ppm 1,4-dioxane [Kasai et al. \(2009\)](#), well within the range of exposure that followed first order kinetics in [Kasai et al. \(2008\)](#). This evidence in inhalation exposure studies suggests that metabolic saturation may not be a necessary key event for liver tumor formation.

Based on toxicokinetic evidence for metabolic saturation and the lack of increase in toxicity following induction of CYP450 metabolism, [Dourson et al. \(2017; 2014\)](#) proposed that the parent compound is the toxic moiety. This is consistent with the fact that 1,4-Dioxane is known to be metabolized by CYP450s into beta-hydroxyethoxyacetic acid (HEAA) which is then excreted through urine. Alternate metabolic pathways for 1,4-dioxane may also be present. One plausible explanation for the lack of increased toxicity following CYP induction is the possibility that toxicity is mediated by metabolites generated through alternate metabolic pathways. Therefore, liver toxicity due to metabolites of 1,4-dioxane cannot be ruled out.

Strength of evidence for hepatocellular toxicity (Key Event 1 in Table J-1.)

Evidence for hepatocellular toxicity following 1,4-dioxane exposure includes significant increases in cytoplasmic vacuolar degeneration, hepatocellular necrosis and non-neoplastic lesions, and/or increased liver enzymes [Kasai et al. \(2009\)](#); [Kano et al. \(2008\)](#); [Kasai \(2008\)](#); [JBRC \(1998\)](#); [Stott et al. \(1981\)](#); [Drew et al. \(1978\)](#). In 13-week studies [Kano et al. \(2008\)](#); [Kasai \(2008\)](#), evidence for cytotoxicity in the liver was reported at dose levels above those associated with tumor formation in subsequent cancer bioassays. While evidence of cytotoxicity was also observed in some 2-year cancer bioassays [McConnell \(2013\)](#); [Kociba et al. \(1974\)](#), it was not consistently seen as a precursor to carcinogenic lesions in all studies. For example, liver tumors in female mice were observed in the absence of hepatocellular toxicity [Kano et al. \(2009\)](#). As discussed below, the dose-response relationships to tumor formation are not established in rat and mouse data and are inconsistent among bioassays and across exposure duration, suggesting it is not necessary key event in the MOA of 1,4-dioxane liver carcinogenesis. Evidence for liver tumors in the

absence of hepatocellular toxicity is consistent with the alternate hypothesis articulated in MOA2 (see Section J.2).

There is insufficient information on metabolic and mechanistic processes that may lead to cytotoxicity in rodents exposed to 1,4-dioxane. There is no clear evidence that metabolic saturation is a necessary precursor to cytotoxicity, as represented by the dashed line between these key events in Figure 6-1. Hypothesized Liver Tumor MOA1 for 1,4-dioxane. There are also no *in vitro* or *in vivo* assays that have conclusively identified the toxic moieties resulting from 1,4-dioxane exposure. The mechanism of a cytotoxic response to 1,4-dioxane is therefore unknown. This data gap is represented by the black box in Figure 6-1.

Strength of evidence for regenerative cell proliferation (Key Event 2 in Table J-1.)

Evidence in rat bioassays supports the occurrence of cell proliferation prior to liver tumor formation, [McConnell \(2013\)](#); [Miyagawa et al. \(1999\)](#); [JBRC \(1998\)](#); [Goldsworthy et al. \(1991\)](#); [Stott et al. \(1981\)](#); [Kociba et al. \(1975\)](#); [Kociba et al. \(1974\)](#); however, the dose-response relationship for induction of cell proliferation has not been characterized, and it is unknown if there is a dose-response relationship between cell proliferation and liver tumors in the 2-year cancer bioassays in rat and mouse studies.

Increases in cell proliferation in hepatocytes were reported using replicative DNA synthesis as a surrogate marker at doses observed to be tumorigenic. It is unknown whether the increased rates of DNA synthesis observed in response to 1,4-dioxane exposure represent a true increase in cellular proliferation rates or if this increase is a cellular response to DNA damage and the repair of those lesions. It is also unknown whether observed cell proliferation is a direct response to cytotoxicity and whether it is caused by 1,4-dioxane or a metabolite. Cell proliferation in the absence of cytotoxicity would be consistent with the alternate hypothesis articulated in MOA2 (see Section J.2).

Strength of evidence for hyperplasia (Key Event 3 in Table J-1.)

Hepatocyte hyperplasia was reported in rats and mice following 1,4-dioxane exposure in several studies [McConnell \(2013\)](#); [JBRC \(1998\)](#); [Yamazaki et al. \(1994\)](#); [NCI \(1978\)](#); however, the hyperplasia originally reported by Yamazaki et al. and JBRC was subsequently reexamined histopathologically and changed to hepatocellular adenoma and altered hepatocellular foci [Kano et al. \(2009\)](#). EPA also considered previously unavailable incidence data from [Kociba et al. \(1974\)](#). This new data suggests there may be a dose-response relationship between 1,4-dioxane and bile duct epithelial hyperplasia, but did not show a dose-response relationship between 1,4-dioxane and hepatocellular hyperplasia or demonstrate that hyperplasia precedes tumor formation.

Strength of evidence for preneoplastic foci development and clonal expansion (Key Event 4 in Table J-1.)

The sequence of cellular events leading to hepatocarcinogenesis are represented by increased clear and acidophilic foci, glycogen depletion, increased cellular proliferation linked with the gradual appearance of mixed and basophilic cell foci [Bannasch et al. \(1982\)](#). There is limited evidence of foci development and clonal expansion following 1,4-dioxane exposure in a tumor promotion study. Following initiation with diethylnitrosoamine, a high dose (1000 mg/kg/day by oral gavage) of 1,4-dioxane administered to rats 5 times a week for 6 weeks was associated with a significant increase in the number and volume of foci [Lundberg et al. \(1987\)](#). There is also evidence available in rats for acidophilic, mixed, and basophilic foci development [Kano et al. \(2009\)](#); [Kasai et al. \(2009\)](#) (Tables I-4, I-6 and I-8) and glutathione S-transferase placental form (GST-P)-positive foci [Kano et al. \(2008\)](#) that are a possible early predictor of hepatocarcinogenicity [Ito et al. \(2000\)](#). These findings were not dose-responsive, but were correlative

with increased incidence of hepatocellular adenoma and/or carcinoma at the highest administered dose. Foci development and progression to hepatocarcinogenesis is an unclear process that may be reversible, persistent, transient, and/or progressive. Further, foci of altered hepatocytes may progress to hepatocarcinogenesis with or without an intermediary neoplastic nodular stage (that may lag for weeks or months after foci development and before progression to hepatocarcinomas). The presence of basophilic foci is marked by a strong increase in glucose 6 phosphate dehydrogenase activity, suggesting a switch from glycogenolysis to pentose phosphate pathway and glycolysis as the predominant metabolic pathways [Bannasch et al. \(1982\)](#). Neoplastic nodules (also known as hyperplastic nodules) contain a mixture of precancerous and diverse intermediary cells [Bannasch et al. \(1980\)](#) and in the rat liver, is morphologically similar to human hepatic adenomas whereas comparable nodules in mice have been classified as hepatocellular nodules [Walker et al. \(1973\)](#), neoplastic nodules [Bannasch et al. \(1979\)](#), or adenomas [Williams et al. \(1979\)](#). While the observations of foci, nodules and adenomas in rats is expected to be relevant to humans, mice are more susceptible to the development of spontaneous carcinomas and liver nodules following carcinogen exposure [Ohmori et al. \(1981\)](#); [Grasso and Crampton \(1972\)](#). Therefore, the human applicability of the mouse data from [McConnell \(2013\)](#) may be further reduced in addition to study design characteristics described below. While the current available evidence consistently identified foci development correlative with tumor formation in rats in the absence of a dose- response relationship, it is assumed that foci development is a precursor to hepatocarcinogenesis..

Strength of evidence for tumor formation (Key Event 5 in Table J-1.)

There is clear and consistent evidence of a significant increase in liver tumor formation (including adenomas and carcinomas) in rats and mice exposed to 1,4-dioxane through drinking water and in rats exposed through inhalation [McConnell \(2013\)](#); [Kano et al. \(2009\)](#); [JBRC \(1998\)](#); [Yamazaki et al. \(1994\)](#); [NCI \(1978\)](#); [Kociba et al. \(1975\)](#); [Kociba et al. \(1974\)](#). While a significant increase in liver tumor formation has been observed in male and female rats and mice following 1,4-dioxane exposure, female mice appear to be most sensitive [Kano et al. \(2009\)](#).

J.3.4 Dose-response concordance between observed tumors and events in the proposed MOA

This section considers the dose-response relationships for key events and tumor incidence in each of the cancer bioassay datasets, and examines the concordance of data across studies.

Dose response data indicate that hepatocellular toxicity and non-neoplastic lesions may not be a necessary precursor to carcinogenic lesions in liver following 1,4-dioxane exposure. As described previously [U.S. EPA \(2013d\)](#), the doses in hepatotoxicity studies where cytotoxicity and cell proliferation were observed were greater than doses associated with increased tumor incidence in cancer bioassays.

Bioassays of 1,4- dioxane in rats and mice conducted by the JBRC (Tables I-2 through I-12) provide the most substantial basis for evaluating liver cancer induction by 1,4-dioxane. These studies utilized both rats and mice [Kano et al. \(2009\)](#), both ingestion [Kano et al. \(2009\)](#) and inhalation [Kasai et al. \(2009\)](#) exposure pathways, and include chronic duration cancer studies [Kano et al. \(2009\)](#); [Kasai et al. \(2009\)](#) as well as 13-week sub-chronic studies [Kano et al. \(2008\)](#); [Kasai \(2008\)](#) to evaluate toxic effects. In 13-week drinking water and inhalation studies in rats and mice, evidence of liver toxicity included hepatocyte swelling, single cell necrosis in the liver and increased liver enzymes, (Figure 6-2), however these effects are not consistently demonstrated in 2-year cancer bioassays at or below doses associated with liver tumor formation. Liver tumors identified in 2-year rodent liver bioassays occurred in the absence of reported lesions related to cytotoxicity [Kano et al. \(2009\)](#); [JBRC \(1998\)](#). Liver adenomas

observed in female mice in a 2-year drinking water study [Kano et al. \(2009\)](#) occurred at doses below those associated with increased plasma ALT in the same study (Figure 6-2). Observations of increased incidence of liver tumors below doses associated with hepatocellular toxicity suggest that cytotoxicity may not be a necessary key event in 1,4-dioxane exposure leading to liver carcinogenesis.

Dourson et al. [2017](#)) compared doses that caused liver toxicity in the 13-week JBRC studies to doses associated with liver tumors in 2-year rat JBRC studies, by adjusting doses from 13-week studies to “chronic equivalents”. Based on comparison to time-adjusted doses in sub-chronic studies, Dourson et al. [2017](#)) concluded that hepatocellular toxicity occurs below doses associated with liver tumor formation; however, this approach for time-adjusting doses is not clearly explained or justified. EPA does not typically apply a scaling factor to compare sub-chronic and chronic dose rates in different studies. There remains a lack of consistent dose-response data for hepatocellular toxicity at dose levels comparable to doses associated with liver tumor formation.

Other studies do report evidence consistent with hepatocellular toxicity at doses below those associated with tumor formation (Tables I-13 through I-16). In one 2-year study, mild hepatocellular vacuolar degeneration and necrosis were reported at doses as low as 94 mg/kg/day, below doses associated increased incidence of hepatocellular carcinomas in male rats exposed via drinking water [Kociba et al. \(1974\)](#). A re-evaluation of mouse pathology data from the NCI, 1978 study [McConnell \(2013\)](#) also established the presence of previously unreported non-neoplastic lesions in mice exposed chronically to 1,4-dioxane in drinking water, but the following study limitations limit confidence in the dose-response relationship between these effects and tumor formation:

- Dose spacing in males was not adequate for characterizing a dose-response relationship likely due to decreased drinking water consumption in the high-dose male group leading to a high dose only slightly greater than the low-dose group (830 and 720 mg/kg/d, respectively).
- A dose-response relationship was not apparent for hyperplastic foci in the liver of male and female mice. The combined incidence for total foci in males was higher for the low dose group than the high dose group, and in females the incidence for combined total foci were approximately the same.
- Female mouse data are confounded by the presence of murine hepatitis infection and should not be combined with male mice to evaluate dose response patterns.

EPA also considered dose-response information for cell proliferation. Some data support the occurrence of cell proliferation prior to liver tumor formation in rat models [JBRC \(1998\)](#); [Kociba et al. \(1974\)](#), but the dose-response relationship for induction of cell proliferation has not been characterized or the relationship between cell proliferation and liver tumors is unknown.

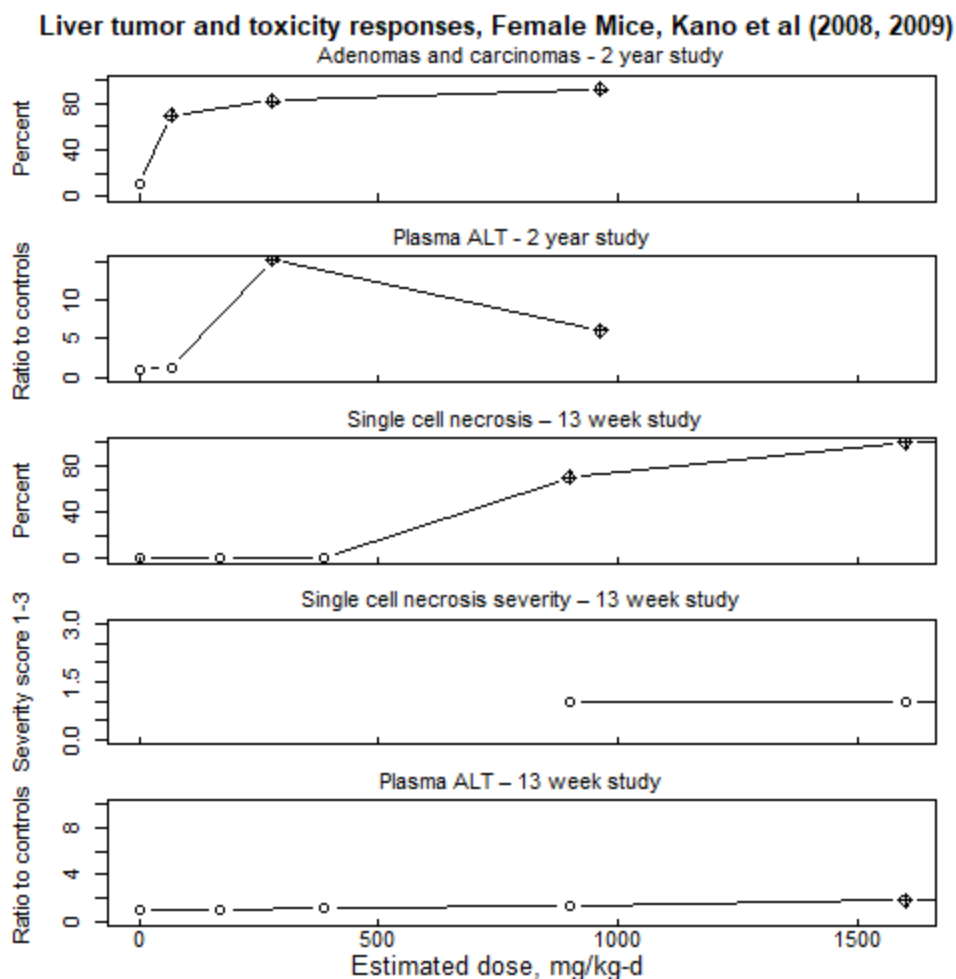


Figure 6-2. Comparison of dose levels associated with increased incidence of liver tumor and various liver toxicity responses in 2-year and 13-week drinking water studies in female mice

J.3.5 Temporal relationship

Dose-response and temporal data support the occurrence of cell proliferation and hyperplasia prior to the development of liver tumors [JBRC \(1998\)](#) in the rat model following 1,4-dioxane exposure. The underlying mechanism behind these observations is not established.

Conflicting data from rat and mouse bioassays [JBRC \(1998\)](#); [Kociba et al. \(1974\)](#) suggest that cytotoxicity may not be a required precursor event for 1,4-dioxane-induced cell proliferation. A 13-week inhalation study in rats and drinking water exposure studies in rats and mice reported evidence of hepatocellular toxicity, including hepatocellular swelling, single cell necrosis, and elevated levels of liver enzymes in plasma [Kano et al. \(2008\)](#); [Kasai \(2008\)](#). These effects reflect several key events in the proposed MOA and are observed preceding timepoints where tumor incidence was observed in subsequent 2-year bioassays [Kano et al. \(2009\)](#); [Kasai et al. \(2009\)](#); however, they are not consistently demonstrated to occur at relevant doses in the same experiments in which tumors were observed.

J.3.6 Biological plausibility and coherence

The proposed MOA is biologically plausible and experimental evidence supports several of the proposed key events, but several critical inconsistencies and data gaps remain. For example, several studies demonstrate that liver tumors may occur in the absence of cytotoxicity, indicating that cytotoxicity may not be a necessary key event. In addition, the mechanisms that lead to observed cytotoxicity and proliferation following 1,4-dioxane exposure are not clearly established. It is also unknown whether these mechanisms are primarily mediated by metabolites or by the parent compound.

J.3.7 Consideration of the Possibility of Other MOAs

Some of the experimental evidence in support of the proposed MOA may be explained by alternate key events:

- **Metabolite-mediate toxicity.** Alternate (non CYP-mediated) metabolic pathways may play a role in producing active metabolites that contribute to the carcinogenicity of 1,4-dioxane through a range of plausible MOAs. The mutagenicity or genotoxicity of potential metabolites of 1,4-dioxane are not known.
- **Proliferation in the absence of cytotoxicity.** Evidence for liver carcinogenesis in the absence of cytotoxicity in some studies suggests an alternate MOA in which 1,4-dioxane or a metabolite induce proliferation through alternate mechanisms. This is consistent with what is proposed in MOA2 (see Section J.2).
- **Nuclear receptors.** One plausible MOA of liver carcinogenicity of 1,4-dioxane is activation of nuclear receptors CAR/PXR. While there is evidence that CAR/PXR-mediated pathways can contribute to liver carcinogenesis, there is no direct evidence on the potential for 1,4-dioxane to lead to CAR/PXR activation. This is consistent with what is proposed in MOA4 (see Section J.2).
- **DNA damage.** Several studies show that 1,4-dioxane exposure increased DNA synthesis in rat hepatocytes at dose levels (1,000 mg/kg/d) higher than doses that promoted liver tumors [Miyagawa et al. \(1999\)](#); [Uno et al. \(1994\)](#); [Goldsworthy et al. \(1991\)](#); [Stott et al. \(1981\)](#) and this result has been interpreted as increased cell proliferation. However, it is unknown whether the increased rates of DNA synthesis observed in response to 1,4-dioxane exposure represent a true increase in cellular proliferation, or if the increase is a cellular response to DNA damage and the repair of hepatic lesions. In *in vitro* screening assays (ToxCast), 1,4-dioxane was observed to increase the transcriptional activity of the p53 tumor suppressor protein in human colon cancer cells (HCT116) 24 hours after 1,4-dioxane exposure, indicative of an active DNA damage and repair response (<https://comptox.epa.gov/dashboard> accessed 03/27/2019). These studies do not rule out MOAs for either mutagenicity or cytotoxicity and regenerative proliferation.

J.3.8 Conclusions About the Hypothesized MOA

Integrating data across studies, dose-response relationships between cytotoxicity and tumor formation are not well established in the rat and mouse data and are inconsistent across bioassays and exposure durations. Though several publications [2017](#); [Dourson et al. \(2014\)](#); [McConnell \(2013\)](#) provide evidence of cytoplasmic vacuolar degeneration and hepatocellular necrosis in rat and non-neoplastic lesions, the animal data does not support a dose-response relationship between cell proliferation, hyperplasia, and liver tumors in rat and mouse studies.

Based on evidence that cytotoxicity is not a necessary key event, a lack of consistent dose-response concordance between key events in the MOA and carcinogenicity, remaining data gaps in support of

specific key events, and the plausibility of alternate MOAs that would also be consistent with experimental observations, EPA determined that existing evidence is not sufficient to support the MOA for liver tumors proposed by Dourson et al. [2017](#); [2014](#)).

Table J-2. Liver histopathology and plasma enzymes in male F344/DuCrj rats exposed to 1,4-dioxane by inhalation for 13 weeks [Kasai \(2008\)](#)

Air conc. (ppm)	Control	100	200	400	800	1,600	3,200
Estimated inhaled dose (alveolar) (mg/kg-day) ^a	0	27	54	110	210	430	870
Body weight (g)	323 ± 14	323 ± 14	304 ± 11*	311 ± 19	317 ± 12	312 ± 14	301 ± 11**
Liver (% of BW)	2.6 ± 0.07	2.7 ± 0.09	2.6 ± 0.08	2.7 ± 0.08	2.7 ± 0.08*	2.8 ± 0.09**	3.0 ± 0.10**
<i>Liver Histopathology (grade)^b</i>							
Hepatocyte swelling	0/10	0/10	0/10	0/10	0/10	1/10	10/10** (1.0)
Vacuolic change	None reported						
Single cell necrosis	0/10	0/10	0/10	0/10	0/10	1/10 (1.0)	8/10** (1.0)
<i>Plasma enzyme levels</i>							
AST/GOT (IU/l)	73 ± 8	5 ± 14	73 ± 10	72 ± 5	72 ± 3	70 ± 4	73 ± 4
ALT/GPT (IU/l)	27 ± 3	27 ± 4	27 ± 4	28 ± 1	27 ± 2	27 ± 2	30 ± 2*

^a Alveolar ventilation in rats calculated as QPC*BW^{0.75} (l/hr) where normalized rate QPC = 13 and BW is weight in kg [Sweeney et al. \(2008\)](#). Alveolar inhaled dose = Conc (converted to mg/l) * alveolar ventilation (l/hr)/ BW (kg) * 6 hr exposure * 5/7 days per week. Assumes ventilation not reduced with inhaled conc.

^b Values in parentheses average severity grade in affected animals; 1=slight, 2=moderate, 3=severe.

Table J-3. Liver histopathology and plasma enzymes in female F344/DuCrj rats exposed to 1,4-dioxane by inhalation for 13 weeks [Kasai \(2008\)](#)

Air conc. (ppm)	Control	100	200	400	800	1,600	3,200
Body weight (g)	187 ± 5	195 ± 8	174 ± 10**	180 ± 5	175 ± 6**	173 ± 8**	168 ± 4**
Liver (% of BW)	2.4 ± 0.08	2.3 ± 0.09	2.4 ± 0.09	2.4 ± 0.07	2.5 ± 0.08**	2.6 ± 0.14**	2.9 ± 0.14**
<i>Liver Histopathology (grade)^a</i>							
Hepatocyte swelling	0/10	0/10	0/10	0/10	0/10	1/10	8/10** (1.0)
Vacuolic change	None reported						
Single cell necrosis	0/10	0/10	0/10	0/10	0/10	0/10	3/10** (1.0)
<i>Plasma enzyme levels</i>							
AST/GOT (IU/l)	64 ± 6	65 ± 3	74 ± 14*	69 ± 5	68 ± 6	70 ± 5	76 ± 5**
ALT/GPT (IU/l)	23 ± 3	21 ± 2	26 ± 10	25 ± 3	24 ± 4	25 ± 3	30 ± 3**

* p ≤ 0.05; **p ≤ 0.01, per authors. Cancer incidence using Fishers exact test, noncancer incidence Chi-square test.

^a Values in parentheses average severity grade in affected animals; 1=slight, 2=moderate, 3=severe.

Table J-4. Liver tumors, histopathology and plasma enzymes in male F344/DuCrj rats exposed to 1,4-dioxane by inhalation for 2 years [Kasai et al. \(2009\)](#)

Air concentration (ppm)	Control	50	250	1250
Estimated inhaled dose (alveolar) (mg/kg-day) ^a	0	13	64	324
Survival, 2 yr	37/50	37/50	28/50	25/50
Body weight, 2 yr (g)	383 ± 50	383 ± 53	376 ± 38	359 ± 29*
Liver (% of body weight), 2 yr	3.6 ± 0.7	3.9 ± 1.1	3.6 ± 0.5	4.5 ± 0.7**
<i>Liver Tumors</i>				
Hepatocellular adenoma	1/50	2/50	3/50	21/50**
Hepatocellular carcinoma	0/50	0/50	1/50	2/50
Either adenoma or carcinoma	Not reported			
<i>Liver Histopathology^b</i>				
Nuclear enlargement, centrilobular	0/50	0/50	1/50	30/50**
Necrosis, centrilobular	1/50	3/50	6/50	12/50**
Spongiosis hepatitis	7/50	6/50	13/50	19/50**
Clear cell foci	15/50	17/50	20/50	23/50
Acidophilic cell foci	5/50	10/50	12/50	25/50**
Basophilic cell foci	17/50	20/50	15/50	44/50 **
Mixed-cell foci	5/50	3/50	4/50	14/50
<i>Plasma enzymes</i>				
AST/GOT (IU/l)	67 ± 31	95 ± 99	95 ± 116	98 ± 52**
ALT/GPT (IU/l)	37 ± 12	42 ± 21	49 ± 30	72 ± 36**
ALP (IU/L)	185 ± 288	166 ± 85	145 ± 71	212 ± 109**
γ-GTP (IU/L)	6 ± 3	8 ± 5	10 ± 8	40 ± 26**

* p ≤ 0.05; **p ≤ 0.01, per authors. Cancer incidence using Fishers exact test, noncancer incidence Chi-square test.

^a Alveolar ventilation in rats calculated as QPC*BW^{0.75} (l/hr) where normalized rate QPC = 13 and BW is weight in kg [Sweeney et al. \(2008\)](#). Alveolar inhaled dose = Conc (converted to mg/l) * alveolar ventilation (l/hr)/ BW (kg) * 6 hr exposure * 5/7 days per week. Assumes ventilation not reduced with inhaled conc.

^b Values in parentheses average severity grade in affected animals; 1=slight, 2=moderate, 3=severe.

Table J-5. Liver histopathology and plasma enzymes in male F344/DuCrj rats exposed to 1,4-dioxane in drinking water for 13 weeks [Kano et al. \(2008\)](#)

Dose (mg/kg-day) ^a	0	52	126	274	657	1,554
DW conc. (ppm)	Control	640	1600	4000	10000	25000
Body weight (g)	331 ± 13	335 ± 9	337 ± 7	322 ± 15	309 ± 7**	263 ± 22**
Liver (% of BW)	2.5 ± 0.07	2.5 ± 0.07	2.5 ± 0.08	2.5 ± 0.07	2.6 ± 0.04*	2.7 ± .12**
<i>Liver Histopathology (grade)^b</i>						
Hepatocyte swelling	0/10	0/10	9/10**(1.0)	10/10**(1.1)	10/10**(2.0)	10/10**(2.9)
Vacuolic change	0/10	0/10	1/10 (1.0)	0/10	10/10**(1.5)	10/10**(3.0)
Single cell necrosis	0/10	0/10	0/10	5/10* (1.0)	2/10 (1.0)	10/10**(1.1)
<i>Plasma Enzymes</i>						
AST/GOT (IU/l)	75 ± 16	79 ± 15	80 ± 9	78 ± 11	83 ± 6	104 ± 15**
ALT/GPT (IU/l)	26 ± 5	27 ± 4	29 ± 3	28 ± 3	29 ± 2	43 ± 9 **

* $p \leq 0.05$; ** $p \leq 0.01$, per authors. Cancer incidence using Fishers exact test, noncancer incidence Chi-square test.

^a Concentration in drinking-water multiplied by the daily volume of water consumed divided by body weight.

^b Values in parentheses average severity grade in affected animals; 1=slight, 2=moderate, 3=severe.

Table J-6. Liver tumors and histopathology in male F344/DuCrj rats exposed to 1,4-dioxane in drinking water for 2 years [Kano et al. \(2009\)](#); [JBRC \(1998\)](#)

Dose (mg/kg-day) ^a	0	11	55	274
DW concentration (ppm)	Control	200	1000	5000
Survival, 2 yr	40/50	45/50	35/50	22/50
Body weight, 2 yr (g)	428 ± 36	433 ± 32	410 ± 53	391 ± 71**
Liver (% of body weight), 2 yr	2.9 ± 0.3	3.0 ± 0.6	3.3 ± 0.5**	5.0 ± 1.1**
<i>Liver Tumors</i>				
Hepatocellular adenoma	3/50	4/50	7/50	32/50**
Hepatocellular carcinoma	0/50	0/50	0/50	14/50**
Either adenoma or carcinoma	3/50	4/50	7/50	39/50**
<i>Liver Histopathology^d</i>				
Spongiosis hepatitis	12/50	20/50	25/50 *	40/50**
Clear cell foci	3/50	3/50	9/50	8/50
Acidophilic cell foci	12/50	8/50	7/50	5/50
Basophilic cell foci	7/50	11/50	8/50	16/50 *
Mixed-cell foci	2/50	8/50	14/50 **	13/50 **
<i>Plasma Enzymes^c</i>				
AST/GOT (IU/l)	67	67	68	172 **
ALT/GPT (IU/l)	18	19	29	68 **
γ-GTP (IU/L)	6	7	8	57**

* $p \leq 0.05$; ** $p \leq 0.01$, per authors. Cancer incidence using Fishers exact test, noncancer incidence Chi-square test.

^a Concentration in drinking-water multiplied by the daily volume of water consumed divided by body weight.

^b Values in parentheses average severity grade in affected animals; 1=slight, 2=moderate, 3=severe.

^c LDH, ALP, CPK also significantly elevated at high dose only in male and female rats, ALP also elevated in high dose female rats

^d Samples originally identified as liver hyperplasia in Yamazaki et al. [1994](#)) and JBRC [1998](#)) were re-examined according to updated criteria and reclassified as either hepatocellular adenoma or altered foci in Kano et al. [2009](#))

Table J-7. Liver weights, histopathology and plasma enzymes in female F344/DuCrj rats exposed to 1,4-dioxane in drinking water for 13 weeks [Kano et al. \(2008\)](#)

Dose (mg/kg-day) ^a	0	83	185	427	756	1,614
DW conc. (ppm)	Control	640	1600	4000	10000	25000
Body weight (g)	194 ± 6	197 ± 7	188 ± 8	183 ± 7**	172 ± 7**	155 ± 7**
Liver (% of BW)	2.3 ± 0.05	2.4 ± 0.08	2.6 ± 0.1**	2.4 ± 0.07*	2.6 ± .08**	2.9 ± 0.1**
<i>Liver Histopathology (grade)^b</i>						
Hepatocyte swelling	0/10	0/10	1/10 (1.0)	0/10	9/10**(1.0)	9/9**(1.7)
Vacuolic change	0/10	0/10	0/10	0/10	0/10	9/9**(2.2)
Single cell necrosis	2/10 (1.0)	0/10	1/10 (1.0)	5/10 (1.0)	5/10 (1.2)	8/9**(1.5)
<i>Plasma Enzymes</i>						
AST/GOT (IU/l)	88 ± 19	87 ± 30	89 ± 18	87 ± 29	93 ± 14	139 ± 35**
ALT/GPT (IU/l)	17 ± 4	17 ± 5	20 ± 5	22 ± 6	30 ± 6**	50 ± 8**

* p ≤ 0.05; **p ≤ 0.01, per authors. Cancer incidence using Fishers exact test, noncancer incidence Chi-square test.

^a Concentration in drinking-water multiplied by the daily volume of water consumed divided by body weight.

^b Values in parentheses average severity grade in affected animals; 1=slight, 2=moderate, 3=severe.

Table J-8. Liver tumors, histopathology, and plasma enzymes in female F344/DuCrj rats exposed to 1,4-dioxane in drinking water for 2 years [Kano et al. \(2009\)](#); [JBRC \(1998\)](#)

Dose (mg/kg-day) ^a	0	18	83	429
DW concentration (ppm)	Control	200	1000	5000
Survival, 2 yr	38/50	37/50	38/50	24/50
Body weight, 2 yr (g)	303 ± 41	301 ± 38	296 ± 29	242 ± 42**
Liver (% of body weight), 2 yr	2.7 ± 0.7	2.6 ± 0.6	2.7 ± 0.4	7.3 ± 2.3**
<i>Liver Tumors</i>				
Hepatocellular adenoma	3/50	1/50	6/50	48/50**
Hepatocellular carcinoma	0/50	0/50	0/50	10/50**
Either adenoma or carcinoma	3/50	1/50	6/50	48/50**
<i>Liver Histopathology^d</i>				
Spongiosis hepatitis	0/50	0/50	1/50	20/50**
Clear cell foci	0/50	1/50	1/50	8/50
Acidophilic cell foci	1/50	1/50	1/50	1/50
Basophilic cell foci	23/50	27/50	31/50	8/50**
Mixed-cell foci	1/50	1/50	5/50	4/50
<i>Plasma Enzymes^c</i>				
AST/GOT (IU/l)	122	117	118	813**
ALT/GPT (IU/l)	32	32	34	244**
γ-GTP (IU/L)	4	4	5	70**

* $p \leq 0.05$; ** $p \leq 0.01$, per authors. Cancer incidence using Fishers exact test, noncancer incidence Chi-square test.

^a Concentration in drinking-water multiplied by the daily volume of water consumed divided by body weight.

^b Values in parentheses average severity grade in affected animals; 1=slight, 2=moderate, 3=severe.

^c LDH, ALP, CPK also significantly elevated at high dose only in male and female rats, ALP also elevated in high dose female rats

^d Samples originally identified as liver hyperplasia in Yamazaki et al. [1994](#)) and JBRC [1998](#)) were re-examined according to updated criteria and reclassified as either hepatocellular adenoma or altered foci in Kano et al. [2009](#))

Table J-9. Liver histopathology and plasma enzymes in male Crj:BDF1 mice exposed to 1,4-dioxane in drinking water for 13 weeks [Kano et al. \(2008\)](#)

Dose (mg/kg-day) ^a	0	86	231	585	882	1,570
DW conc. (ppm)	Control	640	1600	4000	10000	25000
Body weight (g)	30.9 ± 2.6	32.3 ± 3.0	31.3 ± 3.3	30.7 ± 4.0	29.4 ± 2.5	22.2 ± 2.0**
Liver (% of BW)	3.6 ± 0.26	3.7 ± 0.21	3.8 ± 0.21	3.9 ± 0.23	3.8 ± 0.16	3.9 ± 0.37
<i>Liver Histopathology (grade)^b</i>						
Hepatocyte swelling	0/10	0/10	0/10	10/10**(1.1)	10/10**(1.0)	9/9**(2.0)
Single cell necrosis	0/10	0/10	0/10	5/10**(1.0)	10/10**(1.0)	9/9**(1.0)
<i>Plasma Enzymes</i>						
AST/GOT (IU/l)	48 ± 10	49 ± 1	144 ± 8	43 ± 10	44 ± 6	70 ± 12**
ALT/GPT (IU/l)	11 ± 2	13 ± 3	10 ± 2	12 ± 2	13 ± 2	25 ± 9**

* p ≤ 0.05; **p ≤ 0.01, per authors. Cancer incidence using Fishers exact test, noncancer incidence Chi-square test.

^a Concentration in drinking-water multiplied by the daily volume of water consumed divided by body weight.

^b Values in parentheses average severity grade in affected animals; 1=slight, 2=moderate, 3=severe.

Table J-10. Liver tumors, histopathology and plasma enzymes in male Crj:BDF1 mice exposed to 1,4-dioxane in drinking water for 2 years [Kano et al. \(2009\)](#); [JBRC \(1998\)](#)

Dose (mg/kg-day) ^a	0	49	191	677
DW concentration (ppm)	Control	500	2000	8000
Survival, 2 yr	31/50	33/50	25/50	26/50
Body weight, 2 yr (g)	48.7 ± 6.1	47.3 ± 6.8	44.1 ± 7.6*	27.0 ± 3.0**
Liver (% of body weight), 2 yr	4.4 ± 2.6	4.9 ± 2.4	6.2 ± 4.3*	6.5 ± 2.6*
<i>Liver Tumors</i>				
Hepatocellular adenoma	9/50	17/50	23/50 **	11/50
Hepatocellular carcinoma	15/50	20/50	23/50	36/50 **
Either adenoma or carcinoma	23/50	31/50	37/50 ^c	40/50 **
<i>Liver Histopathology^d</i>				
Angiectasis	2/50	3/50	4/50	16/50
<i>Plasma Enzymes^c</i>				
AST/GOT (IU/l)	288	180	333**	1994**
ALT/GPT (IU/l)	110	78	136**	512**

* $p \leq 0.05$; ** $p \leq 0.01$, per authors. Cancer incidence using Fishers exact test, noncancer incidence Chi-square test.

^a Concentration in drinking-water multiplied by the daily volume of water consumed divided by body weight.

^b Values in parentheses average severity grade in affected animals; 1=slight, 2=moderate, 3=severe.

^c LDH, ALP, and CPK also elevated in mid and high dose male and female mice.

^d Samples originally identified as liver hyperplasia in Yamazaki et al. [1994](#)) and JBRC [1998](#)) were re-examined according to updated criteria and reclassified as either hepatocellular adenoma or altered foci in Kano et al. [2009](#))

Table J-11. Liver weights, histopathology and plasma enzymes in female Crj:BDF1 mice exposed to 1,4-dioxane in drinking water for 13 weeks [Kano et al. \(2008\)](#)

Dose (mg/kg-day) ^a	0	170	387	898	1,620	2,669
DW conc. (ppm)	Control	640	1600	4000	10000	25000
Body weight (g)	20.0 ± 1.2	20.5 ± 1.1	20.3 ± 1.1	21.0 ± 1.6	20.8 ± 1.6	19.5 ± 1.2
Liver (% of BW)	4.6 ± 0.26	4.4 ± 0.19	4.6 ± 0.28	4.6 ± 0.19	4.4 ± 0.34	4.3 ± 0.10*
<i>Liver Histopathology (grade)^b</i>						
Hepatocyte swelling	0/10	1/10 (1.0)	1/10 (1.0)	10/10**(1.0)	10/10**(1.0)	9/10**(2.0)
Single cell necrosis	0/10	0/10	0/10	7/10**(1.0)	10/10**(1.0)	9/10**(1.0)
<i>Plasma enzyme levels</i>						
AST/GOT (IU/l)	88 ± 19	87 ± 30	89 ± 18	87 ± 29	93 ± 14	139 ± 35**
ALT/GPT (IU/l)	17 ± 4	17 ± 5	20 ± 5	22 ± 6	30 ± 6**	50 ± 8**

* p ≤ 0.05; **p ≤ 0.01, per authors. Cancer incidence using Fishers exact test, noncancer incidence Chi-square test.

^a Concentration in drinking-water multiplied by the daily volume of water consumed divided by body weight.

^b Values in parentheses average severity grade in affected animals; 1=slight, 2=moderate, 3=severe.

Table J-12. Liver tumors, weights, histopathology and plasma enzymes in female Crj:BDF1 mice exposed to 1,4-dioxane in drinking water for 2 years [Kano et al. \(2009\)](#); [JBRC \(1998\)](#)

Dose (mg/kg-day) ^a	0	66	278	964
DW concentration (ppm)	Control	500	2000	8000
Survival, 2 yr	29/50	29/50	17/50	5/50
Body weight, 2 yr (g)	303 ± 41	301 ± 38	296 ± 29	242 ± 42**
Liver (% of body weight), 2 yr	4.5 ± 1.2	4.4 ± 1.4	5.1 ± 0.94	6.6 ± 2.0**
<i>Liver Tumors</i>				
Hepatocellular adenoma	5/50	31/50 **	20/50 **	3/50
Hepatocellular carcinoma	0/50	6/50c	30/50a	45/50 **
Either adenoma or carcinoma	5/50	35/50a	41/50a	46/50 **
<i>Liver histopathology^d</i>				
No nonneoplastic lesions reported				
<i>Plasma enzymes^c</i>				
AST/GOT (IU/l)	107	150	1518**	714**
ALT/GPT (IU/l)	29	39	441**	175**

* $p \leq 0.05$; ** $p \leq 0.01$, per authors. Cancer incidence using Fishers exact test, noncancer incidence Chi-square test.

^a Concentration in drinking-water multiplied by the daily volume of water consumed divided by body weight.

^b Values in parentheses average severity grade in affected animals; 1=slight, 2=moderate, 3=severe.

^c LDH, ALP, and CPK also elevated in mid and high dose male and female mice.

^d Samples originally identified as liver hyperplasia in Yamazaki et al. [1994](#)) and [JBRC 1998](#)) were re-examined according to updated criteria and reclassified as either hepatocellular adenoma or altered foci in [Kano et al. 2009](#))

Table J-13. Tumor and histopathology incidence in male Sherman rats exposed to 1,4-dioxane in drinking water for 2 years [Kociba et al. \(1974\)](#)

Dose (mg/kg-day) ^a	0	10	94	1020
DW concentration (ppm)	Control	100	1000	10,000
Survival, 2 yr	20/60	24/60	14/60	1/60
Body weight, 2 yr (g) ^b	378 ± 40	377 ± 57	387 ± 68	-
Liver (% of body weight), 2 yr ^b	2.5 ± 0.3	2.6 ± 0.3	2.7 ± 0.5	-
<i>Liver Tumors</i>				
Hepatocellular carcinoma (No adenomas reported)	1/60	0/60	0/60	6/60*
<i>Liver Histopathology^c</i>				
Hepatocellular vacuolar degeneration	4/60 (1)	1/60 (1)	14/60 (1.4)	17/60 (1.7)
Hepatocellular necrosis	2/60 (1.5)	6/60 (1.2)	12/60 (1.7)	24/60 (1.7)
Hepatocellular anisonucleosis	1/60	1/60	0/60	15/60
Bile duct epithelial hyperplasia	4/60	0/60	3/60	10/60
Elevated nodules (gross path)	1/60	1/60	2/60	7/60
Hepatocellular hyperplastic nodules	1/60	1/60	2/60	1/60

* $p \leq 0.05$; ** $p \leq 0.01$; $p \leq 0.001$, for tumor findings per authors. Not indicated for noncancer results.

^a Concentration in drinking-water multiplied by the daily volume of water consumed divided by body weight. Based on measurements for days 114-198, reported in [Kociba et al. \(1974\)](#), Table 1.

^b Based on surviving animals at final sacrifice

^c Values in parentheses average severity grade in, affected animals; 1=minimal, 2=moderate, 3=severe.

The term hepatocellular cytoplasmic degeneration as used by [Kociba](#) includes both “hepatocyte swelling” and “vacuolic change”. For comparison these changes were diagnosed separately in [Kano \(2008\)](#) for male and female rats, and swelling was seen at a lower dose than vacuolic change in that study.

Table J-14. Tumor and histopathology incidence in female Sherman rats exposed to 1,4-dioxane in drinking water for 2 years [Kociba et al. \(1974\)](#)

Dose (mg/kg-day) ^a	0	19	148	1600
DW concentration (ppm)	Control	100	1000	10,000
Survival, 2 yr	37/60	36/60	32/60	3/60
Body weight, 2 yr (g) ^b	285 ± 47	289 ± 42	280 ± 47	212 ± 42**
Liver (% of body weight), 2 yr ^b	2.9± 0.7	2.9 ± 0.5	3.0 ± 0.4	5.8 ± 1.5*
<i>Liver Tumors</i>				
Hepatocellular carcinoma (adenomas not reported)	0/60	0/60	1/60	4/60
<i>Liver Histopathology^c (All counts numbers out of 60 animals)</i>				
Hepatocellular vacuolar degeneration	5/60 (1.2)	4/60 (1.0)	14/60 (1.3)	25/60 (1.8)
Hepatocellular necrosis	1/60 (3)	2/60 (1.0)	11/60 (1.3)	31/60 (2.0)
Hepatocellular anisonucleosis	0/60	0/60	2/60	19/60
Bile duct epithelial hyperplasia	6/60	1/60	6/60	13/60
Elevated nodules (gross path)	0/60	0/60	2/60	12/60
Hepatocellular hyperplastic nodules	0/60	0/60	1/60	8/60

* $p \leq 0.05$; ** $p \leq 0.01$; $p \leq 0.001$, per authors.

^a Concentration in drinking-water multiplied by the daily volume of water consumed divided by body weight. Based on measurements for days 114-198, reported in [Kociba et al. 1974](#), Table 1.

^b Based on surviving animals at final sacrifice

^c Values in parentheses average severity grade in affected animals; 1=slight, 2=moderate, 3=severe.

Table J-15. Tumor and histopathology incidence in male B6C3F1 mice exposed to 1,4-dioxane in drinking water 90 weeks [McConnell \(2013\)](#) reexamination of slides from NCI [1978](#))

Dose (mg/kg-day) ^a	0	720	830
DW concentration (ppm)	Control	5000	10000
Survival, 91 weeks ^b	48/50	45/50	46/50
Body weight, 91 weeks (g)	39	35	35
Liver (% of body weight), 2 yr	NA	NA	NA
<i>Liver Tumors: NCI (1978) – McConnell (2013)^c</i>			
Hepatocellular adenoma	6/49 -- 2/44	1/50 – 1/48	4/47 – 3/48
Hepatocellular carcinoma	2/49 – 4/44	18/50*** – 16/48	24/47*** – 21/48
Either adenoma or carcinoma	8/49 – 5/44	19/50* – 17/48	28/47*** – 22/48
<i>Liver Histopathology (McConnell, 2013)^d</i>			
Hepatocellular hypertrophy	3/44 (1.5)	41/43 (1.6)	41/42 (1.7)
Hepatocyte glycogen (scored as “none”)	11/44	32/43	35/42
Hepatocellular necrosis	4/48 (1.0)	37/41 (1.7)	33/40 (1.5)
Inflammation	4/48 (1.0)	37/41 (1.7)	32/40 (1.5)
Kupffer cell hyperplasia	4/48 (1.2)	29/43 (1.3)	31/42 (1.6)
Hepatocellular foci, total ^e	4/44	13/43	7/42

* $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$, per NCI [1978](#)), using Fishers exact test. Significance not provided by NCI for adenomas alone. Significance results not provided in McConnell [2013](#)).

^a Concentration in drinking-water multiplied by the daily volume of water consumed divided by body weight.

^b From graph

^c Tumor count from original NCI study followed by count from reread of slides by McConnell

^d Frequency for lesions scored minimal or greater. Values in parentheses average severity grade in affected animals; 1=minimal, 2=mild, 3=moderate, 4=marked. Statistical significance not reported. McConnell reported severity averaged across both affected and nonaffected (severity=0) animals, here this value is divided by fraction affected to apply to affected animals only.

^e Basophilic, eosinophilic, clear cell and mixed cell foci combined, considered as preneoplastic indicators

NA: Not available

Table J-16. Tumor and histopathology incidence in female B6C3F1 mice exposed to 1,4-dioxane in drinking water 90 weeks [McConnell \(2013\)](#) reexamination of slides from NCI [1978](#))

Dose (mg/kg-day) ^a	0	380	820
DW concentration (ppm)	Control	5000	10000
Survival, 91 weeks	45/50	39/50	28/50
Body weight, 91 weeks (g) ^b	37	36	27
Liver (% of body weight), 2 yr	NA	NA	NA
<i>Liver Tumors: NCI (1978) – McConnell (2013)^c</i>			
Hepatocellular adenoma	0 /50 – 0/49	9/48 – 7/45	6/37 – 11/37
Hepatocellular carcinoma	0 /50 -- 0/49	12/48*** –7/45	29/37*** – 23/37
Either adenoma or carcinoma	0/50 – 0/49	21/48*** – 14/45	35/37*** – 29/37
<i>Liver Histopathology (McConnell, 2013)^d</i>			
Hepatocellular hypertrophy	0/46	17/37 (1.2)	29/30 (1.7)
Hepatocyte glycogen (scored as “none”)	18/46	17/37	21/30
Hepatocellular necrosis	27/46 (1.0)	17/37 (1.3)	17/19 (1.3)
Inflammation	26/46 (1.1)	17/37 (1.3)	16/19 (1.3)
Kupffer cell hyperplasia	0/46	1/37 (1)	9/30 (1.7)
Hepatocellular foci, total ^e	1/46	10/37	8/30

* $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$, per NCI [1978](#)), using Fishers exact test. Significance not provided by NCI for adenomas alone. Significance results not provided in McConnell [2013](#)).

^a Concentration in drinking-water multiplied by the daily volume of water consumed divided by body weight.

^b From graph

^c Tumor count from original NCI study followed by count from reread of slides by McConnell

^d Frequency for lesions scored minimal or greater. Values in parentheses average severity grade in affected animals; 1=minimal, 2=mild, 3=moderate, 4=marked. McConnell reported severity averaged across both affected and nonaffected (severity=0) animals, here this value is divided by fraction affected to apply to affected animals only.

^e Basophilic, eosinophilic, clear cell and mixed cell foci combined, considered as preneoplastic indicators

Appendix K BENCHMARK DOSE ANALYSIS

U.S. EPA relied on the following guidance and support documents for data requirements and other considerations for dose-response modeling: EPA's *Benchmark Dose Technical Guidance* [U.S. EPA \(2012b\)](#), EPA's *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* [U.S. EPA \(1994b\)](#), EPA's *Review of the Reference Dose and Reference Concentration Processes* [U.S. EPA \(2002\)](#), *Guidelines for Carcinogen Risk Assessment* [U.S. EPA \(2005a\)](#), and EPA's *Recommended Use of Body Weight^{3/4} as the Default Method in Derivation of the Oral Reference Dose* [U.S. EPA \(2011b\)](#).

For studies that had suitable data, dose-response analysis was performed and point of departures (PODs) were identified. The POD, an estimated dose (expressed in human-equivalent terms) near the lower end of the observed range without significant extrapolation to lower doses, is used as the starting point for subsequent extrapolations and analyses. PODs can be a NOAEL or LOAEL for an observed incidence, or change in level of response, or the lower confidence limit on the dose at the benchmark dose (BMD). The preferred approach is to use dose response modeling to incorporate as much of the data set as possible into the analysis to yield a POD. EPA evaluates a range of dose response models thought to be consistent with underlying biological processes to determine how best to empirically model the dose response relationship in the range of the observed data. If the procedure fails to yield reliable results, expert judgment or alternative analyses are used. For example, a model fit may be considered poor if the goodness-of-fit p value is below a critical value (*i.e.*, <0.1), or the largest scaled residual exceeds 2 in absolute value [[U.S. EPA \(2012b\)](#) §2.3.5]. If none of the models provide a reasonable fit to certain datasets, the dose-response modeling may be re-done using only data for the lower doses, or the NOAEL/LOAEL could be used as the POD.

In general, the benchmark response level (BMR) at which the POD is calculated is guided by the severity of the endpoint. As stated in EPA's *Benchmark Dose Technical Guidance* [U.S. EPA \(2012b\)](#), EPA does not currently have explicit guidance to assist in making such judgments for the selection of response levels for most applications (*e.g.*, for calculating reference doses). However, the guidance provides general principles to consider for different types of data. For dichotomous data, a response level of 10% extra risk is generally used for minimally adverse effects, 5% or lower for more severe effects. For continuous data, a response level is ideally based on an established definition of biologic significance. In the absence of such definition, one control standard deviation from the control mean is often used for minimally adverse effects, one-half standard deviation for more severe effects. For cancer data, U.S. EPA's *Guidelines for Carcinogen Risk Assessment* [U.S. EPA \(2005a\)](#) address BMRs for cancer risk estimation. Standard values near the low end of the observable range are generally used (for example, 10% extra risk for cancer bioassay data, 1% for epidemiologic data, lower for rare cancers).

For 1,4-dioxane, both linear and nonlinear approaches were evaluated for the human health endpoints because comparing both approaches can provide insights into uncertainties related to model choice and mechanisms. Information regarding the degree of change in the selected endpoints that is considered biologically significant was not available. Therefore, a BMR of 10% extra risk was selected under the assumption that it represents a minimally biologically significant response level [U.S. EPA \(2012b\)](#).

Decision trees summarizing the general progression of steps in a BMD/BMDL calculation are presented below.

Noncancer

Basic statistical background and guidance on choosing a model structure for the data being analyzed, fitting models, comparing models, and calculating confidence limits to derive a BMDL to use as a POD is outlined in EPA's *Benchmark Dose Technical Guidance* [U.S. EPA \(2012b\)](#) Sections 2.3.9 and 2.5. Empirical models that provide the best fit to the dose-response data are typically used in the absence of data to develop a biologically-based model. While these models are empirical, parameters are typically constrained on some of them for the purposes of strengthening the biological plausibility of the results (*i.e.*, many toxic effects exhibit a monotonic dose-response), and to prevent imprecise BMDs/BMDLs resulting from steeply supralinear models [[U.S. EPA \(2012b\)](#) §2.3.3.3]. Consistent with EPA's *Benchmark Dose Technical Guidance* [U.S. EPA \(2012b\)](#), initial runs of the LogProbit and Dichotomous Hill models did not constrain their slope parameter, whereas initial runs of the Gamma, Weibull, and LogLogistic models constrained their slope or power parameters to be ≥ 1 .

For each candidate endpoint/study the following steps were taken:

Goodness-of-fit was assessed for all models [[U.S. EPA \(2012b\)](#) §2.3.5]

Models having a goodness-of-fit p value of less than 0.1 were rejected.²⁹

Models not adequately describing the dose response relationship (especially in the low-dose region) were rejected based on examining the dose-group scaled residuals³⁰ and graphs of models and data.

The models that remained (after rejecting those that did not meet the recommended default statistical criteria for adequacy and fail in visual inspection of model fit) were used for determining the BMDL. The default selection criteria are listed below [[U.S. EPA \(2012b\)](#) §2.3.9]:

If the BMDL estimates from the remaining models were sufficiently close (generally defined as being within threefold, as in the case of this assessment), it was assumed there was no particular influence of the individual models on the estimates. In this case, the model with the lowest AIC was chosen.

If the BMDL estimates from the remaining models were not sufficiently close, it was assumed there was some model dependence (*i.e.*, model uncertainty) of the estimate. In this case, if there was no clear remaining biological or statistical basis on which to choose among them, the lowest BMDL was selected as a reasonable conservative estimate ([U.S. EPA \(2012b\)](#) Section 2.3.9).

In some cases, modeling attempts did not yield useful results. When this occurred, the NOAEL (or LOAEL) was used as a candidate POD.

Modeling considerations specific to noncancer data

The highest dose in the oral study by [Kano et al. \(2009\)](#) was removed from all analyses because of concerns regarding decreased water intake rate at the highest dose. Data in male OM rats from the [NCI \(1978\)](#) study were not modeled, because the data quality was determined to be unacceptable (see Appendix G).

²⁹ For the χ^2 goodness-of-fit test and a p-value of α , the critical value is the $1 - \alpha$ percentile of the χ^2 distribution at the appropriate degrees of freedom. Models are rejected if there are large values of χ^2 corresponding to p-values less than 0.1, the limiting probability of a Type I error (false positive) selected for this purpose.

³⁰ Scaled residuals reported by BMDS for dichotomous responses are defined as (Observed - Expected)/SE, where "Expected" is the predicted number of responders and SE equals the estimated standard error of that predicted number. For dichotomous models, the estimated standard error is equal to $\sqrt{[n \times pp \times (1 - pp)]}$, where n is the sample size, and p is the model-predicted probability of response. Model fit is considered questionable if the scaled residual value for any dose group, particularly the control or low dose group, is greater than 2 or less than -2.

For inhalation data that were not amenable to BMD modeling, NOAECs/NOAELs and LOAECs/LOAELs were obtained from Appendix G.

Cancer

Following EPA's *Benchmark Dose Technical Guidance* [U.S. EPA \(2012b\)](#) Sections 2.3.9 and 2.5, and EPA's *Choosing Appropriate Stage of a Multistage Model for Cancer Modeling* [U.S. EPA \(2014b\)](#):

All orders of the Multistage model up to two less than the number of dose groups were fit (*e.g.*, up to model order $k-2$ if there are k dose groups).

If all parameter (γ , β_1 , .. , β_{k-2}) estimates were positive, then the model with the lowest AIC was chosen as the best-fitting model if at least one of the models provides an adequate fit to the data. Consistent with EPA's guidance when there is an a priori reason to prefer a specific model(s) [[U.S. EPA \(2012b\)](#) §2.3.5 and §2.3.9], Multistage models having a goodness-of-fit p value of less than 0.05 were rejected. Otherwise (*i.e.*, if any parameter is estimated to be zero and is thus at a boundary), the following procedure (2) was followed:

Model fits of order 1 and 2 (linear and quadratic, respectively) were examined for adequate fit. The linear model parameters (γ , β_1), and the quadratic model parameters (γ , β_1 , β_2) were examined.

If only one of the models exhibited adequate fit, that model was chosen.

If both models exhibited adequate fit:

The model with the lowest AIC was chosen if all of the parameters (γ , β_1 , and β_2) were positive.

Otherwise, the model with the lower BMDL (more health protective) was chosen. If the BMD/BMDL ratio is larger than 3, the matter was referred to EPA statisticians and health assessors for a decision.

The MS-Combo model (which is implemented using BMDS) was utilized to calculate the dose associated with a specified composite risk (the risk of developing any combination of tumors at any site), under the assumption that tumors in different tissues arise independently. MS-Combo is a peer-reviewed [Versar \(2011\)](#) module within BMDS that employs a combined probability function to calculate composite risk using the best-fitting BMDS multistage model parameters determined for each individual tumor.

Modeling considerations specific to cancer data for the oral route

The [U.S. EPA \(2013d\)](#) IRIS assessment applied all available noncancer models and did not evaluate multiple tumors using MS-Combo. Thus, points of departure differ from the [U.S. EPA \(2013d\)](#) IRIS assessment.

Subcutis fibroma in male rats exposed via drinking water from the [Kano et al. \(2009\)](#) study exhibited a statistically significant ($p < 0.01$) increasing trend by the Peto test. It should be noted that these data were not used for dose-response of the oral portion of the [U.S. EPA \(2013d\)](#) IRIS assessment. However, data for subcutis fibroma from the [Kasai et al. \(2009\)](#) study was modeled for the inhalation update of the [U.S. EPA \(2013d\)](#) IRIS assessment.

Female mouse hepatocellular carcinoma data from [Kano et al. \(2009\)](#) were not initially amenable to modeling due to the difficulties that were previously noted in the [U.S. EPA \(2013d\)](#) IRIS assessment. Specifically, this endpoint exhibited a low control group incidence, and a high (70% incidence) response rate at the lowest dose followed by a plateau. While the [U.S. EPA \(2013d\)](#) IRIS assessment did perform BMD modeling on these data, it was necessary to increase the BMR, omit the highest dose group, and apply a non-multistage model. EPA therefore used individual animal data obtained from study authors to

model the time-to-tumor effect in this dataset using the Multistage Weibull Model and applying an Extra Risk of 50% as the BMR to avoid excess extrapolation.

For studies that observed liver tumors, which were amenable to BMD modeling, MS-Combo was applied twice to evaluate uncertainties related to model choice and mechanisms: one MS-Combo model run included all tumors, while an additional model run excluded liver tumors.

The [Kano et al. \(2009\)](#) data are based on the data of the laboratory report by JBRC [1998](#)), which were also published as conference proceedings [Yamazaki et al. \(1994\)](#). There are data discrepancies between these publications. This is explained in 0 of the [U.S. EPA \(2013d\)](#) IRIS assessment. It was determined that the differences in tumor counts have a negligible impact on the final PODs. The analysis presented here assumes that the data by [Kano et al. \(2009\)](#) (which was used in the IRIS assessment) are a suitable representation of the 2-year drinking water bioassay data.

Data in male OM rats from the [NCI \(1978\)](#) study were not modeled, because the data quality was determined to be unacceptable (see Appendix G).

Modeling considerations specific to cancer data for the inhalation route

The [U.S. EPA \(2013d\)](#) IRIS assessment applied MS-Combo to the inhalation cancer data (the model was not available during the development of the oral assessment, which preceded the inhalation update). However, MS-Combo under BMDS version 2.704 produced slightly different results from the [U.S. EPA \(2013d\)](#) IRIS assessment. This was due to differences in multistage model selection using current guidance [U.S. EPA \(2014b, 2012b\)](#), and differences in software versions (MS-Combo under BMDS version 2.2Beta was used for the [U.S. EPA \(2013d\)](#) IRIS assessment).

MS-Combo was applied to the BMD modeling results from the [Kasai et al. \(2009\)](#) study. To evaluate uncertainties related to model choice and mechanisms, MS-Combo was applied twice: one model run included all tumors, while an additional model run excluded liver tumors.

Incidences of tumors in rats (hepatocellular adenomas or carcinomas) from the [Kasai et al. \(2009\)](#) study were corrected to account for rats that exhibited both adenomas and carcinomas. These data were provided to U.S. EPA by a personal communication with the study author [Kasai \(2008\)](#), and were extracted from Table 5-8 of [U.S. EPA \(2013d\)](#).

The high concentration group for subcutis fibroma was omitted from the dose-response analysis. As noted in the U.S. [U.S. EPA \(2013d\)](#) IRIS assessment, the incidence data for subcutis fibroma were monotonic non-decreasing functions of dose for the control (0 ppm), low (50 ppm), and mid-dose (250 ppm); however, the incidence rate at the high dose (1,250 ppm) was lower than observed at the mid-dose. No BMDS model exhibited a reasonable fit to the data without dropping the high dose.

K.1 BMD5 Summary of Centrilobular necrosis of the liver in male F344/DuCrj rats [Kasai et al. \(2009\)](#)

Table K-1. Summary of BMD Modeling Results for Centrilobular necrosis of the liver in male F344/DuCrj rats [Kasai et al. \(2009\)](#)

Model ^a	Goodness of fit		BMD _{10Pct} (ppm)	BMDL _{10Pct} (ppm)	Basis for model selection
	p-value	AIC			
Gamma ^b	0.510	129.69	502	308	Lowest BMDL model chosen when adequate-fitting models are not sufficiently close in range.
Dichotomous-Hill	0.746	130.40	220	59.6	
Logistic	0.279	131.04	795	609	
LogLogistic	0.568	129.47	453	259	
Probit	0.299	130.89	756	567	
LogProbit	0.952	130.31	232	44.0	
Weibull ^c Quantal-Linear ^d	0.510	129.69	502	308	
Multistage 3 ^{°e} Multistage 2 ^{°f}	0.510	129.69	502	308	

The restricted dichotomous Hill results are reported here because the unrestricted dichotomous Hill model resulted in zero degrees of freedom (number of estimated parameters equal to number of dose groups), precluding the derivation of a p-value and AIC for that model.

^a Selected model in bold; scaled residuals for selected model for doses 0, 50, 250, and 1250 ppm were -0.01, 0.03, -0.04, 0.02, respectively.

^b The Gamma model may appear equivalent to the Weibull model, however differences exist in digits not displayed in the table. This also applies to the Multistage 3[°] model. This also applies to the Multistage 2[°] model. This also applies to the Quantal-Linear model.

^c For the Weibull model, the power parameter estimate was 1. The models in this row reduced to the Quantal-Linear model.

^d The Quantal-Linear model may appear equivalent to the Gamma model, however differences exist in digits not displayed in the table. This also applies to the Multistage 3[°] model. This also applies to the Multistage 2[°] model.

^e For the Multistage 3[°] model, the beta coefficient estimates were 0 (boundary of parameters space). The models in this row reduced to the Multistage 2[°] model.

^f The Multistage 2[°] model may appear equivalent to the Gamma model, however differences exist in digits not displayed in the table. This also applies to the Weibull model. This also applies to the Quantal-Linear model.

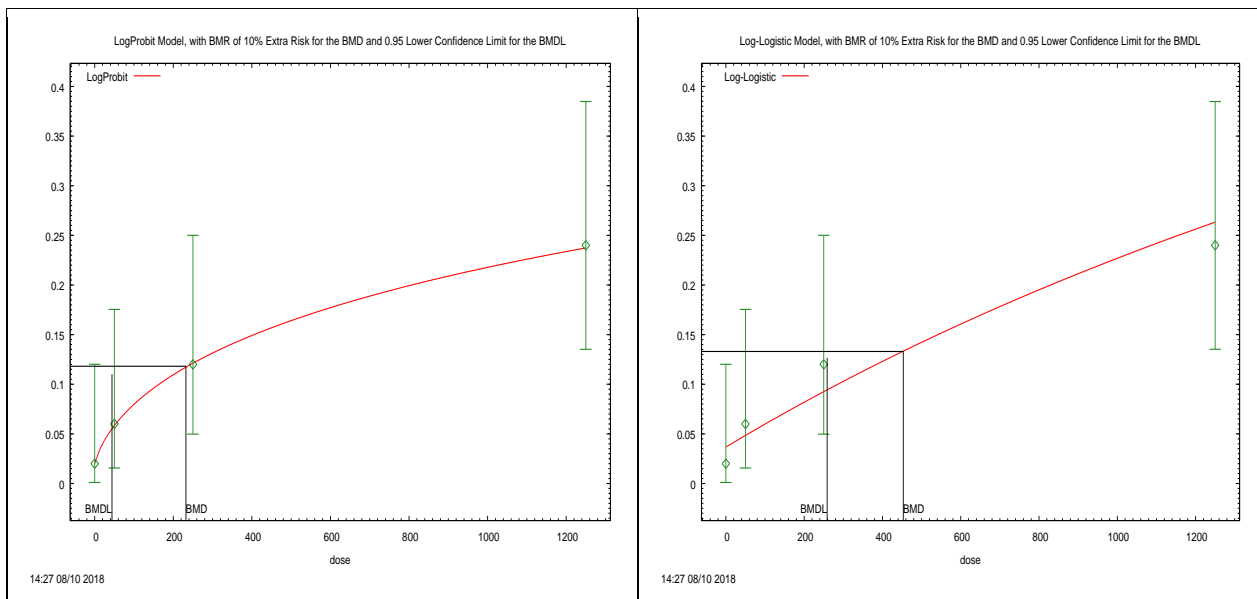


Figure K-1. Plot of incidence rate by dose with fitted curve for the unrestricted LogProbit (left) and restricted LogLogistic (right) models for Centrilobular necrosis of the liver in male F344/DuCrj rats [Kasai et al. \(2009\)](#); dose shown in ppm. Restricted LogLogistic has the lowest AIC but exhibits higher residuals for all dose groups.

LogProbit Model. (Version: 3.4; Date: 5/21/2017)

The form of the probability function is: $P[\text{response}] = \text{Background} + (1 - \text{Background}) * \text{CumNorm}(\text{Intercept} + \text{Slope} * \text{Log}(\text{Dose}))$, where $\text{CumNorm}(\cdot)$ is the cumulative normal distribution function

Slope parameter is not restricted

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 232.245

BMDL at the 95% confidence level = 43.9928

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
background	0.0201374	0.02
intercept	-2.9660E+00	-2.9443E+00
slope	0.309189	0.305751

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-62.15	4			
Fitted model	-62.15	3	0.00361134	1	0.95
Reduced model	-69.3	1	14.305	3	0

AIC: = 130.305

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0.0201	1.007	1	50	-0.01
50	0.0589	2.943	3	50	0.03
250	0.1221	6.105	6	50	-0.04
1250	0.2389	11.946	12	50	0.02

Chi² = 0 d.f = 1 P-value = 0.9521

K.2 BMD5 Summary of Squamous cell metaplasia of respiratory epithelium in male F433/DuCrj rats [Kasai et al. \(2009\)](#)

Table K-2. Summary of BMD Modeling Results for Squamous cell metaplasia of respiratory epithelium in male F433/DuCrj rats [Kasai et al. \(2009\)](#)

Model ^a	Goodness of fit		BMD _{10Pct} (ppm)	BMDL _{10Pct} (ppm)	Basis for model selection
	p-value	AIC			
Gamma	0.868	81.687	218	150	Lowest AIC. BMDL estimates for models not excluded (based on goodness-of-fit p values less than 0.1, or high scaled residuals) are sufficiently close.
Dichotomous-Hill	1.000	83.189	241	162	
Logistic	0.0464	89.415	370	289	
LogLogistic	0.914	81.525	218	158	
Probit	0.0779	87.936	338	268	
LogProbit	0.989	81.230	218	160	
Weibull	0.768	82.124	218	145	
Multistage 3°	0.619	82.688	231	140	
Multistage 2°	0.619	82.688	231	141	
Quantal-Linear	0.0198	92.922	87.7	68.8	

^a Selected model in bold; scaled residuals for selected model for doses 0, 50, 250, and 1250 ppm were 0, -0.14, 0.03, -0.02, respectively.

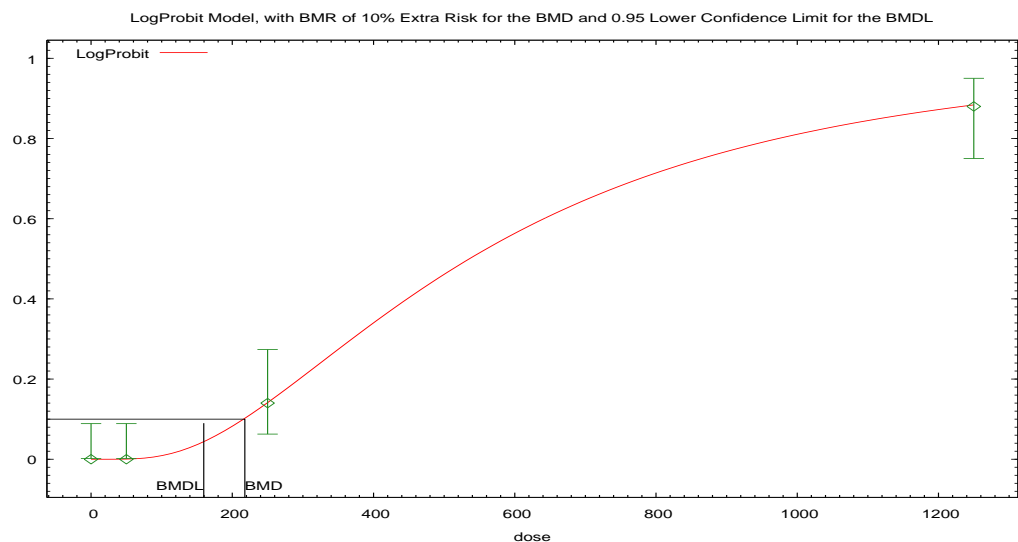


Figure K-2. Plot of incidence rate by dose with fitted curve for LogProbit model for Squamous cell metaplasia of respiratory epithelium in male F433/DuCrj rats [Kasai et al. \(2009\)](#); dose shown in ppm.

LogProbit Model. (Version: 3.4; Date: 5/21/2017)

The form of the probability function is: $P[\text{response}] = \text{Background} + (1 - \text{Background}) * \text{CumNorm}(\text{Intercept} + \text{Slope} * \text{Log}(\text{Dose}))$, where $\text{CumNorm}(\cdot)$ is the cumulative normal distribution function

Slope parameter is not restricted

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 217.79

BMDL at the 95% confidence level = 159.619

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
background	0	0
intercept	-8.8618E+00	-6.7651E+00
slope	1.40803	1.09006

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-38.59	4			
Fitted model	-38.62	2	0.041197	2	0.98
Reduced model	-113.55	1	149.916	3	<.0001

AIC: = 81.23

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	50	0
50	0.0004	0.02	0	50	-0.14
250	0.1384	6.922	7	50	0.03
1250	0.8808	44.038	44	50	-0.02

$\chi^2 = 0.02$ d.f = 2 P-value = 0.9894

K.3 BMDs Summary of Squamous cell hyperplasia of respiratory epithelium in male F433/DuCrj rats [Kasai et al. \(2009\)](#)

Table K-3. Summary of BMD Modeling Results for Squamous cell hyperplasia of respiratory epithelium in male F433/DuCrj rats [Kasai et al. \(2009\)](#)

Model ^a	Goodness of fit		BMD _{10Pct} (ppm)	BMDL _{10Pct} (ppm)	Basis for model selection
	p-value	AIC			
Gamma	0.961	63.981	761	487	Lowest AIC. BMDL estimates for models not excluded (based on goodness-of-fit p values less than 0.1, or high scaled residuals) are sufficiently close. Note: Dichotomous Hill did not converge
Dichotomous-Hill	1.000	65.844	316	280	
Logistic	0.582	65.208	1013	847	
LogLogistic	0.960	63.988	760	473	
Probit	0.631	65.018	962	786	
LogProbit	0.987	63.893	704	437	
Weibull	0.956	64.001	776	486	
Multistage 3 ^{ob}	0.926	64.099	812	481	
Multistage 2 ^{oc}	0.926	64.099	812	481	
Quantal-Linear	0.795	63.342	679	429	

^a Selected model in bold; scaled residuals for selected model for doses 0, 50, 250, and 1250 ppm were 0, -0.62, -0.67, 0.44, respectively.

^b The Multistage 3^o model may appear equivalent to the Multistage 2^o model; however, differences exist in digits not displayed in the table.

^c The Multistage 2^o model may appear equivalent to the Multistage 3^o model; however, differences exist in digits not displayed in the table.

For results based on a power or slope parameter that hits the bound of 1, EPA [2012b](#)) states (footnote 10) "...the nominal coverage of the confidence interval is not exact (asymptotically) and could be much less than intended if the true (unknown) parameter is <1, and this should also be reported"

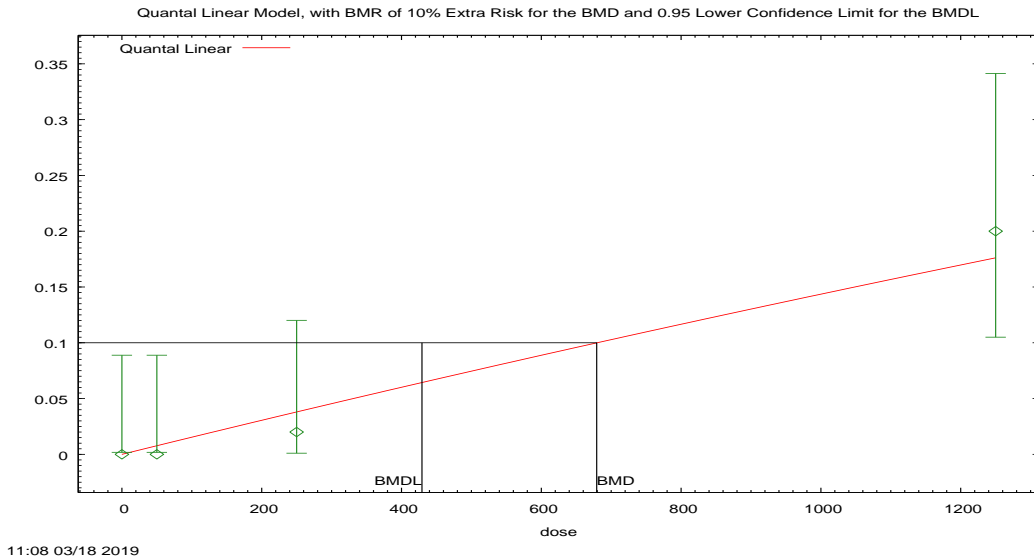


Figure K-3. Plot of incidence rate by dose with fitted curve for Quantal-Linear model for Squamous cell hyperplasia of respiratory epithelium in male F433/DuCrj rats; dose shown in ppm.

Quantal Linear Model using Weibull Model (Version: 2.17; Date: 6/23/2017)

The form of the probability function is: $P[\text{response}] = \text{background} + (1 - \text{background}) * [1 - \text{EXP}(-\text{slope} * \text{dose})]$

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 679.311

BMDL at the 95% confidence level = 429.287

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0	0.0192308
Slope	0.000155099	0.000174603
Power	n/a	1

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-29.92	4			
Fitted model	-30.67	1	1.49818	3	0.68
Reduced model	-42.6	1	25.3487	3	<.0001

AIC: = 63.3423

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	50	0
50	0.0077	0.386	0	50	-0.62
250	0.038	1.902	1	50	-0.67
1250	0.1762	8.812	10	50	0.44

Chi² = 1.03 d.f = 3 P-value = 0.7945

K.4 Benchmark dose analysis of respiratory metaplasia of the olfactory epithelium in the nasal cavity of male F344/DuCrj rats [Kasai et al. \(2009\)](#)

As reported in the EPA 1,4-dioxane IRIS assessment, no models in the software provided adequate fits to the data for the incidence of respiratory metaplasia of the olfactory epithelium in male rats (χ^2 $p \geq 0.1$) when all dose groups are included in the analysis ([U.S. EPA \(2013d\)](#) Table F-8). While the model uncertainty associated with data for which the response at the lowest non-control dose (34/50) is 46% higher than the control response (11/50) was acknowledged, the IRIS assessment determined that modeling this dataset without the high dose group would be consistent with BMD Technical Guidance Document [U.S. EPA \(2012b\)](#). As a result, all models were fit to the incidence data with the highest dose group omitted ([U.S. EPA \(2013d\)](#), Table F-9). Using BMDS 2.1.1, it was determined that, of the adequately fitting models (p -value > 0.1), “the AIC values for gamma, multistage, quantal-linear, and Weibull models in Table F-9 are equivalent and the lowest and, in this case, essentially represent the same model” and, because they all result in the same BMDL value of 4.7 ppm, “consistent with the Benchmark Dose Technical Guidance [U.S. EPA \(2012b\)](#), any of them with equal AIC values (gamma, multistage, quantal-linear, or Weibull) could be used to identify a POD for this endpoint.” This report confirms these findings of BMDS 2.1.1 for this dataset using the latest version of BMDS, BMDS 3.1.

The table below shows the BMR, BMD, BMDL, p -value, AIC and scaled residual for the dose-group nearest the BMD (the 50 ppm dose group) for the suite of BMDS dichotomous models available in BMDS 3.1 using standard model restriction settings (default settings in BMDS 3.1) recommended in the EPA BMD technical guidance [U.S. EPA \(2012b\)](#). The Gamma, Multistage and Weibull models all converge to the same BMD and goodness-of-fit results, the same (lowest) AIC value and the same BMDL estimate of 4.7 ppm, which is virtually the same result obtained from BMDS 2.1.1 in the 2013 IRIS assessment ([U.S. EPA \(2013d\)](#) Table F-9). Several aspects of this analysis support dropping the highest dose group data, including the inability to adequately fit the dose-response data for all four dose groups (see [U.S. EPA \(2013d\)](#) Table F-8), acceptable fit (p -value > 0.1) to the dose-response data when the highest dose group is removed (see table summary of BMD modeling results below), visual inspection of the plots for the acceptable models with the three models with the lowest AIC (see detailed results for individual Gamma, Multistage and Weibull models below), and the low scaled residuals (-0.106) reported for these models at the (50 ppm) dose group nearest the BMD. In general, models that result in low scaled residuals for dose groups near the BMD are preferred ([U.S. EPA \(2012b\)](#) Sections 2.3.5 and 2.5.). The concern over model uncertainty due to the nearly 10-fold difference between the BMD and the lowest non-control dose group is partially offset in this case by the fact that six different models, including three saturated models (models for which p -values could not be derived due to the use of as many or more parameters than dose groups, resulting in 0 degrees of freedom), reported BMDLs within a very small range of 3-5 ppm.

Summary of BMD modeling results for respiratory metaplasia of olfactory epithelium in the nasal cavity of male F344/DuCrj rats [Kasai et al. \(2009\)](#)¹

Model	Restriction	BM R	BMD (ppm)	BMDL (ppm)	P -Value	AIC	Scaled Residual for Dose Group near BMD	BMDS Recommendation Notes
Gamma	Restricted	0.1	6.468	4.737	0.581	129.46	-0.106	Lowest AIC BMDL 10x lower than lowest non-zero dose
Multistage Degree 2 ²	Restricted	0.1	6.468	4.737	0.581	129.46	-0.106	
Multistage Degree 1	Restricted	0.1	6.468	4.737	0.581	129.46	-0.106	
Weibull	Restricted	0.1	6.468	4.737	0.581	129.46	-0.106	BMDL 10x lower than lowest non-zero dose d.f.=0, saturated model (Goodness of fit test cannot be calculated)
Log-Logistic	Restricted	0.1	14.207	3.771	NA	131.18	-1.24E-05	
Dichotomous Hill	Restricted	0.1	14.204	3.771	NA	131.18	-0.0002	
Log-Probit	Unrestricted	0.1	12.211	3.075	NA	131.18	-8.44E-07	Goodness of fit p-value < 0.1
Logistic	Unrestricted	0.1	12.520	9.345	0.012	133.58	-1.031	
Probit	Unrestricted	0.1	15.288	11.687	0.007	136.12	-1.511	

¹ High dose response was not included because of inadequate model fits and the fact that maximal response was reached at the mid-dose.

² Multistage 2 is the same model as Multistage 1 due to parameter convergence.

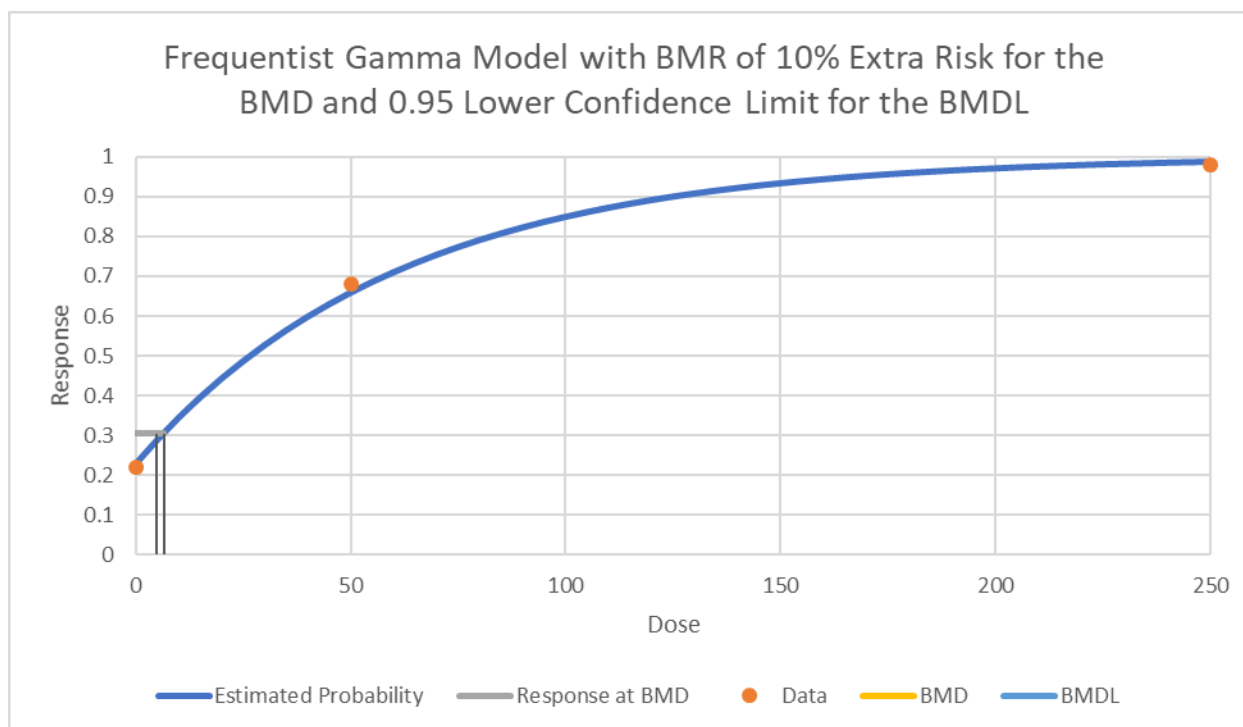
Data

Respiratory metaplasia		
Respiratory metaplasia of the olfactory epithelium (male F344 rats, Kasai et al., 2009)		
Dose	N	Incidence
[Dose]	[N]	[Incidence]
0	50	11
50	50	34
250	50	49

Restricted Gamma

User Input																																																																	
<table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr style="background-color: #add8e6;"> <th style="text-align: left; padding: 2px;">Info</th> <th style="padding: 2px;"></th> </tr> </thead> <tbody> <tr> <td style="padding: 2px;">Model</td> <td style="padding: 2px;">Restricted Gamma</td> </tr> <tr> <td style="padding: 2px;">Dataset Name</td> <td style="padding: 2px;">Respiratory metaplasia</td> </tr> <tr> <td style="padding: 2px;">User notes</td> <td style="padding: 2px;">Respiratory metaplasia of olfactory epithelium (male F344 rats, Kasai et al., 2009))</td> </tr> </tbody> </table>	Info		Model	Restricted Gamma	Dataset Name	Respiratory metaplasia	User notes	Respiratory metaplasia of olfactory epithelium (male F344 rats, Kasai et al., 2009))	<table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr style="background-color: #add8e6;"> <th style="text-align: left; padding: 2px;">Model Options</th> <th style="padding: 2px;"></th> </tr> </thead> <tbody> <tr> <td style="padding: 2px;">Risk Type</td> <td style="padding: 2px;">Extra Risk</td> </tr> <tr> <td style="padding: 2px;">BMR</td> <td style="padding: 2px;">0.1</td> </tr> <tr> <td style="padding: 2px;">Confidence Level</td> <td style="padding: 2px;">0.95</td> </tr> <tr> <td style="padding: 2px;">Background</td> <td style="padding: 2px;">Estimated</td> </tr> </tbody> </table>	Model Options		Risk Type	Extra Risk	BMR	0.1	Confidence Level	0.95	Background	Estimated	<table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr style="background-color: #add8e6;"> <th style="text-align: left; padding: 2px;">Model Data</th> <th style="padding: 2px;"></th> </tr> </thead> <tbody> <tr> <td style="padding: 2px;">Dependent Variable</td> <td style="padding: 2px;">ppm</td> </tr> <tr> <td style="padding: 2px;">Independent Variable</td> <td style="padding: 2px;">Respiratory metaplasia</td> </tr> <tr> <td style="padding: 2px;">Total # of Observations</td> <td style="padding: 2px;">3</td> </tr> </tbody> </table>	Model Data		Dependent Variable	ppm	Independent Variable	Respiratory metaplasia	Total # of Observations	3																																					
Info																																																																	
Model	Restricted Gamma																																																																
Dataset Name	Respiratory metaplasia																																																																
User notes	Respiratory metaplasia of olfactory epithelium (male F344 rats, Kasai et al., 2009))																																																																
Model Options																																																																	
Risk Type	Extra Risk																																																																
BMR	0.1																																																																
Confidence Level	0.95																																																																
Background	Estimated																																																																
Model Data																																																																	
Dependent Variable	ppm																																																																
Independent Variable	Respiratory metaplasia																																																																
Total # of Observations	3																																																																
Model Results																																																																	
<table border="1" style="width: 100%; border-collapse: collapse; margin-bottom: 10px;"> <thead> <tr style="background-color: #add8e6;"> <th colspan="2" style="text-align: center; padding: 5px;">Benchmark Dose</th> </tr> </thead> <tbody> <tr> <td style="padding: 5px;">BMD</td> <td style="padding: 5px;">6.468479372</td> </tr> <tr> <td style="padding: 5px;">BMDL</td> <td style="padding: 5px;">4.737250177</td> </tr> <tr> <td style="padding: 5px;">BMDU</td> <td style="padding: 5px;">15.58341107</td> </tr> <tr> <td style="padding: 5px;">AIC</td> <td style="padding: 5px;">129.46256</td> </tr> <tr> <td style="padding: 5px;">P-value</td> <td style="padding: 5px;">0.581473595</td> </tr> <tr> <td style="padding: 5px;">D.O.F.</td> <td style="padding: 5px;">1</td> </tr> <tr> <td style="padding: 5px;">Chi²</td> <td style="padding: 5px;">0.303858409</td> </tr> </tbody> </table> <table border="1" style="width: 100%; border-collapse: collapse; margin-bottom: 10px;"> <thead> <tr style="background-color: #add8e6;"> <th colspan="2" style="text-align: center; padding: 5px;">Model Parameters</th> </tr> </thead> <tbody> <tr> <td style="padding: 5px;"># of Parameters</td> <td style="padding: 5px;">4</td> </tr> <tr style="background-color: #cccccc;"> <td style="padding: 5px;">Variable</td> <td style="padding: 5px;">Estimate</td> </tr> <tr> <td style="padding: 5px;">g</td> <td style="padding: 5px;">0.226248926</td> </tr> <tr> <td style="padding: 5px;">a</td> <td style="padding: 5px;">1</td> </tr> <tr> <td style="padding: 5px;">b</td> <td style="padding: 5px;">0.016288297</td> </tr> </tbody> </table> <table border="1" style="width: 100%; border-collapse: collapse; margin-bottom: 10px;"> <thead> <tr style="background-color: #add8e6;"> <th colspan="6" style="text-align: center; padding: 5px;">Goodness of Fit</th> </tr> <tr style="background-color: #cccccc;"> <th style="padding: 5px;">Dose</th> <th style="padding: 5px;">Estimated Probability</th> <th style="padding: 5px;">Expected</th> <th style="padding: 5px;">Observed</th> <th style="padding: 5px;">Size</th> <th style="padding: 5px;">Scaled Residual</th> </tr> </thead> <tbody> <tr> <td style="padding: 5px;">0</td> <td style="padding: 5px;">0.226248926</td> <td style="padding: 5px;">11.31244628</td> <td style="padding: 5px;">11</td> <td style="padding: 5px;">50</td> <td style="padding: 5px;">-0.105608</td> </tr> <tr> <td style="padding: 5px;">50</td> <td style="padding: 5px;">0.657306883</td> <td style="padding: 5px;">32.86534417</td> <td style="padding: 5px;">34</td> <td style="padding: 5px;">50</td> <td style="padding: 5px;">0.3380978</td> </tr> <tr> <td style="padding: 5px;">250</td> <td style="padding: 5px;">0.986813734</td> <td style="padding: 5px;">49.34068668</td> <td style="padding: 5px;">49</td> <td style="padding: 5px;">50</td> <td style="padding: 5px;">-0.422369</td> </tr> </tbody> </table> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr style="background-color: #add8e6;"> <th style="text-align: center; padding: 5px;">Analysis of Deviance</th> </tr> </thead> <tbody> <tr> <td style="height: 20px;"> </td> </tr> </tbody> </table>						Benchmark Dose		BMD	6.468479372	BMDL	4.737250177	BMDU	15.58341107	AIC	129.46256	P-value	0.581473595	D.O.F.	1	Chi ²	0.303858409	Model Parameters		# of Parameters	4	Variable	Estimate	g	0.226248926	a	1	b	0.016288297	Goodness of Fit						Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual	0	0.226248926	11.31244628	11	50	-0.105608	50	0.657306883	32.86534417	34	50	0.3380978	250	0.986813734	49.34068668	49	50	-0.422369	Analysis of Deviance	
Benchmark Dose																																																																	
BMD	6.468479372																																																																
BMDL	4.737250177																																																																
BMDU	15.58341107																																																																
AIC	129.46256																																																																
P-value	0.581473595																																																																
D.O.F.	1																																																																
Chi ²	0.303858409																																																																
Model Parameters																																																																	
# of Parameters	4																																																																
Variable	Estimate																																																																
g	0.226248926																																																																
a	1																																																																
b	0.016288297																																																																
Goodness of Fit																																																																	
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual																																																												
0	0.226248926	11.31244628	11	50	-0.105608																																																												
50	0.657306883	32.86534417	34	50	0.3380978																																																												
250	0.986813734	49.34068668	49	50	-0.422369																																																												
Analysis of Deviance																																																																	

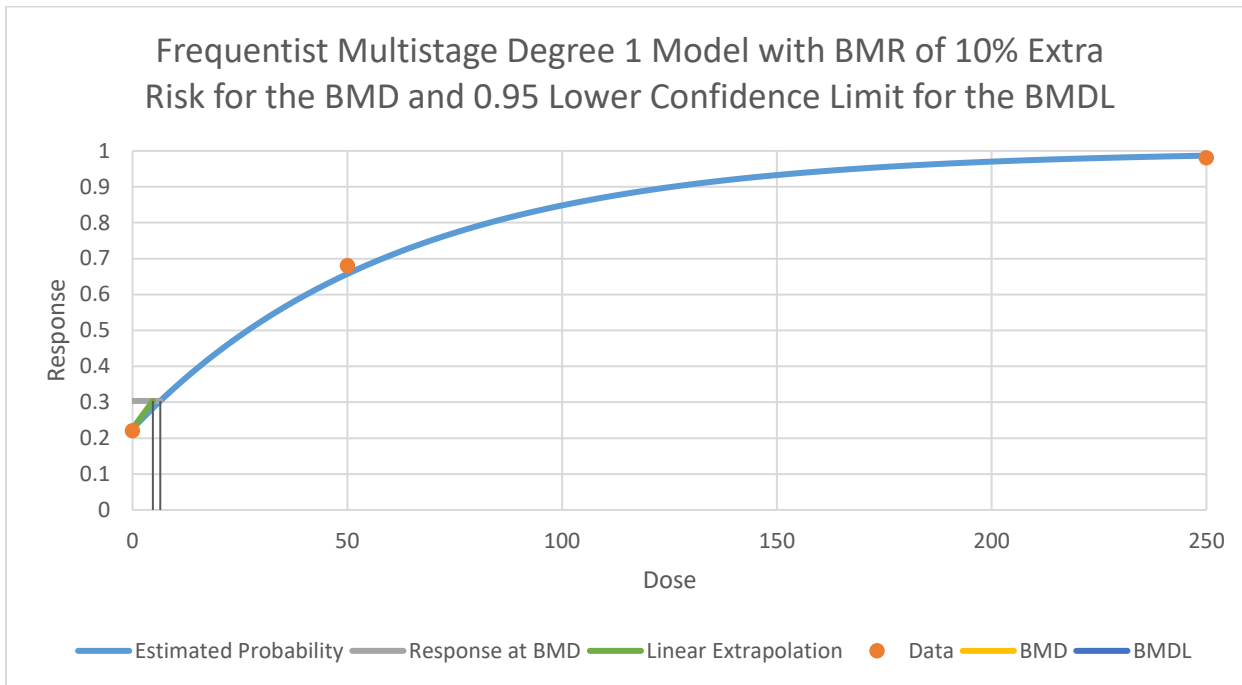
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-62.59082662	0	-	-	-
Fitted Model	-62.73127999	2	0.28090675	1	0.5961075
Reduced Model	-99.1058899	1	73.0301266	2	<0.0001



Restricted Multistage 1

User Input																																																																															
<table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr style="background-color: #add8e6;"> <th style="text-align: left; padding: 2px;">Info</th> <th style="padding: 2px;"></th> </tr> </thead> <tbody> <tr> <td style="padding: 2px;">Model</td> <td style="padding: 2px;">Restricted Multistage 1</td> </tr> <tr> <td style="padding: 2px;">Dataset Name</td> <td style="padding: 2px;">Respiratory metaplasia</td> </tr> <tr> <td style="padding: 2px;">User notes</td> <td style="padding: 2px;">Respiratory metaplasia of olfactory epithelium (male F344 rats, Kasai et al. 2009))</td> </tr> </tbody> </table>	Info		Model	Restricted Multistage 1	Dataset Name	Respiratory metaplasia	User notes	Respiratory metaplasia of olfactory epithelium (male F344 rats, Kasai et al. 2009))	<table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr style="background-color: #add8e6;"> <th style="text-align: left; padding: 2px;">Model Options</th> <th style="padding: 2px;"></th> </tr> </thead> <tbody> <tr> <td style="padding: 2px;">Risk Type</td> <td style="padding: 2px;">Extra Risk</td> </tr> <tr> <td style="padding: 2px;">BMR</td> <td style="padding: 2px;">0.1</td> </tr> <tr> <td style="padding: 2px;">Confidence Level</td> <td style="padding: 2px;">0.95</td> </tr> <tr> <td style="padding: 2px;">Background</td> <td style="padding: 2px;">Estimated</td> </tr> </tbody> </table>	Model Options		Risk Type	Extra Risk	BMR	0.1	Confidence Level	0.95	Background	Estimated	<table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr style="background-color: #add8e6;"> <th style="text-align: left; padding: 2px;">Model Data</th> <th style="padding: 2px;"></th> </tr> </thead> <tbody> <tr> <td style="padding: 2px;">Dependent Variable</td> <td style="padding: 2px;">ppm</td> </tr> <tr> <td style="padding: 2px;">Independent Variable</td> <td style="padding: 2px;">Respiratory metaplasia</td> </tr> <tr> <td style="padding: 2px;">Total # of Observations</td> <td style="padding: 2px;">3</td> </tr> </tbody> </table>	Model Data		Dependent Variable	ppm	Independent Variable	Respiratory metaplasia	Total # of Observations	3																																																			
Info																																																																															
Model	Restricted Multistage 1																																																																														
Dataset Name	Respiratory metaplasia																																																																														
User notes	Respiratory metaplasia of olfactory epithelium (male F344 rats, Kasai et al. 2009))																																																																														
Model Options																																																																															
Risk Type	Extra Risk																																																																														
BMR	0.1																																																																														
Confidence Level	0.95																																																																														
Background	Estimated																																																																														
Model Data																																																																															
Dependent Variable	ppm																																																																														
Independent Variable	Respiratory metaplasia																																																																														
Total # of Observations	3																																																																														
Model Results																																																																															
<table border="1" style="width: 100%; border-collapse: collapse; margin-bottom: 10px;"> <thead> <tr style="background-color: #add8e6;"> <th colspan="2" style="text-align: center; padding: 5px;">Benchmark Dose</th> </tr> </thead> <tbody> <tr> <td style="padding: 5px;">BMD</td> <td style="padding: 5px;">6.468474487</td> </tr> <tr> <td style="padding: 5px;">BMDL</td> <td style="padding: 5px;">4.737235003</td> </tr> <tr> <td style="padding: 5px;">BMDU</td> <td style="padding: 5px;">9.087463619</td> </tr> <tr> <td style="padding: 5px;">AIC</td> <td style="padding: 5px;">129.46256</td> </tr> <tr> <td style="padding: 5px;">P-value</td> <td style="padding: 5px;">0.581473253</td> </tr> <tr> <td style="padding: 5px;">D.O.F.</td> <td style="padding: 5px;">1</td> </tr> <tr> <td style="padding: 5px;">Chi²</td> <td style="padding: 5px;">0.303858959</td> </tr> </tbody> </table> <table border="1" style="width: 100%; border-collapse: collapse; margin-bottom: 10px;"> <thead> <tr style="background-color: #add8e6;"> <th colspan="2" style="text-align: center; padding: 5px;">Model Parameters</th> </tr> </thead> <tbody> <tr> <td style="padding: 5px;"># of Parameters</td> <td style="padding: 5px;">2</td> </tr> <tr style="background-color: #cccccc;"> <td style="padding: 5px;">Variable</td> <td style="padding: 5px;">Estimate</td> </tr> <tr> <td style="padding: 5px;">g</td> <td style="padding: 5px;">0.226248831</td> </tr> <tr> <td style="padding: 5px;">b1</td> <td style="padding: 5px;">0.01628831</td> </tr> </tbody> </table> <table border="1" style="width: 100%; border-collapse: collapse; margin-bottom: 10px;"> <thead> <tr style="background-color: #add8e6;"> <th colspan="6" style="text-align: center; padding: 5px;">Goodness of Fit</th> </tr> <tr style="background-color: #cccccc;"> <th style="padding: 5px;">Dose</th> <th style="padding: 5px;">Estimated Probability</th> <th style="padding: 5px;">Expected</th> <th style="padding: 5px;">Observed</th> <th style="padding: 5px;">Size</th> <th style="padding: 5px;">Scaled Residual</th> </tr> </thead> <tbody> <tr> <td style="padding: 5px;">0</td> <td style="padding: 5px;">0.226248831</td> <td style="padding: 5px;">11.31244157</td> <td style="padding: 5px;">11</td> <td style="padding: 5px;">50</td> <td style="padding: 5px;">-0.105606</td> </tr> <tr> <td style="padding: 5px;">50</td> <td style="padding: 5px;">0.657307053</td> <td style="padding: 5px;">32.86535263</td> <td style="padding: 5px;">34</td> <td style="padding: 5px;">50</td> <td style="padding: 5px;">0.3380953</td> </tr> <tr> <td style="padding: 5px;">250</td> <td style="padding: 5px;">0.986813773</td> <td style="padding: 5px;">49.34068863</td> <td style="padding: 5px;">49</td> <td style="padding: 5px;">50</td> <td style="padding: 5px;">-0.422372</td> </tr> </tbody> </table> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr style="background-color: #add8e6;"> <th colspan="6" style="text-align: center; padding: 5px;">Analysis of Deviance</th> </tr> <tr style="background-color: #cccccc;"> <th style="padding: 5px;">Model</th> <th style="padding: 5px;">Log Likelihood</th> <th style="padding: 5px;"># of Parameters</th> <th style="padding: 5px;">Deviance</th> <th style="padding: 5px;">Test d.f.</th> <th style="padding: 5px;">P Value</th> </tr> </thead> <tbody> <tr> <td style="padding: 5px;"> </td> <td style="padding: 5px;"> </td> <td style="padding: 5px;"> </td> <td style="padding: 5px;"> </td> <td style="padding: 5px;"> </td> <td style="padding: 5px;"> </td> </tr> </tbody> </table>						Benchmark Dose		BMD	6.468474487	BMDL	4.737235003	BMDU	9.087463619	AIC	129.46256	P-value	0.581473253	D.O.F.	1	Chi ²	0.303858959	Model Parameters		# of Parameters	2	Variable	Estimate	g	0.226248831	b1	0.01628831	Goodness of Fit						Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual	0	0.226248831	11.31244157	11	50	-0.105606	50	0.657307053	32.86535263	34	50	0.3380953	250	0.986813773	49.34068863	49	50	-0.422372	Analysis of Deviance						Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value						
Benchmark Dose																																																																															
BMD	6.468474487																																																																														
BMDL	4.737235003																																																																														
BMDU	9.087463619																																																																														
AIC	129.46256																																																																														
P-value	0.581473253																																																																														
D.O.F.	1																																																																														
Chi ²	0.303858959																																																																														
Model Parameters																																																																															
# of Parameters	2																																																																														
Variable	Estimate																																																																														
g	0.226248831																																																																														
b1	0.01628831																																																																														
Goodness of Fit																																																																															
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual																																																																										
0	0.226248831	11.31244157	11	50	-0.105606																																																																										
50	0.657307053	32.86535263	34	50	0.3380953																																																																										
250	0.986813773	49.34068863	49	50	-0.422372																																																																										
Analysis of Deviance																																																																															
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value																																																																										

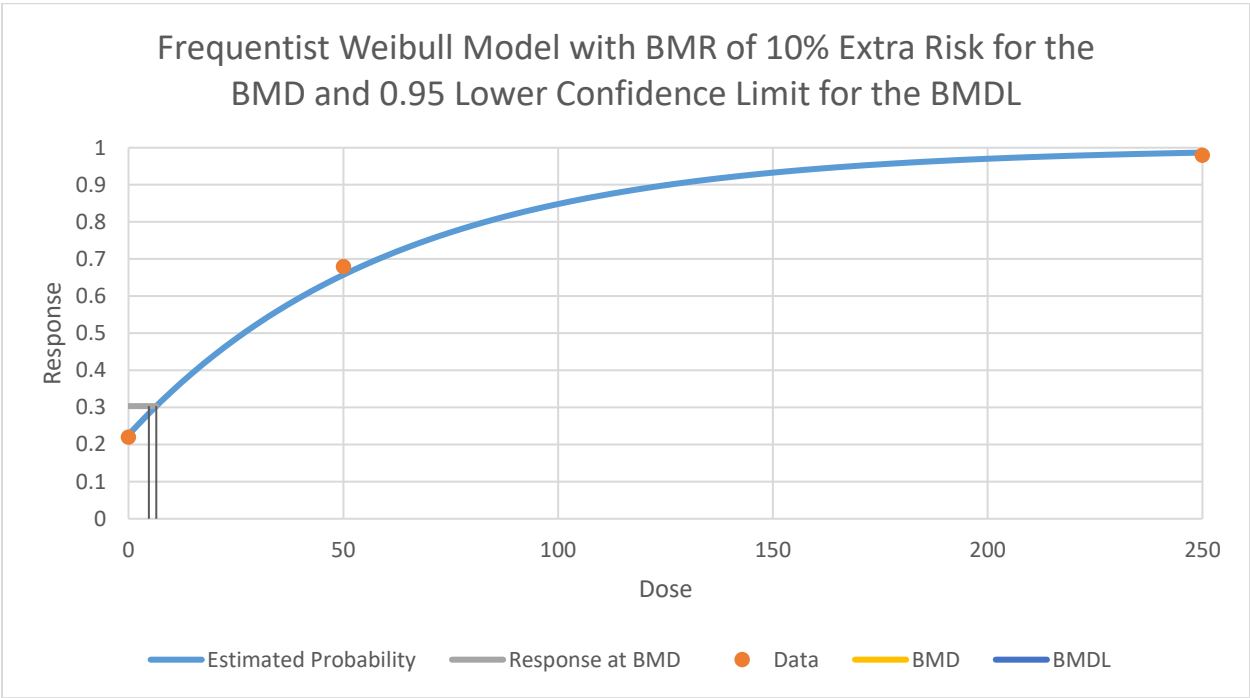
Full Model	-62.59082662	0	-	-	-
Fitted Model	-62.73127999	2	0.28090675	1	0.5961075
Reduced Model	-99.1058899	1	73.0301266	2	<0.0001



Restricted Weibull

User Input																																																															
<table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr style="background-color: #add8e6;"> <th style="text-align: left; padding: 2px;">Info</th> <th style="padding: 2px;"></th> </tr> </thead> <tbody> <tr> <td style="padding: 2px;">Model</td> <td style="padding: 2px;">Restricted Weibull</td> </tr> <tr> <td style="padding: 2px;">Dataset Name</td> <td style="padding: 2px;">Respiratory metaplasia</td> </tr> <tr> <td style="padding: 2px;">User notes</td> <td style="padding: 2px;">Respiratory metaplasia of olfactory epithelium (male F344 rats, Kasai et al., 2009))</td> </tr> </tbody> </table>	Info		Model	Restricted Weibull	Dataset Name	Respiratory metaplasia	User notes	Respiratory metaplasia of olfactory epithelium (male F344 rats, Kasai et al., 2009))	<table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr style="background-color: #add8e6;"> <th style="text-align: left; padding: 2px;">Model Options</th> <th style="padding: 2px;"></th> </tr> </thead> <tbody> <tr> <td style="padding: 2px;">Risk Type</td> <td style="padding: 2px;">Extra Risk</td> </tr> <tr> <td style="padding: 2px;">BMR</td> <td style="padding: 2px;">0.1</td> </tr> <tr> <td style="padding: 2px;">Confidence Level</td> <td style="padding: 2px;">0.95</td> </tr> <tr> <td style="padding: 2px;">Background</td> <td style="padding: 2px;">Estimated</td> </tr> </tbody> </table>	Model Options		Risk Type	Extra Risk	BMR	0.1	Confidence Level	0.95	Background	Estimated	<table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr style="background-color: #add8e6;"> <th style="text-align: left; padding: 2px;">Model Data</th> <th style="padding: 2px;"></th> </tr> </thead> <tbody> <tr> <td style="padding: 2px;">Dependent Variable</td> <td style="padding: 2px;">ppm</td> </tr> <tr> <td style="padding: 2px;">Independent Variable</td> <td style="padding: 2px;">Respiratory metaplasia</td> </tr> <tr> <td style="padding: 2px;">Total # of Observations</td> <td style="padding: 2px;">3</td> </tr> </tbody> </table>	Model Data		Dependent Variable	ppm	Independent Variable	Respiratory metaplasia	Total # of Observations	3																																			
Info																																																															
Model	Restricted Weibull																																																														
Dataset Name	Respiratory metaplasia																																																														
User notes	Respiratory metaplasia of olfactory epithelium (male F344 rats, Kasai et al., 2009))																																																														
Model Options																																																															
Risk Type	Extra Risk																																																														
BMR	0.1																																																														
Confidence Level	0.95																																																														
Background	Estimated																																																														
Model Data																																																															
Dependent Variable	ppm																																																														
Independent Variable	Respiratory metaplasia																																																														
Total # of Observations	3																																																														
Model Results																																																															
<table border="1" style="width: 100%; border-collapse: collapse; margin-bottom: 10px;"> <thead> <tr style="background-color: #add8e6;"> <th colspan="2" style="text-align: center; padding: 5px;">Benchmark Dose</th> </tr> </thead> <tbody> <tr> <td style="padding: 5px;">BMD</td> <td style="padding: 5px;">6.468485055</td> </tr> <tr> <td style="padding: 5px;">BMDL</td> <td style="padding: 5px;">4.737254339</td> </tr> <tr> <td style="padding: 5px;">BMDU</td> <td style="padding: 5px;">13.26149794</td> </tr> <tr> <td style="padding: 5px;">AIC</td> <td style="padding: 5px;">129.46256</td> </tr> <tr> <td style="padding: 5px;">P-value</td> <td style="padding: 5px;">0.581473996</td> </tr> <tr> <td style="padding: 5px;">D.O.F.</td> <td style="padding: 5px;">1</td> </tr> <tr> <td style="padding: 5px;">Chi²</td> <td style="padding: 5px;">0.303857764</td> </tr> </tbody> </table> <table border="1" style="width: 100%; border-collapse: collapse; margin-bottom: 10px;"> <thead> <tr style="background-color: #add8e6;"> <th colspan="2" style="text-align: center; padding: 5px;">Model Parameters</th> </tr> </thead> <tbody> <tr> <td style="padding: 5px;"># of Parameters</td> <td style="padding: 5px;">3</td> </tr> <tr style="background-color: #cccccc;"> <td style="padding: 5px;">Variable</td> <td style="padding: 5px;">Estimate</td> </tr> <tr> <td style="padding: 5px;">g</td> <td style="padding: 5px;">0.226249018</td> </tr> <tr> <td style="padding: 5px;">a</td> <td style="padding: 5px;">1</td> </tr> <tr> <td style="padding: 5px;">b</td> <td style="padding: 5px;">0.016288283</td> </tr> </tbody> </table> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr style="background-color: #add8e6;"> <th colspan="6" style="text-align: center; padding: 5px;">Goodness of Fit</th> </tr> <tr style="background-color: #cccccc;"> <th style="padding: 5px;">Dose</th> <th style="padding: 5px;">Estimated Probability</th> <th style="padding: 5px;">Expected</th> <th style="padding: 5px;">Observed</th> <th style="padding: 5px;">Size</th> <th style="padding: 5px;">Scaled Residual</th> </tr> </thead> <tbody> <tr> <td style="padding: 5px;">0</td> <td style="padding: 5px;">0.226249018</td> <td style="padding: 5px;">11.31245092</td> <td style="padding: 5px;">11</td> <td style="padding: 5px;">50</td> <td style="padding: 5px;">-0.105609</td> </tr> <tr> <td style="padding: 5px;">50</td> <td style="padding: 5px;">0.657306679</td> <td style="padding: 5px;">32.86533396</td> <td style="padding: 5px;">34</td> <td style="padding: 5px;">50</td> <td style="padding: 5px;">0.3381008</td> </tr> <tr> <td style="padding: 5px;">250</td> <td style="padding: 5px;">0.986813688</td> <td style="padding: 5px;">49.3406844</td> <td style="padding: 5px;">49</td> <td style="padding: 5px;">50</td> <td style="padding: 5px;">-0.422365</td> </tr> </tbody> </table>						Benchmark Dose		BMD	6.468485055	BMDL	4.737254339	BMDU	13.26149794	AIC	129.46256	P-value	0.581473996	D.O.F.	1	Chi ²	0.303857764	Model Parameters		# of Parameters	3	Variable	Estimate	g	0.226249018	a	1	b	0.016288283	Goodness of Fit						Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual	0	0.226249018	11.31245092	11	50	-0.105609	50	0.657306679	32.86533396	34	50	0.3381008	250	0.986813688	49.3406844	49	50	-0.422365
Benchmark Dose																																																															
BMD	6.468485055																																																														
BMDL	4.737254339																																																														
BMDU	13.26149794																																																														
AIC	129.46256																																																														
P-value	0.581473996																																																														
D.O.F.	1																																																														
Chi ²	0.303857764																																																														
Model Parameters																																																															
# of Parameters	3																																																														
Variable	Estimate																																																														
g	0.226249018																																																														
a	1																																																														
b	0.016288283																																																														
Goodness of Fit																																																															
Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual																																																										
0	0.226249018	11.31245092	11	50	-0.105609																																																										
50	0.657306679	32.86533396	34	50	0.3381008																																																										
250	0.986813688	49.3406844	49	50	-0.422365																																																										

Analysis of Deviance					
Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-59.3166114	0	-	-	-
Fitted Model	-59.31661362	2	4.4538E-06	2	0.9999978
Reduced Model	-123.8201329	1	129.007043	3	<0.0001



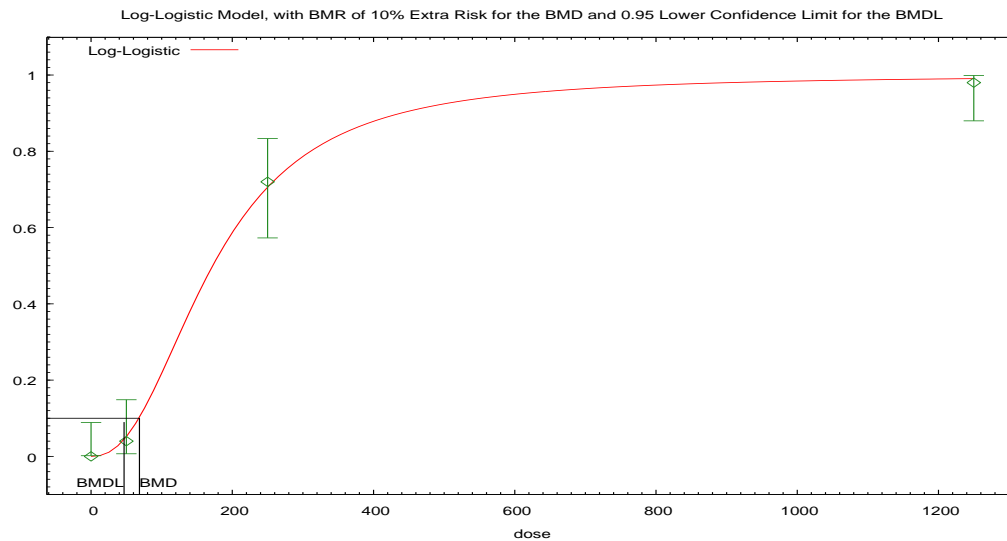
K.5 BMD5 Summary of Hydropic change (lamina propria) [Kasai et al. \(2009\)](#)

Table K-4. Summary of BMD Modeling Results for Hydropic change (lamina propria) [Kasai et al. \(2009\)](#)

Model ^a	Goodness of fit		BMD _{10Pct} (ppm)	BMDL _{10Pct} (ppm)	Basis for model selection
	p-value	AIC			
Gamma	2.00E-04	98.344	52.0	28.8	Lowest AIC. BMDL estimates for models not excluded (based on goodness-of-fit p values less than 0.1, or high scaled residuals) are sufficiently close.
Dichotomous-Hill	1.000	91.894	73.1	49.3	
Logistic	0	117.96	89.3	70.6	
LogLogistic	0.682	90.539	68.5	46.8	
Probit	0	136.59	92.6	74.4	
LogProbit	0.346	91.588	63.1	44.6	
Weibull	0.0033	100.23	39.1	24.0	
Multistage 3 ^{ob} Multistage 2 ^o Quantal-Linear	0.0256	99.348	28.8	22.7	

^a Selected model in bold; scaled residuals for selected model for doses 0, 50, 250, and 1250 ppm were 0, -0.33, 0.32, -0.74, respectively.

^b For the Multistage 3^o model, the beta coefficient estimates were 0 (boundary of parameters space). The models in this row reduced to the Multistage 2^o model.



14:16 08/10 2018

Figure K-4. Plot of incidence rate by dose with fitted curve for LogLogistic model for Hydropic change (lamina propria) [Kasai et al. \(2009\)](#); dose shown in ppm.

LogLogistic Model. (Version: 2.15; Date: 3/20/2017)

The form of the probability function is: $P[\text{response}] = \text{background} + (1 - \text{background}) / [1 + \text{EXP}(-\text{intercept} - \text{slope} * \text{Log}(\text{dose}))]$

Slope parameter is restricted as slope ≥ 1

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 68.5266

BMDL at the 95% confidence level = 46.7808

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
background	0	0
intercept	-1.2132E+01	-1.1575E+01
slope	2.3501	2.19638

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-42.95	4			
Fitted model	-43.27	2	0.645129	2	0.72
Reduced model	-136.94	1	187.976	3	<.0001

AIC: = 90.5388

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	50	0
50	0.0503	2.515	2	50	-0.33
250	0.6994	34.969	36	50	0.32
1250	0.9903	49.515	49	50	-0.74

Chi² = 0.77 d.f = 2 P-value = 0.6819

K.6 BMDs Summary of Nasal cavity squamous cell carcinoma (male F344/DuCrj rats) [Kasai et al. \(2009\)](#)

Table K-5. Summary of BMD Modeling Results for Nasal cavity squamous cell carcinoma (male F344/DuCrj rats) [Kasai et al. \(2009\)](#)

Model ^a	Goodness of fit		BMD _{10Pct} (ppm)	BMDL _{10Pct} (ppm)	Basis for model selection
	p-value	AIC			
One	0.961	49.031	1107	630	Lowest AIC. All parameter estimates positive in both models.
Two	0.909	50.828	1087	642	

^a Selected model in bold; scaled residuals for selected model for doses 0, 50, 250, and 1250 ppm were 0, -0.49, -0.16, 0.18, respectively.

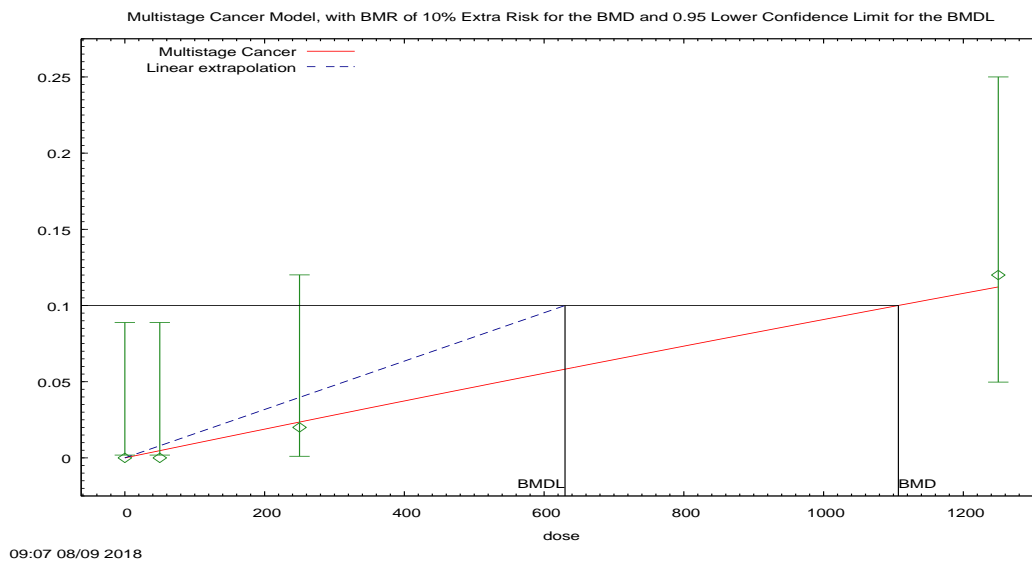


Figure K-5. Plot of incidence rate by dose with fitted curve for Multistage-Cancer 1° model for Nasal cavity squamous cell carcinoma (male F344/DuCrj rats) [Kasai et al. \(2009\)](#); dose shown in ppm.

Multistage Model. (Version: 3.4; Date: 05/02/2014)

The form of the probability function is: $P[\text{response}] = \text{background} + (1-\text{background}) * [1 - \text{EXP}(-\text{beta1} * \text{dose}^1 - \text{beta2} * \text{dose}^2)]$

The parameter betas are restricted to be positive

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 1107.04

BMDL at the 95% confidence level = 629.948

BMDU at the 95% confidence level = 2215.11

Taken together, (629.948, 2215.11) is a 90% two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.000158743

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0	0
Beta(1)	0.0000951733	0.000104666

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-23.25	4			
Fitted model	-23.52	1	0.534383	3	0.91
Reduced model	-30.34	1	14.1894	3	0

AIC: = 49.0308

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	50	0
50	0.0047	0.237	0	50	-0.49
250	0.0235	1.176	1	50	-0.16
1250	0.1122	5.608	6	50	0.18

Chi^2 = 0.3 d.f = 3 P-value = 0.9607

K.7 BMD5 Summary of Zymbal gland adenoma (male F344/DuCrj rats) Kasai et al. (2009)

Table K-6. Summary of BMD Modeling Results for Zymbal gland adenoma (male F344/DuCrj rats) Kasai et al. (2009)

Model ^a	Goodness of fit		BMD _{10Pct} (ppm)	BMDL _{10Pct} (ppm)	Basis for model selection
	p-value	AIC			
One	0.800	31.663	1975	958	Lowest BMDL. Some parameter values were zero for both models.
Two	0.982	30.217	1435	999	

^a Selected model in bold; scaled residuals for selected model for doses 0, 50, 250, and 1250 ppm were 0, -0.36, -0.82, 0.45, respectively.

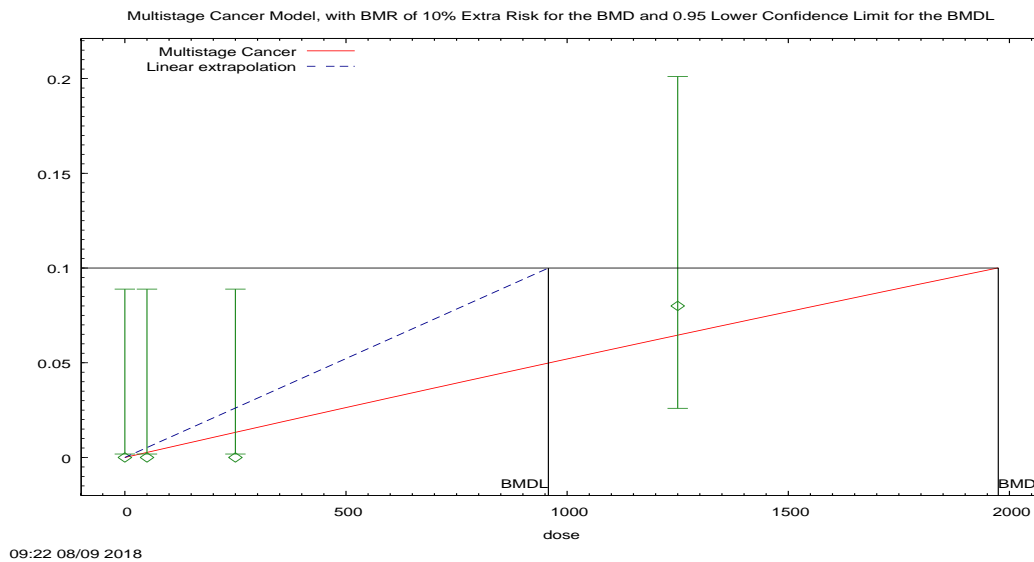


Figure K-6. Plot of incidence rate by dose with fitted curve for Multistage-Cancer 1° model for Zymbal gland adenoma (male F344/DuCrj rats) Kasai et al. (2009); dose shown in ppm.

Multistage Model. (Version: 3.4; Date: 05/02/2014)

The form of the probability function is: $P[\text{response}] = \text{background} + (1-\text{background}) * [1 - \text{EXP}(-\text{beta1} * \text{dose}^1 - \text{beta2} * \text{dose}^2)]$

The parameter betas are restricted to be positive

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 1974.78

BMDL at the 95% confidence level = 957.63

BMDU at the 95% confidence level = 5118.88

Taken together, (957.63, 5118.88) is a 90% two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.000104424

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0	0
Beta(1)	0.0000533531	0.0000700345

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-13.94	4			
Fitted model	-14.83	1	1.78598	3	0.62
Reduced model	-19.61	1	11.3387	3	0.01

AIC: = 31.6629

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	50	0
50	0.0027	0.133	0	50	-0.36
250	0.0132	0.662	0	50	-0.82
1250	0.0645	3.226	4	50	0.45

Chi^2 = 1 d.f = 3 P-value = 0.8004

K.8 MS-Combo portal of entry tumors [Kasai et al. \(2009\)](#)

Portal of entry tumors (nasal cavity squamous cell carcinoma, zymbal gland adenoma)

Output information	
Tumor Output Directory	C:\Users\ \Documents\MODELS\14dioxane\inhalation\
Tumor Output File Name	kasai_noliv_POE.out
Combined BMD and BMDL Calculations	
Combined Log-Likelihood	-38.34685652
Combined Log-likelihood Constant	32.84040568
Benchmark Dose Computation	
Specified effect	0.1
Risk Type	Extra risk
Confidence level	0.95
BMD	709.372
BMDL	448.544
Multistage Cancer Slope Factor	0.000222944

**** Start of combined BMD and BMDL Calculations.****

Combined Log-Likelihood -38.346856517733208
 Combined Log-likelihood Constant 32.840405681643567

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

 BMD = 709.372

 BMDL = 448.544

 BMDU = 1218.18

Multistage Cancer Slope Factor = 0.000222944

K.9 BMDS Summary of Hepatocellular adenoma or carcinoma (male F344/DuCrj rats) [Kasai et al. \(2009\)](#)

Table K-7. Summary of BMD Modeling Results for Hepatocellular adenoma or carcinoma (male F344/DuCrj rats) [Kasai et al. \(2009\)](#)

Model ^a	Goodness of fit		BMD _{10Pct} (ppm)	BMDL _{10Pct} (ppm)	Basis for model selection
	p-value	AIC			
One	0.693	127.86	253	182	Lowest AIC. All parameter estimates positive in both models.
Two	0.764	129.16	377	190	

^a Selected model in bold; scaled residuals for selected model for doses 0, 50, 250, and 1250 ppm were 0.16, 0.1, -0.76, 0.34, respectively.

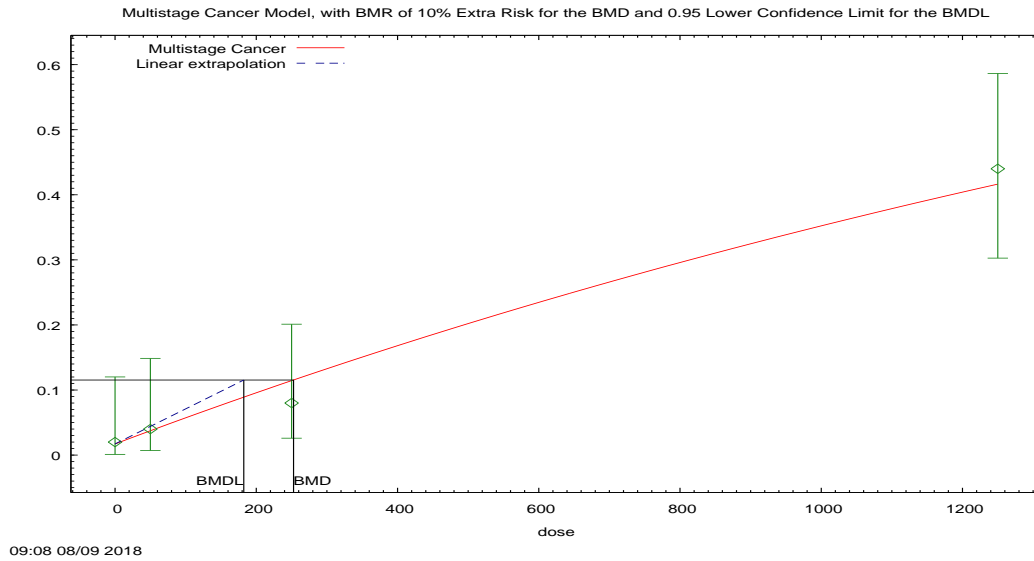


Figure K-7. Plot of incidence rate by dose with fitted curve for Multistage-Cancer 1^o model for Hepatocellular adenoma or carcinoma (male F344/DuCrj rats) [Kasai et al. \(2009\)](#); dose shown in ppm.

Multistage Model. (Version: 3.4; Date: 05/02/2014)

The form of the probability function is: $P[\text{response}] = \text{background} + (1-\text{background}) * [1 - \text{EXP}(-\text{beta1} * \text{dose} - \text{beta2} * \text{dose}^2)]$

The parameter betas are restricted to be positive

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 252.799

BMDL at the 95% confidence level = 182.256

BMDU at the 95% confidence level = 371.457

Taken together, (182.256, 371.457) is a 90% two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.000548678

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0.0170678	0.00480969
Beta(1)	0.000416776	0.0004548

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-61.53	4			
Fitted model	-61.93	2	0.792109	2	0.67
Reduced model	-82.79	1	42.5066	3	<.0001

AIC: = 127.86

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0.0171	0.853	1	50	0.16
50	0.0373	1.867	2	50	0.1
250	0.1143	5.716	4	50	-0.76
1250	0.4162	20.81	22	50	0.34

Chi² = 0.73 d.f = 2 P-value = 0.6928

K.10 BMDS Summary of Renal cell carcinoma (male F344/DuCrj rats)
[Kasai et al. \(2009\)](#)

Table K-8. Summary of BMD Modeling Results for Renal cell carcinoma (male F344/DuCrj rats)
[Kasai et al. \(2009\)](#)

Model ^a	Goodness of fit		BMD _{10Pct} (ppm)	BMDL _{10Pct} (ppm)	Basis for model selection
	<i>p</i> -value	AIC			
One	0.800	31.663	1975	958	Lowest BMDL. Some parameter values were zero for both models.
Two	0.982	30.217	1435	999	

^a Selected model in bold; scaled residuals for selected model for doses 0, 50, 250, and 1250 ppm were 0, -0.36, -0.82, 0.45, respectively.

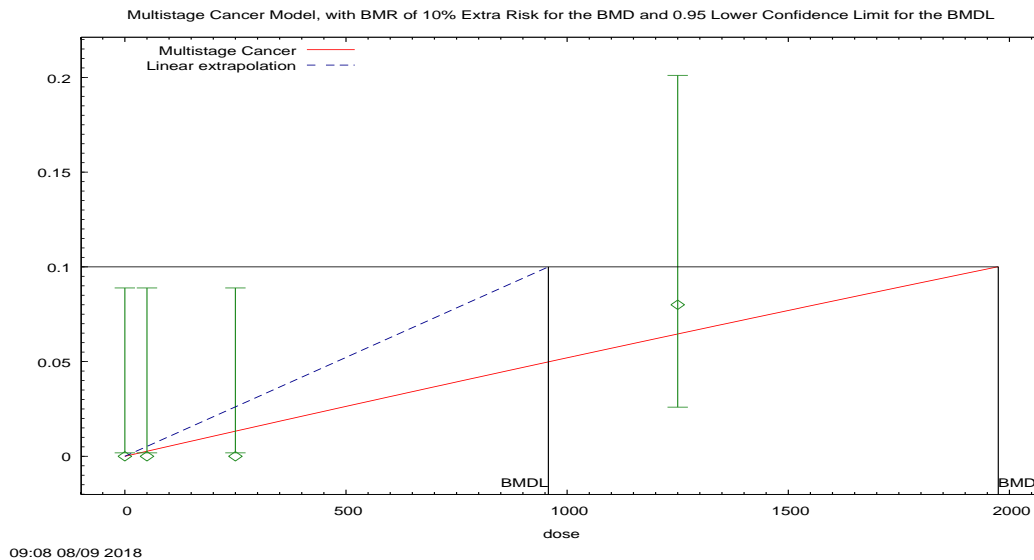


Figure K-8. Plot of incidence rate by dose with fitted curve for Multistage-Cancer 1° model for Renal cell carcinoma (male F344/DuCrj rats) [Kasai et al. \(2009\)](#); dose shown in ppm.

Multistage Model. (Version: 3.4; Date: 05/02/2014)

The form of the probability function is: $P[\text{response}] = \text{background} + (1-\text{background}) * [1 - \text{EXP}(-\text{beta1} * \text{dose}^1 - \text{beta2} * \text{dose}^2)]$

The parameter betas are restricted to be positive

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 1974.78

BMDL at the 95% confidence level = 957.63

BMDU at the 95% confidence level = 5118.88

Taken together, (957.63, 5118.88) is a 90% two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.000104424

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0	0
Beta(1)	0.0000533531	0.0000700345

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-13.94	4			
Fitted model	-14.83	1	1.78598	3	0.62
Reduced model	-19.61	1	11.3387	3	0.01

AIC: = 31.6629

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	50	0
50	0.0027	0.133	0	50	-0.36
250	0.0132	0.662	0	50	-0.82
1250	0.0645	3.226	4	50	0.45

Chi² = 1 d.f = 3 P-value = 0.8004

K.11 BMDS Summary of Peritoneal mesothelioma (male F344/DuCrj rats) [Kasai et al. \(2009\)](#)

Table K-9. Summary of BMD Modeling Results for Peritoneal mesothelioma (male F344/DuCrj rats) [Kasai et al. \(2009\)](#)

Model ^a	Goodness of fit		BMD _{10Pct} (ppm)	BMDL _{10Pct} (ppm)	Basis for model selection
	<i>p</i> -value	AIC			
One	0.851	155.43	82.2	64.4	Lowest AIC. All parameter estimates positive in both models.
Two	0.805	157.17	96.2	65.1	

^a Selected model in bold; scaled residuals for selected model for doses 0, 50, 250, and 1250 ppm were 0.25, -0.33, -0.29, 0.26, respectively.

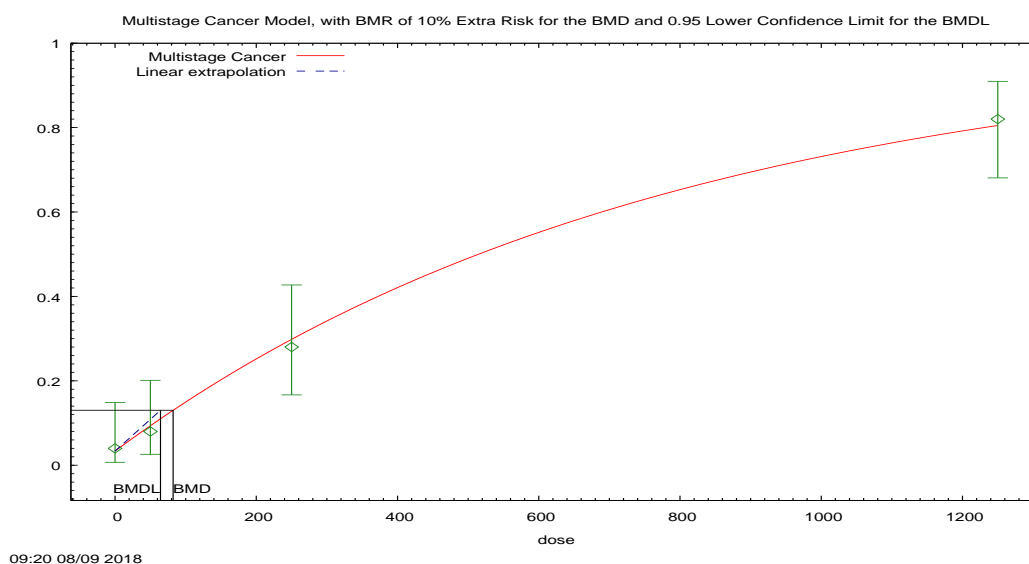


Figure K-9. Plot of incidence rate by dose with fitted curve for Multistage-Cancer 1° model for Peritoneal mesothelioma (male F344/DuCrj rats) [Kasai et al. \(2009\)](#); dose shown in ppm.

Multistage Model. (Version: 3.4; Date: 05/02/2014)

The form of the probability function is: $P[\text{response}] = \text{background} + (1-\text{background}) * [1 - \text{EXP}(-\text{beta1} * \text{dose}^1 - \text{beta2} * \text{dose}^2)]$

The parameter betas are restricted to be positive

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 82.2057

BMDL at the 95% confidence level = 64.3808

BMDU at the 95% confidence level = 107.497

Taken together, (64.3808, 107.497) is a 90% two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.00155326

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0.033631	0.0172414
Beta(1)	0.00128167	0.00135351

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-75.55	4			
Fitted model	-75.72	2	0.326905	2	0.85
Reduced model	-123.01	1	94.9105	3	<.0001

AIC: = 155.433

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0.0336	1.682	2	50	0.25
50	0.0936	4.681	4	50	-0.33
250	0.2986	14.928	14	50	-0.29
1250	0.8053	40.265	41	50	0.26

Chi² = 0.32 d.f = 2 P-value = 0.8509

K.12 BMDS Summary of Mammary gland fibroadenoma (male F344/DuCrj rats) [Kasai et al. \(2009\)](#)

Table K-10. Summary of BMD Modeling Results for Mammary gland fibroadenoma (male F344/DuCrj rats) [Kasai et al. \(2009\)](#)

Model ^a	Goodness of fit		BMD _{10Pct} (ppm)	BMDL _{10Pct} (ppm)	Basis for model selection
	<i>p</i> -value	AIC			
One Two	0.790	86.290	1635	703	All (equivalent) models provide adequate fit.

^a Selected model in bold; scaled residuals for selected model for doses 0, 50, 250, and 1250 ppm were -0.47, 0.2, 0.43, -0.15, respectively.

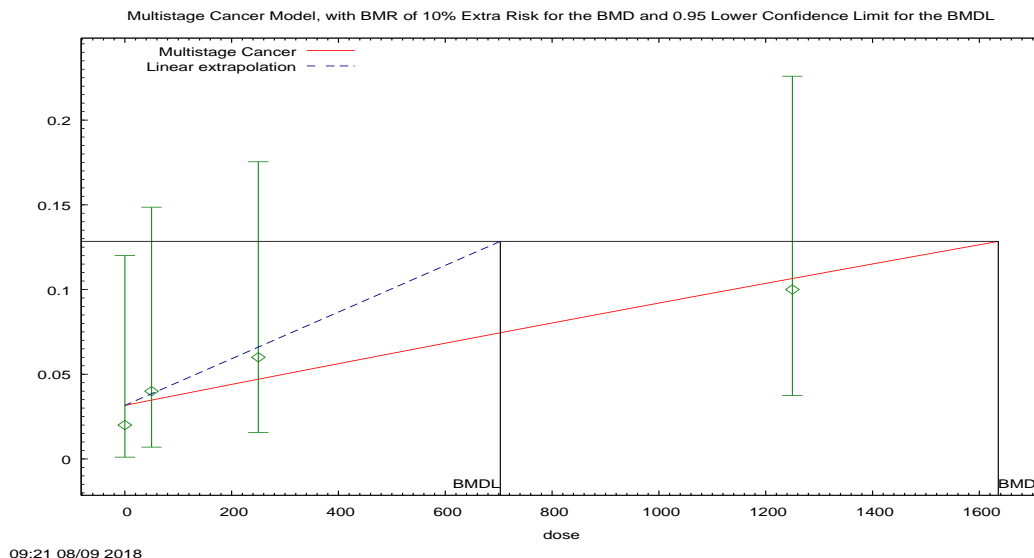


Figure K-10. Plot of incidence rate by dose with fitted curve for Multistage-Cancer 1° model for Mammary gland fibroadenoma (male F344/DuCrj rats) [Kasai et al. \(2009\)](#); dose shown in ppm.

Multistage Model. (Version: 3.4; Date: 05/02/2014)

The form of the probability function is: $P[\text{response}] = \text{background} + (1 - \text{background}) * [1 - \text{EXP}(-\text{beta1} * \text{dose}^1 - \text{beta2} * \text{dose}^2)]$

The parameter betas are restricted to be positive

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 1635.46

BMDL at the 95% confidence level = 703.034

BMDU at the 95% confidence level = 1247200000

Taken together, (703.034, 1247200000) is a 90% two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.000142241

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0.0315836	0.0335609
Beta(1)	0.0000644224	0.0000591694

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-40.9	4			
Fitted model	-41.14	2	0.486662	2	0.78
Reduced model	-42.6	1	3.3895	3	0.34

AIC: = 86.29

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0.0316	1.579	1	50	-0.47
50	0.0347	1.735	2	50	0.2
250	0.0471	2.353	3	50	0.43
1250	0.1065	5.326	5	50	-0.15

Chi² = 0.47 d.f = 2 P-value = 0.7904

K.13 BMD Summary of Subcutis fibroma (male F344/DuCrj rats, high dose dropped) [Kasai et al. \(2009\)](#)

Table K-11. Summary of BMD Modeling Results for Subcutis fibroma (male F344/DuCrj rats, high dose dropped) [Kasai et al. \(2009\)](#)

Model ^a	Goodness of fit		BMD _{10Pct} (ppm)	BMDL _{10Pct} (ppm)	Basis for model selection
	<i>p</i> -value	AIC			
One	0.525	89.209	142	81.9	Model provides adequate fit.

^a Selected model in bold; scaled residuals for selected model for doses 0, 50, and 250 ppm were -0.28, 0.54, -0.2, respectively.

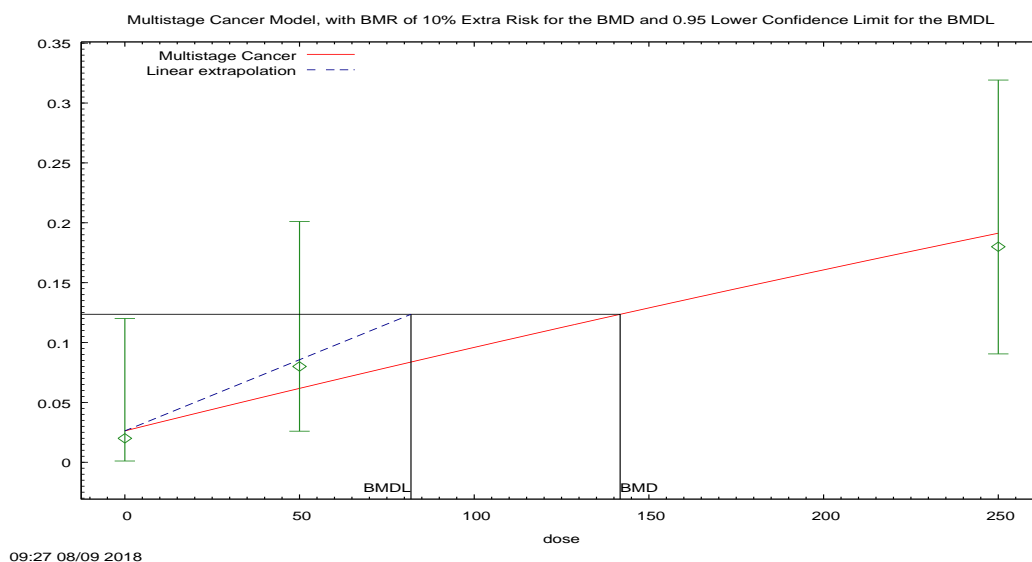


Figure K-11. Plot of incidence rate by dose with fitted curve for Multistage-Cancer 1° model for Subcutis fibroma (male F344/DuCrj rats, high dose dropped) [Kasai et al. \(2009\)](#); dose shown in ppm.

Multistage Model. (Version: 3.4; Date: 05/02/2014)

The form of the probability function is: $P[\text{response}] = \text{background} + (1-\text{background}) * [1 - \text{EXP}(-\text{beta1} * \text{dose} - \text{beta2} * \text{dose}^2)]$

The parameter betas are restricted to be positive

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 141.762

BMDL at the 95% confidence level = 81.9117

BMDU at the 95% confidence level = 364.364

Taken together, (81.9117, 364.364) is a 90% two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.00122083

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0.0262055	0.0327631
Beta(1)	0.00074322	0.000673665

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-42.41	3			
Fitted model	-42.6	2	0.389155	1	0.53
Reduced model	-46.53	1	8.23466	2	0.02

AIC: = 89.2094

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0.0262	1.31	1	50	-0.28
50	0.0617	3.086	4	50	0.54
250	0.1913	9.566	9	50	-0.2

Chi² = 0.41 d.f = 1 P-value = 0.5245

K.14 MS-Combo Systemic (including liver) [Kasai et al. \(2009\)](#)

Systemic tissue tumors, including liver (hepatocellular adenoma or carcinoma, renal cell carcinoma, peritoneal mesothelioma, mammary gland fibroadenoma, subcutis fibroma)

Output information	
Tumor Output Directory	C:\Users\ \Documents\MODELS\14dioxane\inhalation\
Tumor Output File Name	kasai_systemic_wliver.out

Combined BMD and BMDL Calculations	
Combined Log-Likelihood	-236.2277997
Combined Log-likelihood Constant	209.8734852
Benchmark Dose Computation	
Specified effect	0.1
Risk Type	Extra risk
Confidence level	0.95
BMD	41.1654
BMDL	32.7682
Multistage Cancer Slope Factor	0.00305174

**** Start of combined BMD and BMDL Calculations.****

Combined Log-Likelihood -236.22779970471757
 Combined Log-likelihood Constant 209.87348521364675
 Benchmark Dose Computation
 Specified effect = 0.1
 Risk Type = Extra risk
 Confidence level = 0.95
 BMD = 41.1654
 BMDL = 32.7682
 BMDU = 53.265
 Multistage Cancer Slope Factor = 0.00305174

K.15 MS-Combo Systemic (omitting liver) Kasai et al. (2009)

Systemic tissue tumors, excluding liver (renal cell carcinoma, peritoneal mesothelioma, mammary gland fibroadenoma, subcutis fibroma)

Output information	
Tumor Output Directory	C:\Users\ \Documents\MODELS\14dioxane\inhalation\
Tumor Output File Name	Kasai_noliv_systemic.out
Combined BMD and BMDL Calculations	
Combined Log-Likelihood	-174.2976237
Combined Log-likelihood Constant	154.3867855
Benchmark Dose Computation	
Specified effect	0.1
Risk Type	Extra risk
Confidence level	0.95
BMD	49.1727
BMDL	37.8668
Multistage Cancer Slope Factor	0.00264083

**** Start of combined BMD and BMDL Calculations.****

Combined Log-Likelihood -174.29762368979428
 Combined Log-likelihood Constant 154.38678553667452
 Benchmark Dose Computation

Specified effect = 0.1
 Risk Type = Extra risk

Confidence level = 0.95
 BMD = 49.1727
 BMDL = 37.8668
 BMDU = 66.6769

Multistage Cancer Slope Factor = 0.00264083

K.16 MS-Combo portal of entry + systemic (including liver) [Kasai et al. \(2009\)](#)

Portal of entry tumors (nasal cavity squamous cell carcinoma, zymbal gland adenoma) and systemic tissue tumors, including liver (hepatocellular adenoma or carcinoma, renal cell carcinoma, peritoneal mesothelioma, mammary gland fibroadenoma, subcutis fibroma)

Output information	
Tumor Output Directory	C:\Users\ \Documents\MODELS\14dioxane\inhalation\
Tumor Output File Name	Kasai_all.out
Combined BMD and BMDL Calculations	
Combined Log-Likelihood	-274.5746562
Combined Log-likelihood Constant	242.7138909
Benchmark Dose Computation	
Specified effect	0.1
Risk Type	Extra risk
Confidence level	0.95
BMD	38.9076
BMDL	31.2841
Multistage Cancer Slope Factor	0.00319651

**** Start of combined BMD and BMDL Calculations.****

Combined Log-Likelihood -274.57465622245081
 Combined Log-likelihood Constant 242.71389089529029
 Benchmark Dose Computation

Specified effect = 0.1
 Risk Type = Extra risk

Confidence level = 0.95
 BMD = 38.9076
 BMDL = 31.2841
 BMDU = 49.6547

Multistage Cancer Slope Factor = 0.00319651

K.17 MS-Combo portal of entry + systemic (omitting liver) [Kasai et al. \(2009\)](#)

Portal of entry tumors (nasal cavity squamous cell carcinoma, zymbal gland adenoma) and systemic tissue tumors, excluding liver (renal cell carcinoma, peritoneal mesothelioma, mammary gland fibroadenoma, subcutis fibroma)

Output information	
Tumor Output Directory	C:\Users\ \Documents\MODELS\14dioxane\inhalation\
Tumor Output File Name	kasai_noliv.out
Combined BMD and BMDL Calculations	
Combined Log-Likelihood	-212.6444802
Combined Log-likelihood Constant	187.2271912
Benchmark Dose Computation	
Specified effect	0.1
Risk Type	Extra risk
Confidence level	0.95
BMD	45.985
BMDL	35.8978
Multistage Cancer Slope Factor	0.00278569

**** Start of combined BMD and BMDL Calculations.****

Combined Log-Likelihood -212.64448020752749
 Combined Log-likelihood Constant 187.22719121831807

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

 BMD = 45.985

 BMDL = 35.8978

 BMDU = 61.1203

Multistage Cancer Slope Factor = 0.00278569

K.18 BMDS Summary of Hepatocellular mixed foci in male F344/DuCrj rats [Kano et al. \(2009\)](#)

Table K-12. Summary of BMD Modeling Results for Hepatocellular mixed foci in male F344/DuCrj rats [Kano et al. \(2009\)](#)

Model ^a	Goodness of fit		BMD _{10Pct} (mg/kg-d)	BMDL _{10Pct} (mg/kg-d)	Basis for model selection
	p-value	AIC			
Gamma ^b Weibull ^c Multistage 2° Quantal-Linear	0.220	125.50	19.2	11.8	Lowest AIC. BMDL estimates for models not excluded (based on goodness-of-fit p values less than 0.1, or high scaled residuals) are sufficiently close.
Logistic	0.107	126.75	30.9	23.3	
LogLogistic	0.275	125.20	16.7	9.57	
Probit	0.114	126.61	29.4	21.8	
LogProbit (restricted)	0.0555	127.84	33.2	21.8	
LogProbit	N/A ^d	126.06	7.06	error ^e	

Note: There were not enough degrees of freedom to run the Dichotomous Hill model

^a Selected model in bold; scaled residuals for selected model for doses 0, 11, and 55 mg/kg-d were -0.44, 0.91, -0.42, respectively.

^b For the Gamma and Weibull models, the power parameter estimates were 1 (boundary of parameter space). For the Gamma model, the power parameter estimate was 1. The model is equivalent to the Quantal-Linear model.

^c For the Weibull and Gamma models, the power parameter estimates were 1 (boundary of parameter space). For the Weibull model, the power parameter estimate was 1. The models in this row reduced to the Quantal-Linear model.

^d No available degrees of freedom to calculate a goodness of fit value.

^e BMD or BMDL computation failed for this model.

For results based on a power or slope parameter that hits the bound of 1, EPA [2012b](#)) states (footnote 10) "...the nominal coverage of the confidence interval is not exact (asymptotically) and could be much less than intended if the true (unknown) parameter is <1, and this should also be reported"

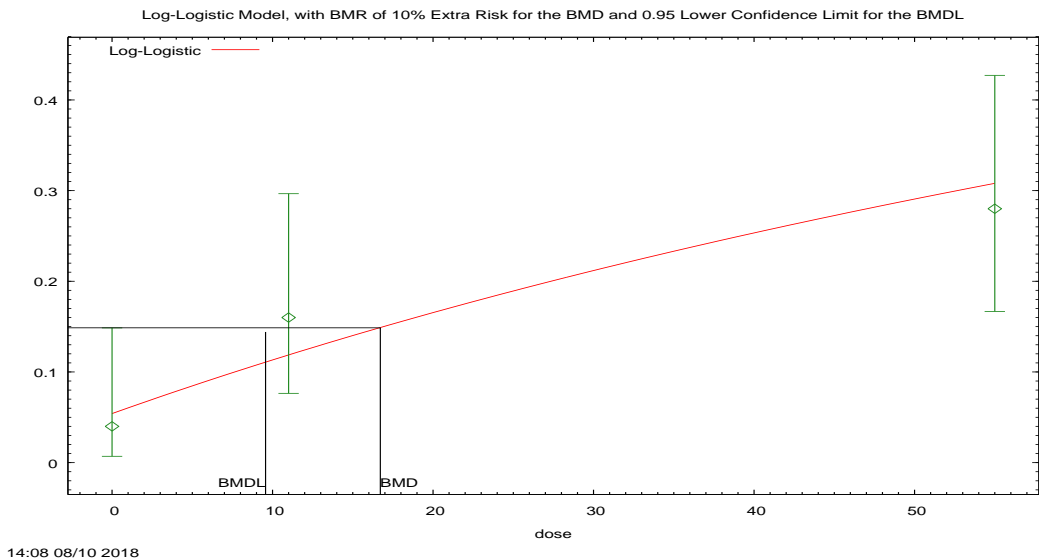


Figure K-12. Plot of incidence rate by dose with fitted curve for LogLogistic model for Hepatocellular mixed foci in male F344/DuCrj rats [Kano et al. \(2009\)](#); dose shown in mg/kg-d.

LogLogistic Model. (Version: 2.15; Date: 3/20/2017)

The form of the probability function is: $P[\text{response}] = \text{background} + (1 - \text{background}) / [1 + \text{EXP}(-\text{intercept} - \text{slope} * \text{Log}(\text{dose}))]$

Slope parameter is restricted as slope ≥ 1

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 16.7141

BMDL at the 95% confidence level = 9.56614

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
background	0.054099	0.04
intercept	-5.0135E+00	-4.7777E+00
slope	1	1

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-60.03	3			
Fitted model	-60.6	2	1.14263	1	0.29
Reduced model	-65.95	1	11.8442	2	0

AIC: = 125.199

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0.0541	2.705	2	50	-0.44
11	0.1186	5.928	8	50	0.91
55	0.3073	15.367	14	50	-0.42

Chi² = 1.19 d.f = 1 P-value = 0.275

K.19 BMDs Summary of Cortical tubule degeneration in female OM rats NCI (1978)

Table K-13. Summary of BMD Modeling Results for Cortical tubule degeneration in female OM rats NCI (1978)

Model ^a	Goodness of fit		BMD _{10Pct} (mg/kg-d)	BMDL _{10Pct} (mg/kg-d)	Basis for model selection
	p-value	AIC			
Gamma	0.945	41.971	525	437	Lowest AIC. BMDL estimates for models not excluded (based on goodness-of-fit p values less than 0.1, or high scaled residuals) are sufficiently close. For the two models that have identical (lowest) AICs, the difference in BMDLs is minor (452 vs 447).
Logistic	1.000	43.750	617	472	
LogLogistic	1.000	41.750	592	447	
Probit	1.000	43.750	596	456	
LogProbit	1.000	43.750	584	436	
Weibull	1.000	41.750	596	452	
Multistage 2°	0.144	48.197	399	298	
Quantal-Linear	0.0300	52.304	306	189	

Note: There were not enough degrees of freedom to run the Dichotomous Hill model

^a Selected model in bold; scaled residuals for selected model for doses 0, 350, and 640 mg/kg-d were 0, -0.02, 0, respectively.

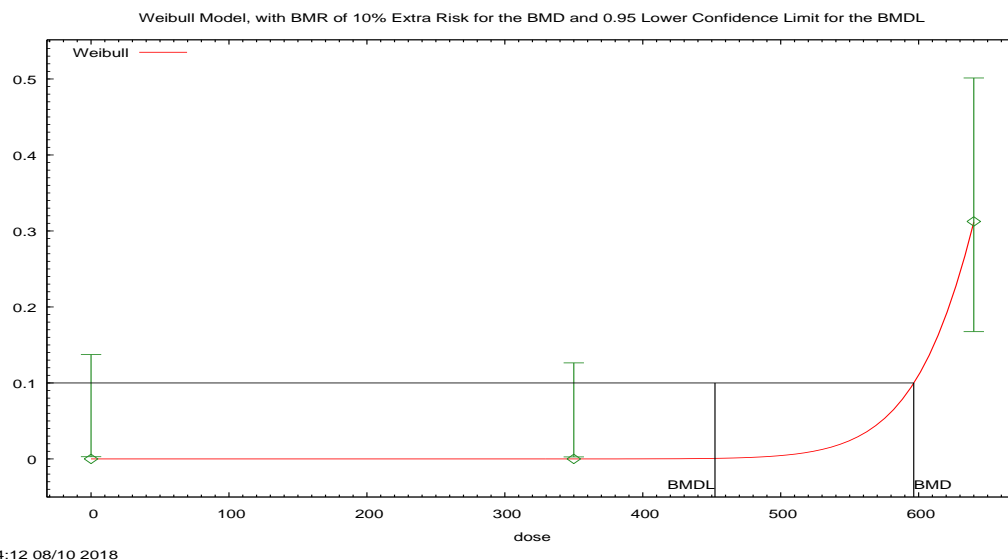


Figure K-13. Plot of incidence rate by dose with fitted curve for Weibull model for Cortical tubule degeneration in female OM rats NCI (1978); dose shown in mg/kg-d.

Weibull Model using Weibull Model (Version: 2.17; Date: 6/23/2017)

The form of the probability function is: $P[\text{response}] = \text{background} + (1 - \text{background}) * [1 - \text{EXP}(-\text{slope} * \text{dose}^{\text{power}})]$

Power parameter is restricted as $\text{power} \geq 1$

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 596.445

BMDL at the 95% confidence level = 452.359

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0	0.030303
Slope	1.1545E-51	7.5210E-10
Power	18	3.09322

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-19.87	3			
Fitted model	-19.88	1	0.000487728	2	1
Reduced model	-32.19	1	24.6247	2	<.0001

AIC: = 41.75

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	31	0
350	0	0	0	34	-0.02
640	0.3125	9.999	10	32	0

$\text{Chi}^2 = 0$ d.f = 2 P-value = 0.9999

K.20 BMDs Summary of Nasal squamous cell carcinoma in Male F344/DuCrj rats [Kano et al. \(2009\)](#)

Table K-14. Summary of BMD Modeling Results for Nasal squamous cell carcinoma in Male F344/DuCrj rats [Kano et al. \(2009\)](#)

Model ^a	Goodness of fit		BMD _{10Pct} (mg/kg-d)	BMDL _{10Pct} (mg/kg-d)	Basis for model selection
	<i>p</i> -value	AIC			
One	0.862	26.028	582	256	Lowest BMDL. Some parameter values were zero for both models.
Two	0.988	24.951	365	242	

^a Selected model in bold; scaled residuals for selected model for doses 0, 11, 55, and 274 mg/kg-d were 0, -0.07, -0.35, 0.07, respectively.

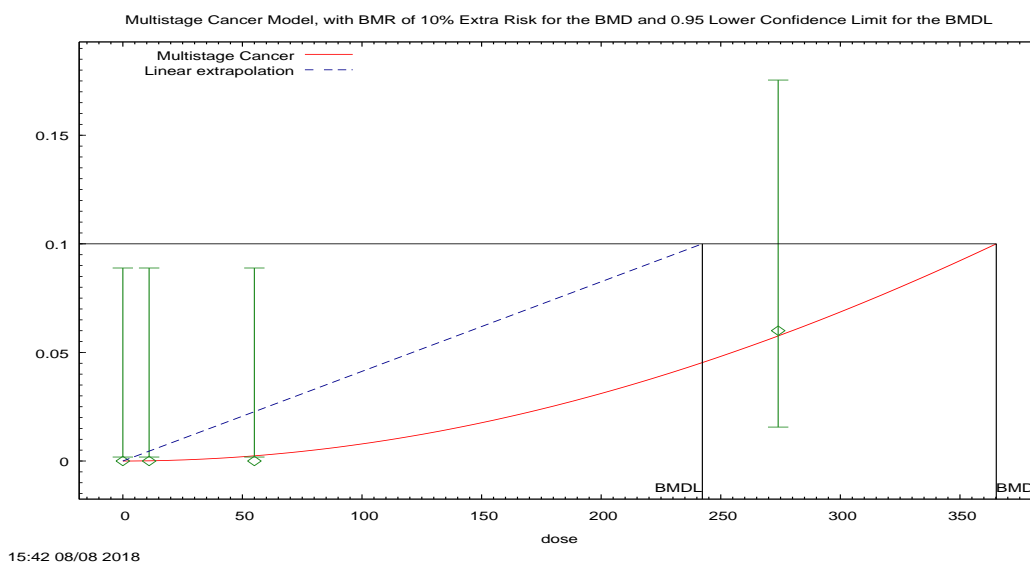


Figure K-14. Plot of incidence rate by dose with fitted curve for Multistage-Cancer 2^o model for Nasal squamous cell carcinoma in Male F344/DuCrj rats [Kano et al. \(2009\)](#); dose shown in mg/kg-d.

Multistage Model. (Version: 3.4; Date: 05/02/2014)

The form of the probability function is: $P[\text{response}] = \text{background} + (1-\text{background}) * [1 - \text{EXP}(-\text{beta1} * \text{dose}^1 - \text{beta2} * \text{dose}^2)]$

The parameter betas are restricted to be positive

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 365.191

BMDL at the 95% confidence level = 242.296

BMDU at the 95% confidence level = 1348.53

Taken together, (242.296, 1348.53) is a 90% two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.000412718

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0	0
Beta(1)	0	0
Beta(2)	7.9002E-07	8.3465E-07

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-11.35	4			
Fitted model	-11.48	1	0.253836	3	0.97
Reduced model	-15.58	1	8.45625	3	0.04

AIC: = 24.9506

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	50	0
11	0.0001	0.005	0	50	-0.07
55	0.0024	0.119	0	50	-0.35
274	0.0576	2.879	3	50	0.07

Chi² = 0.13 d.f = 3 P-value = 0.988

K.21 BMDs Summary of Peritoneum mesothelioma in Male F344/DuCrj rats [Kano et al. \(2009\)](#)

Table K-15. Summary of BMD Modeling Results for Peritoneum mesothelioma in Male F344/DuCrj rats [Kano et al. \(2009\)](#)

Model ^a	Goodness of fit		BMD _{10Pct} (mg/kg-d)	BMDL _{10Pct} (mg/kg-d)	Basis for model selection
	p-value	AIC			
One	0.362	140.83	41.0	30.5	Lowest AIC. All parameter estimates positive in both models.
Two	0.814	140.75	77.7	35.4	

^a Selected model in bold; scaled residuals for selected model for doses 0, 11, 55, and 274 mg/kg-d were 0.13, -0.19, 0.07, -0.01, respectively.

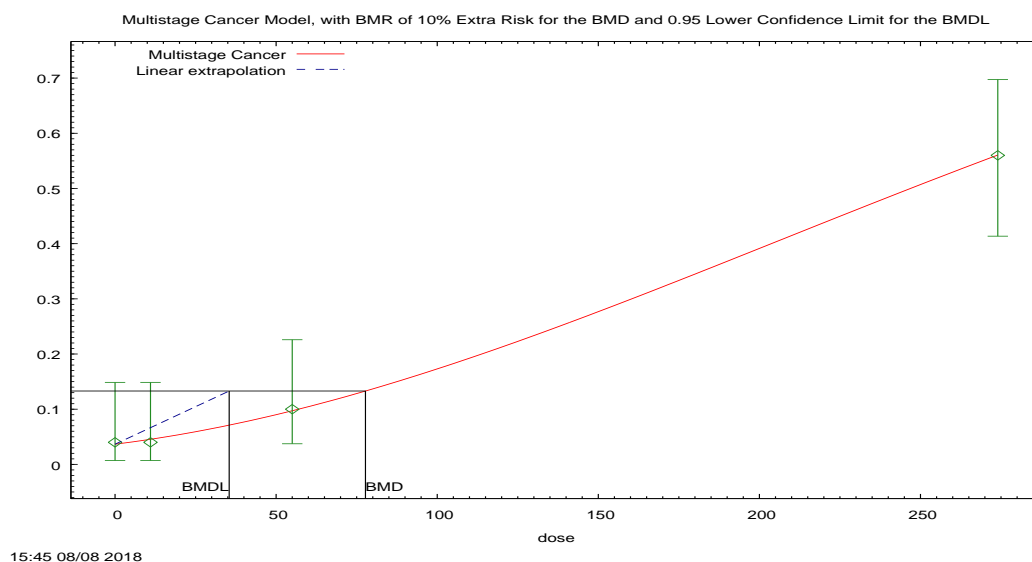


Figure K-15. Plot of incidence rate by dose with fitted curve for Multistage-Cancer 2° model for Peritoneum mesothelioma in Male F344/DuCrj rats [Kano et al. \(2009\)](#); dose shown in mg/kg-d.

Multistage Model. (Version: 3.4; Date: 05/02/2014)

The form of the probability function is: $P[\text{response}] = \text{background} + (1 - \text{background}) * [1 - \text{EXP}(-\text{beta1} * \text{dose}^{1 - \text{beta2} * \text{dose}^2})]$

The parameter betas are restricted to be positive

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 77.7277

BMDL at the 95% confidence level = 35.4296

BMDU at the 95% confidence level = 118.349

Taken together, (35.4296, 118.349) is a 90% two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.0028225

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0.0366063	0.0358706
Beta(1)	0.000757836	0.000816174
Beta(2)	7.6893E-06	7.4706E-06

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-67.35	4			
Fitted model	-67.37	3	0.056567	1	0.81
Reduced model	-95.78	1	56.8663	3	<.0001

AIC: = 140.747

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0.0366	1.83	2	50	0.13
11	0.0455	2.275	2	50	-0.19
55	0.0972	4.859	5	50	0.07
274	0.5605	28.027	28	50	-0.01

Chi² = 0.06 d.f = 1 P-value = 0.8135

K.22 BMDs Summary of Hepatocellular adenoma or carcinoma in Male F344/DuCrj rats [Kano et al. \(2009\)](#)

Table K-16. Summary of BMD Modeling Results for Hepatocellular adenoma or carcinoma in Male F344/DuCrj rats [Kano et al. \(2009\)](#)

Model ^a	Goodness of fit		BMD _{10Pct} (mg/kg-d)	BMDL _{10Pct} (mg/kg-d)	Basis for model selection
	p-value	AIC			
One	0.0978	152.84	23.8	18.3	Lowest AIC. All parameter estimates positive in both models.
Two	0.816	149.81	61.7	28.3	

^a Selected model in bold; scaled residuals for selected model for doses 0, 11, 55, and 274 mg/kg-d were -0.13, 0.18, -0.06, 0.01, respectively.

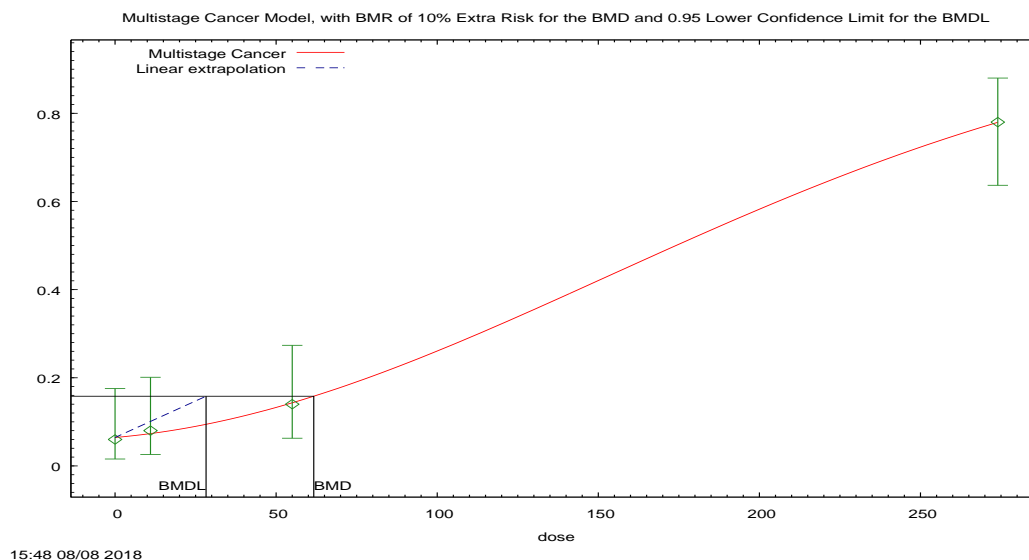


Figure K-16. Plot of incidence rate by dose with fitted curve for Multistage-Cancer 2^o model for Hepatocellular adenoma or carcinoma in Male F344/DuCrj rats [Kano et al. \(2009\)](#); dose shown in mg/kg-d.

Multistage Model. (Version: 3.4; Date: 05/02/2014)

The form of the probability function is: $P[\text{response}] = \text{background} + (1-\text{background}) * [1 - \text{EXP}(-\text{beta1} * \text{dose}^1 - \text{beta2} * \text{dose}^2)]$

The parameter betas are restricted to be positive

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 61.6807

BMDL at the 95% confidence level = 28.2577

BMDU at the 95% confidence level = 85.9896

Taken together, (28.2577, 85.9896) is a 90% two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.00353886

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0.0645254	0.0651805
Beta(1)	0.000672524	0.000611007
Beta(2)	0.0000167903	0.0000170394

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-71.88	4			
Fitted model	-71.91	3	0.0535945	1	0.82
Reduced model	-115.64	1	87.528	3	<.0001

AIC: = 149.814

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0.0645	3.226	3	50	-0.13
11	0.0733	3.665	4	50	0.18
55	0.1431	7.157	7	50	-0.06
274	0.7794	38.971	39	50	0.01

Chi² = 0.05 d.f = 1 P-value = 0.8161

K.23 BMDs Summary of Subcutis fibroma in Male F344/DuCrj rats Kano et al. (2009)

Table K-17. Summary of BMD Modeling Results for Subcutis fibroma in Male F344/DuCrj rats
Kano et al. (2009)

Model ^a	Goodness of fit		BMD _{10Pct} (mg/kg-d)	BMDL _{10Pct} (mg/kg-d)	Basis for model selection
	p-value	AIC			
One	0.662	147.64	154	85.0	Lowest AIC. All parameter estimates positive for both models.
Two	0.440	149.44	198	86.6	

^a Selected model in bold; scaled residuals for selected model for doses 0, 11, 55, and 274 mg/kg-d were 0.66, -0.57, -0.21, 0.11, respectively.

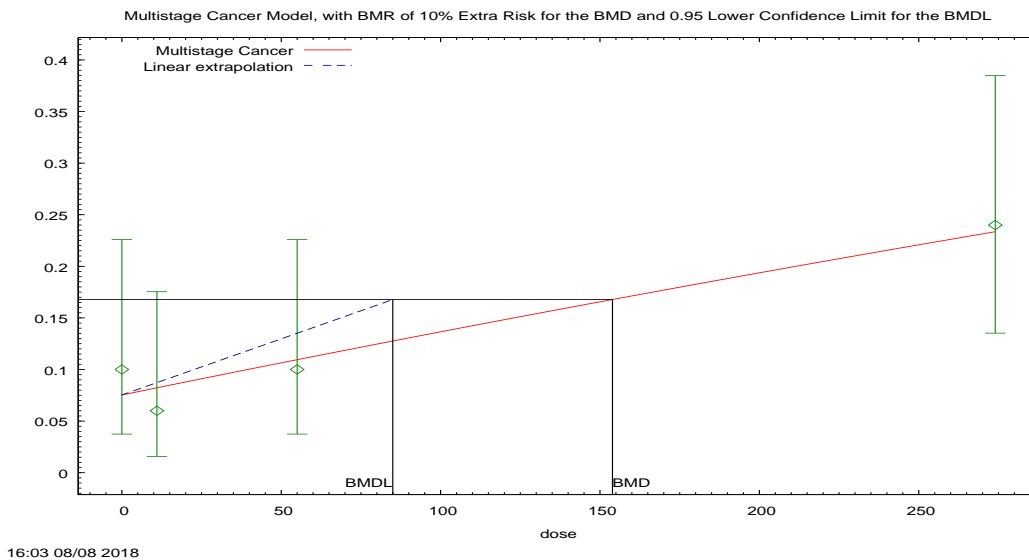


Figure K-17. Plot of incidence rate by dose with fitted curve for Multistage-Cancer 1° model for Subcutis fibroma in Male F344/DuCrj rats Kano et al. (2009); dose shown in mg/kg-d.

Multistage Model. (Version: 3.4; Date: 05/02/2014)

The form of the probability function is: $P[\text{response}] = \text{background} + (1-\text{background}) * [1 - \text{EXP}(-\text{beta1} * \text{dose}^1 - \text{beta2} * \text{dose}^2)]$

The parameter betas are restricted to be positive

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 153.921

BMDL at the 95% confidence level = 84.9898

BMDU at the 95% confidence level = 443.236

Taken together, (84.9898, 443.236) is a 90% two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.00117661

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0.0752804	0.0733151
Beta(1)	0.00068451	0.000713137

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-71.41	4			
Fitted model	-71.82	2	0.818155	2	0.66
Reduced model	-75.35	1	7.88672	3	0.05

AIC: = 147.639

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0.0753	3.764	5	50	0.66
11	0.0822	4.111	3	50	-0.57
55	0.1094	5.472	5	50	-0.21
274	0.2334	11.671	12	50	0.11

Chi² = 0.82 d.f = 2 P-value = 0.6624

K.24 BMDS Summary of Nasal squamous cell carcinoma in female F344/DuCrj rats [Kano et al. \(2009\)](#)

Table K-18. Summary of BMD Modeling Results for Nasal squamous cell carcinoma in female F344/DuCrj rats [Kano et al. \(2009\)](#)

Model ^a	Goodness of fit		BMD _{10Pct} (mg/kg-d)	BMDL _{10Pct} (mg/kg-d)	Basis for model selection
	p-value	AIC			
One	0.618	45.660	376	214	Lowest BMDL. Some parameter values were zero for both models.
Two	0.961	43.075	366	275	

^a Selected model in bold; scaled residuals for selected model for doses 0, 18, 83, and 429 mg/kg-d were 0, -0.5, -1.08, 0.6, respectively.

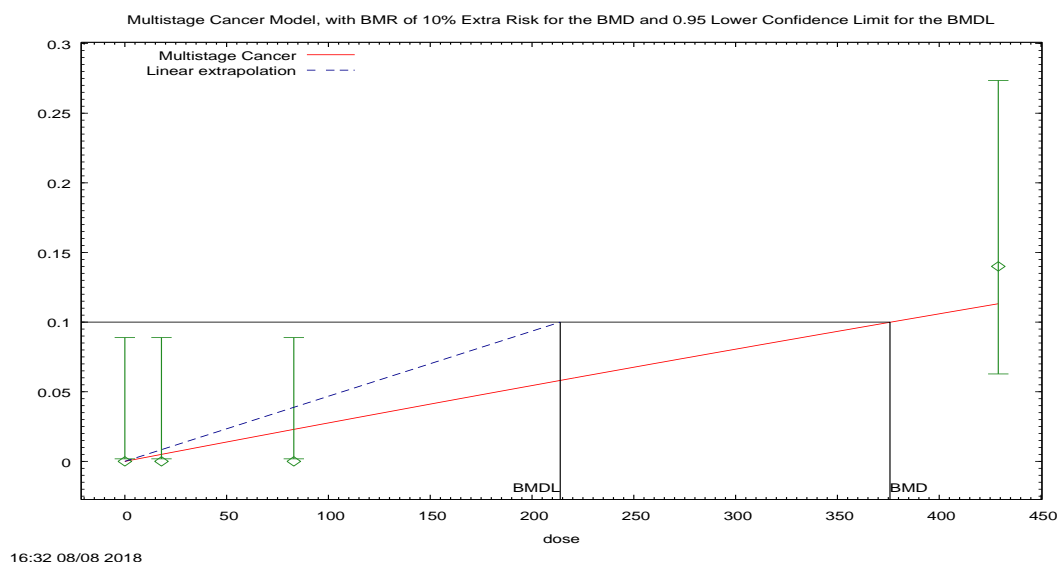


Figure K-18. Plot of incidence rate by dose with fitted curve for Multistage-Cancer 1° model for Nasal squamous cell carcinoma in female F344/DuCrj rats [Kano et al. \(2009\)](#); dose shown in mg/kg-d.

Multistage Model. (Version: 3.4; Date: 05/02/2014)

The form of the probability function is: $P[\text{response}] = \text{background} + (1-\text{background}) * [1 - \text{EXP}(-\text{beta1} * \text{dose} - \text{beta2} * \text{dose}^2)]$

The parameter betas are restricted to be positive

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 375.811

BMDL at the 95% confidence level = 213.836

BMDU at the 95% confidence level = 752.01

Taken together, (213.836, 752.01) is a 90% two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.000467648

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0	0
Beta(1)	0.000280355	0.00036949

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-20.25	4			
Fitted model	-21.83	1	3.16408	3	0.37
Reduced model	-30.34	1	20.1894	3	0

AIC: = 45.6604

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	50	0
18	0.005	0.252	0	50	-0.5
83	0.023	1.15	0	50	-1.08
429	0.1133	5.666	7	50	0.6

Chi² = 1.78 d.f = 3 P-value = 0.6184

K.25 BMDs Summary of Mammary adenoma in female F344/DuCrj rats Kano et al. (2009)

Table K-19. Summary of BMD Modeling Results for Mammary adenoma in female F344/DuCrj rats Kano et al. (2009)

Model ^a	Goodness of fit		BMD _{10Pct} (mg/kg-d)	BMDL _{10Pct} (mg/kg-d)	Basis for model selection
	p-value	AIC			
One Two	0.856	194.22	177	99.1	All (equivalent) models have adequate fit.

^a Selected model in bold; scaled residuals for selected model for doses 0, 18, 83, and 429 mg/kg-d were -0.27, -0.05, 0.46, -0.13, respectively.

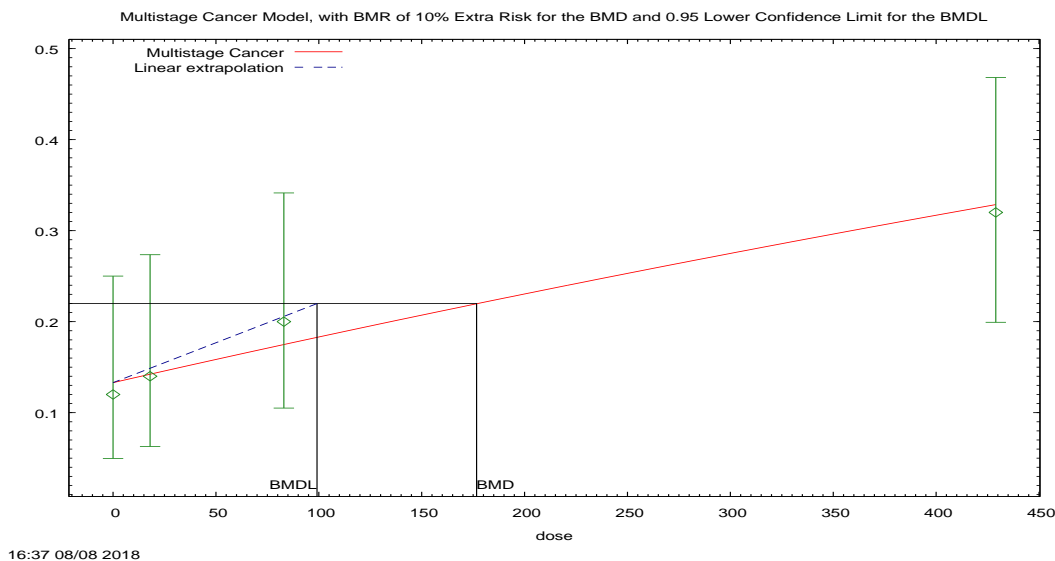


Figure K-19. Plot of incidence rate by dose with fitted curve for Multistage-Cancer 1^o model for Mammary adenoma in female F344/DuCrj rats Kano et al. (2009); dose shown in mg/kg-d.

Multistage Model. (Version: 3.4; Date: 05/02/2014)

The form of the probability function is: $P[\text{response}] = \text{background} + (1-\text{background}) * [1 - \text{EXP}(-\text{beta1} * \text{dose} - \text{beta2} * \text{dose}^2)]$

The parameter betas are restricted to be positive

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 176.663

BMDL at the 95% confidence level = 99.1337

BMDU at the 95% confidence level = 501.523

Taken together, (99.1337, 501.523) is a 90% two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.00100874

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0.133161	0.136033
Beta(1)	0.000596394	0.000570906

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-94.96	4			
Fitted model	-95.11	2	0.305898	2	0.86
Reduced model	-98.68	1	7.4409	3	0.06

AIC: = 194.222

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0.1332	6.658	6	50	-0.27
18	0.1424	7.121	7	50	-0.05
83	0.175	8.751	10	50	0.46
429	0.3288	16.442	16	50	-0.13

Chi² = 0.31 d.f = 2 P-value = 0.8559

K.26 BMDS Summary of Hepatocellular adenomas or carcinomas female F344/DuCrj rats [Kano et al. \(2009\)](#)

Table K-20. Summary of BMD Modeling Results for Hepatocellular adenomas or carcinomas female F344/DuCrj rats [Kano et al. \(2009\)](#)

Model ^a	Goodness of fit		BMD _{10Pct} (mg/kg-d)	BMDL _{10Pct} (mg/kg-d)	Basis for model selection
	p-value	AIC			
One	1.00E-04	114.09	25.6	19.9	1 st -degree multistage has inadequate p-value. 2 nd -degree multistage exhibits adequate fit.
Two	0.452	91.590	79.8	58.1	

^a Selected model in bold; scaled residuals for selected model for doses 0, 18, 83, and 429 mg/kg-d were 0.9, -0.76, -0.41, 0.2, respectively.

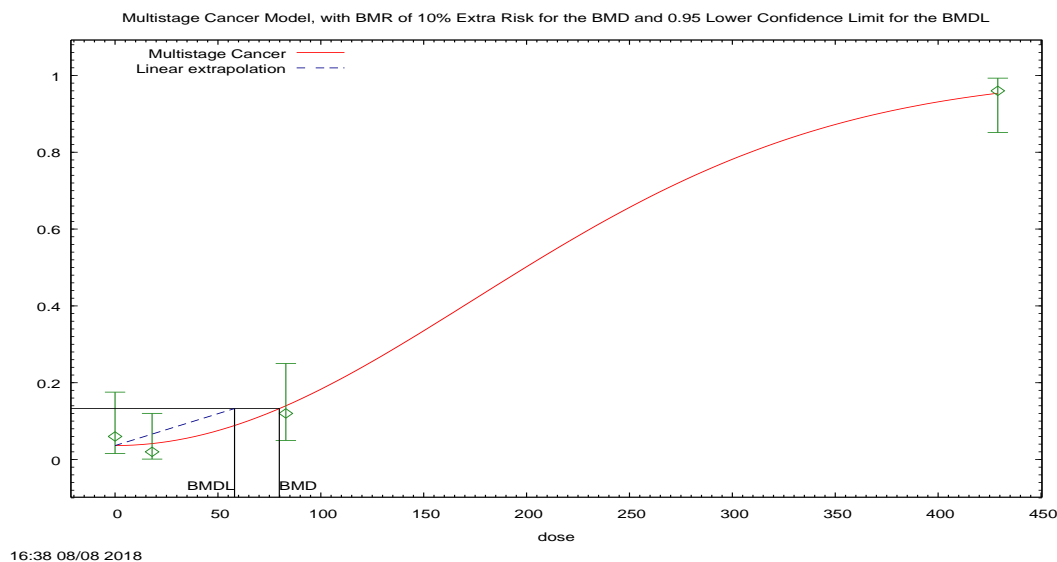


Figure K-20. Plot of incidence rate by dose with fitted curve for Multistage-Cancer 2° model for Hepatocellular adenomas or carcinomas female F344/DuCrj rats [Kano et al. \(2009\)](#); dose shown in mg/kg-d.

Multistage Model. (Version: 3.4; Date: 05/02/2014)

The form of the probability function is: $P[\text{response}] = \text{background} + (1-\text{background}) * [1 - \text{EXP}(-\text{beta1} * \text{dose}^1 - \text{beta2} * \text{dose}^2)]$

The parameter betas are restricted to be positive

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 79.8299

BMDL at the 95% confidence level = 58.085

BMDU at the 95% confidence level = 94.0205

Taken together, (58.085, 94.0205) is a 90% two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.00172161

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0.0362773	0.0281572
Beta(1)	0	0
Beta(2)	0.0000165328	0.0000173306

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-42.99	4			
Fitted model	-43.79	2	1.60218	2	0.45
Reduced model	-120.43	1	154.873	3	<.0001

AIC: = 91.5898

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0.0363	1.814	3	50	0.9
18	0.0414	2.071	1	50	-0.76
83	0.14	7.001	6	50	-0.41
429	0.954	47.701	48	50	0.2

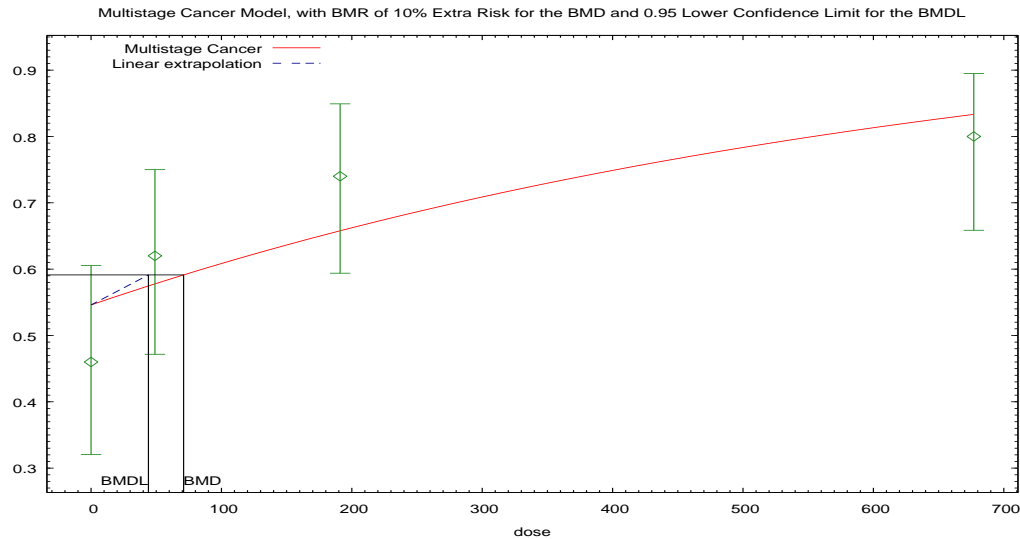
Chi² = 1.59 d.f = 2 P-value = 0.4516

K.27 BMDS Summary of Hepatocellular adenomas or carcinomas in male CrjBDF1 mice [Kano et al. \(2009\)](#)

Table K-21. Summary of BMD Modeling Results for Hepatocellular adenomas or carcinomas in male CrjBDF1 mice [Kano et al. \(2009\)](#)

Model ^a	Goodness of fit		BMD _{10Pct} (mg/kg-d)	BMDL _{10Pct} (mg/kg-d)	Basis for model selection
	p-value	AIC			
One Two	0.153	250.55	71.0	44.0	All (equivalent) models have adequate fit.

^a Selected model in bold; scaled residuals for selected model for doses 0, 49, 191, and 677 mg/kg-d were -1.22, 0.6, 1.22, -0.64, respectively.



16:45 08/08 2018

Figure K-21. Plot of incidence rate by dose with fitted curve for Multistage-Cancer 1^o model for Hepatocellular adenomas or carcinomas in male CrjBDF1 mice [Kano et al. \(2009\)](#); dose shown in mg/kg-d.

Multistage Model. (Version: 3.4; Date: 05/02/2014)

The form of the probability function is: $P[\text{response}] = \text{background} + (1-\text{background}) * [1 - \text{EXP}(-\text{beta1} * \text{dose} - \text{beta2} * \text{dose}^2)]$

The parameter betas are restricted to be positive

Benchmark Dose Computation.

BMR = 10% Extra risk

BMD = 70.9911

BMDL at the 95% confidence level = 44.0047

BMDU at the 95% confidence level = 150.117

Taken together, (44.0047, 150.117) is a 90% two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.00227248

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0.545889	0.573756
Beta(1)	0.00148414	0.00123152

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-121.37	4			
Fitted model	-123.28	2	3.80413	2	0.15
Reduced model	-128.86	1	14.9718	3	0

AIC: = 250.551

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0.5459	27.294	23	50	-1.22
49	0.5777	28.887	31	50	0.6
191	0.658	32.899	37	50	1.22
677	0.8337	41.687	40	50	-0.64

Chi² = 3.76 d.f = 2 P-value = 0.1527

K.28 BMDS Summary of Hepatocellular adenomas or carcinomas in female CrjBDF1 mice [Kano et al. \(2009\)](#)

The IRIS 1,4-Dioxane assessment modeled liver tumors (adenomas or carcinomas) in female mice from Kano et al. [2009](#)), and this site was the most sensitive tumor endpoint for the oral CSF. An adequate fit could not be obtained with any multistage (MS) models at the time due to the steep slope and apparent plateau of the response to a probability less than 100%, so non-MS models were applied. For the current assessment, EPA performed time-to-tumor analysis that provides a better model fit.

EPA obtained individual animal data, with liver tumor incidence, time of death and pathologically diagnosed cause of death, from the study institute JBRC (emails dated October 30 and November 1, 2019, from Dr. Kano, JBRC to Paul White, CPHEA, ORD, U.S. EPA). EPA used two methods to model the time-to-tumor effect in this data set. They were the MSW model (Multistage Weibull Model) and Poly3 method (*i.e.*, BMDS modeling with Poly3-adjusted data). The results were summarized in Table 1.

Extra risk of 0.5 (ER50%) was selected as the primary Benchmark Response (BMR) to calculate CSF to avoid excess extrapolation; this is also consistent with the IRIS assessment. Sensitivity analysis was also done by calculating CSF at other BMRs (*i.e.*, ER10%, 20%, 30% and 40%). With the MSW model, the difference between CSFs was within 32%; with Poly3 method, the difference was within 80%.

EPA selected the MSW model analysis for this dataset, because the multistage model is the preferred model for cancer data in the EPA BMD Technical Guidance [U.S. EPA \(2012b\)](#), and it provided adequate fit with a good sensitivity analysis result. The recommended approach using the ER50% and a Multistage Weibull 1-stage model yielded a BMD of 35 and a BMDL of 27 mg/kg-d estimated daily administered dose. Using the BMDL estimate, the oral cancer slope factor for humans was 0.12 per mg/kg-d. For purposes of comparison an alternate risk estimate developed by applying the Poly-3 adjusted data, with the selected log-logistic (restricted) model from the BMDS model suite yielded BMD and BMDL values of 22 and 13 mg/kg-d, with a human oral cancer slope factor of 0.26 per mg/kg-d.

Comparison of modeling results with different approaches.

Method	BMR	BMD	BMDL	BMDU	BMDL HED ^a	Oral CSF
MSW (Stage1)	ER10%	5.39	4.10	7.14	0.62	0.162
	ER20%	11.42	8.69	15.12	1.31	0.153
	ER30%	18.25	13.89	24.17	2.09	0.143
	ER40%	26.13	19.90	34.62	2.99	0.134
	ER50%	35.46	27.00	46.98	4.06	0.123
BMDS Modeling with Poly3 Adjusted Data (Log-Logistic Model)	ER10%	2.52	1.43	11.25	0.22	0.464
	ER20%	5.65	3.22	18.72	0.49	0.412
	ER30%	9.64	5.53	26.43	0.83	0.361
	ER40%	14.96	8.60	35.31	1.29	0.309
	ER50%	22.38	12.90	46.52	1.94	0.258
IRIS Assessment (Log-Logistic Model)	ER10%	5.54	3.66	N/A	0.55	0.182
	ER50%	49.9	32.9	N/A	4.95	0.101

^a Human equivalent doses (HEDs) were calculated from the administered animal doses using a body weight scaling factor (BW^{0.75}) [U.S. EPA \(2011b\)](#). This was accomplished using the following equation: HED=animal dose (mg/kg) * [animal BW (kg)/human BW (kg)]^{0.25}. For all calculations, a human BW of 70 kg and a female mice BW of 35.9 kg were used [Kano et al. \(2009\)](#).

K.28.1 Time-to-Tumor Modeling with Multistage Weibull Model

The MSW time-to-tumor model is a multistage in dose and Weibull in time, which is used to model both the dose and the time of appearance of a detectable tumor. With this model, the probability of observing a tumor prior to some specific observation time, t , upon exposure to a carcinogen at dose level, d , is given by the function:

$$G(t, d) = G(t, d, c, \beta_0, \beta_1, \dots, \beta_k) = 1 - \exp\left\{-t^c \sum_{i=0}^k \beta_i d^i\right\}$$

The MSW time-to-tumor model was conducted using the MultiStage-Weibull software, which was based on Weibull models drawn from Krewski et al. (1983) and downloaded from the EPA's BMDS website. The model with the lowest AIC was selected from models fit up to stages $n - 1$, where n was the number of dose groups. Parameters were estimated using the method of maximum likelihood.

Before fitting the MSW time-to-tumor models, each animal was classified into one of four response categories: "I" (hepatocellular carcinoma and/or adenoma were detected when the mouse was removed from the study due to unscheduled death - where the hepatocellular tumor was judged *not* to be the cause of death - or final sacrifice), "U" (the presence or absence of hepatocellular carcinoma and/or adenoma could not be determined when the mouse was removed from the study due to unscheduled death or final sacrifice or other reasons), "C" (neither hepatocellular carcinoma nor adenoma was detected when the mouse was removed from the study due to unscheduled death or final sacrifice), and "F" (hepatocellular carcinoma and/or adenoma was judged to be the cause of death). See Table 2 for details.

Using SAS software, the individual animal tumor data (*i.e.*, hepatocellular carcinoma and/or adenoma in female mice) was prepared for the MSW modeling by merging and cleaning results from 0064deadr.xlsx (11012019 email from Dr. Kano) and 0064Mouse_HepaticTumor.xlsx (10302019 email from Dr. Kano). The merged data set was also manually verified. Stage 1, 2 and 3 MSW time-to-tumor models were fit to the data, but only Stage1 and 3 converged to yield estimated parameters. Stage 1 was selected as the best fitting model because it had a lower AIC value (See Table 3).

Extra risk 50% (ER50%) was used as the primary BMR with the MSW time-to-tumor modeling (Output1). Tumor incidental risks of ER 10%, 20%, 30% and 40% were also extrapolated and compared to ER50% as a sensitivity analysis. (See Table 1)

EPA's `gofplot_msw()`, also available for download from the EPA's BMDS website, was used to generate plots to visually assess goodness-of-fit for the MSW time-to-tumor models. Probability vs. Time (PR) Plot is the default plot for `gofplot_msw()` program, where the fitted distribution function was plotted against time, separately for each dose level. Since both fatal and incidental contexts occurred in the data, two smooth curves and two series of points were plotted. The solid curve and filled points were for the fatal tumor response, while a dashed line and unfilled points were for the incidental tumor response (Figure 1). In keeping with usual EPA practice, the risk estimates in the memo apply to all (not just diagnosed as fatal) hepatocellular tumors, hence the "incidental" which reflects both fatal and non-fatal tumors is the measure of direct importance here. The BMD₅₀ and BMDL₅₀ for total hepatocellular tumors were located between the control dose and the 1st dose (66 mg/kg/day) – the BMD and BMDL being, respectively, a factor of 1.9 and 2.4 below the 1st test dose. This was judged a reasonable degree of extrapolation. A Dose-Response (DR) Plot was also generated (Figure 2) to show the incidental risk probability in relation to dose for a fixed time (*i.e.*, 105 weeks in this case), with the BMD and BMDL values displayed.

Table 2: Individual Animal Data with Hepatocellular Carcinoma and/or Adenoma in Female Mice, [Kano et al. \(2009\)](#).

Animal ID	Administered Dose (mg/kg-d)	Tumor Context ^a	Week at Death
2001	0	C	91
2002	0	C	105
2003	0	C	105
2004	0	C	55
2005	0	C	99
2006	0	I	105
2007	0	C	89
2008	0	C	105
2009	0	C	105
2010	0	C	93
2011	0	C	105
2012	0	C	105
2013	0	C	102
2014	0	C	105
2015	0	C	105
2016	0	C	105
2017	0	C	105
2018	0	C	105
2019	0	C	105
2020	0	C	105
2021	0	C	105
2022	0	C	105
2023	0	C	99
2024	0	I	95
2025	0	C	105

2026	0	C	90
2027	0	C	73
2028	0	C	70
2029	0	C	105
2030	0	C	105
2031	0	C	100
2032	0	C	105
2033	0	C	98
2034	0	C	87
2035	0	C	86
2036	0	C	78
2037	0	C	105
2038	0	I	105
2039	0	C	82
2040	0	I	105
2041	0	C	91
2042	0	C	84
2043	0	C	105
2044	0	C	105
2045	0	C	75
2046	0	C	105
2047	0	C	98
2048	0	C	105
2049	0	C	105
2050	0	I	105
2101	66	C	75
2102	66	I	105
2103	66	I	98
2104	66	C	105
2105	66	I	105
2106	66	I	105
2107	66	I	84
2108	66	I	105
2109	66	I	96
2110	66	I	105
2111	66	I	105
2112	66	C	85
2113	66	C	78
2114	66	I	105
2115	66	C	100
2116	66	I	105
2117	66	C	96
2118	66	I	105
2119	66	I	103
2120	66	I	105
2121	66	I	105
2122	66	I	96
2123	66	C	75
2124	66	I	105
2125	66	I	105
2126	66	I	105
2127	66	C	77
2128	66	I	105
2129	66	I	105
2130	66	I	105
2131	66	I	105
2132	66	C	85
2133	66	C	97
2134	66	C	72
2135	66	I	105
2136	66	I	105
2137	66	I	105
2138	66	I	105
2139	66	C	105
2140	66	I	105
2141	66	I	105
2142	66	C	80
2143	66	I	105
2144	66	I	98

2145	66	F	79
2146	66	I	91
2147	66	C	102
2148	66	C	105
2149	66	I	97
2150	66	I	105
2201	278	I	103
2202	278	C	56
2203	278	I	105
2204	278	I	96
2205	278	I	105
2206	278	I	105
2207	278	C	50
2208	278	I	92
2209	278	F	94
2210	278	I	71
2211	278	I	75
2212	278	I	97
2213	278	I	105
2214	278	I	105
2215	278	F	95
2216	278	I	102
2217	278	F	96
2218	278	I	105
2219	278	I	105
2220	278	F	88
2221	278	I	105
2222	278	F	93
2223	278	I	100
2224	278	I	103
2225	278	I	102
2226	278	I	105
2227	278	I	95
2228	278	C	90
2229	278	C	71
2230	278	I	99
2231	278	I	73
2232	278	C	47
2233	278	F	96
2234	278	I	93
2235	278	F	92
2236	278	F	97
2237	278	I	105
2238	278	I	105
2239	278	I	83
2240	278	I	104
2241	278	C	70
2242	278	I	105
2243	278	C	63
2244	278	F	92
2245	278	C	105
2246	278	I	105
2247	278	C	85
2248	278	I	105
2249	278	I	105
2250	278	I	105
2301	964	F	99
2302	964	F	84
2303	964	I	56
2304	964	I	80
2305	964	F	80
2306	964	I	100
2307	964	F	90
2308	964	I	85
2309	964	F	86
2310	964	F	80
2311	964	I	61
2312	964	F	98
2313	964	F	91

2314	964	F	78
2315	964	F	97
2316	964	F	91
2317	964	F	87
2318	964	F	80
2319	964	I	81
2320	964	I	61
2321	964	F	95
2322	964	I	58
2323	964	F	101
2324	964	F	95
2325	964	F	73
2326	964	I	105
2327	964	F	74
2328	964	C	47
2329	964	F	86
2330	964	C	67
2331	964	F	96
2332	964	F	84
2333	964	F	95
2334	964	F	75
2335	964	F	95
2336	964	I	70
2337	964	I	97
2338	964	I	90
2339	964	F	90
2340	964	F	83
2341	964	C	69
2342	964	I	105
2343	964	I	105
2344	964	I	105
2345	964	F	83
2346	964	I	105
2347	964	C	32
2348	964	I	68
2349	964	F	84
2350	964	F	62

^aTumor context:

C: Neither hepatocellular carcinoma nor adenoma was detected when the mouse was removed from the study due to scheduled sacrifice or unscheduled death.

U: The presence or absence of hepatocellular carcinoma and/or adenoma could not be determined when the mouse was removed from the study due to scheduled sacrifice or unscheduled death or other reasons.

I: Hepatocellular carcinoma and/or adenoma were detected when the mouse was removed from the study due to scheduled sacrifice or unscheduled death.

Table 3: Different Stages of MSW Time-to-tumor Models with Hepatocellular Carcinoma and/or Adenoma in Female Mice, [Kano et al. \(2009\)](#)

	MSW Stage	Log(Likelihood)	#Parameter	AIC	BMD ₅₀	BMDL ₅₀	BMDU ₅₀
Incidental Risk	1	-245.823	4	499.65	35.46	27.00	46.98
	2	Model did not work with estimated parameters.					
	3	-244.279	6	500.56	38.27	28.55	52.46

Output1: Stage1 MSW Time-to-tumor Model, with Hepatocellular Carcinoma and/or Adenoma in Female Mice, [Kano et al. \(2009\)](#), BMR= ER50%

=====
 Multistage Weibull Model. (Version: 1.6.1; Date: 11/24/2009)
 Solutions are obtained using donlp2-intv, (c) by P. Spellucci
 Input Data File: LatestLiverFMice1IncidentalER50.(d)
 Fri Nov 01 14:45:29 2019
 =====

Timer to Tumor Model, Liver Tumors, "0064deadr.xlsx" and "0064Mouse_HepaticTumor.xlsx", Female Mice
 ~~~~~

The form of the probability function is:

$$P[\text{response}] = 1 - \text{EXP}\{- (t - t_0)^c * (\beta_0 + \beta_1 * \text{dose}^1)\}$$

The parameter betas are restricted to be positive

Dependent variable = CONTEXT  
 Independent variables = DOSE, TIME

Total number of observations = 200  
 Total number of records with missing values = 0  
 Total number of parameters in model = 4  
 Total number of specified parameters = 0  
 Degree of polynomial = 1

Maximum number of iterations = 64  
 Relative Function Convergence has been set to: 2.22045e-016  
 Parameter Convergence has been set to: 1.49012e-008

Default Initial Parameter Values

c = 6  
 t\_0 = 27.5556  
 beta\_0 = 1.12014e-013  
 beta\_1 = 1.39427e-014

Asymptotic Correlation Matrix of Parameter Estimates

|        | c     | t_0   | beta_0 | beta_1 |
|--------|-------|-------|--------|--------|
| c      | 1     | -0.85 | -0.99  | -1     |
| t_0    | -0.85 | 1     | 0.84   | 0.87   |
| beta_0 | -0.99 | 0.84  | 1      | 0.99   |
| beta_1 | -1    | 0.87  | 0.99   | 1      |

Parameter Estimates

| Variable | Estimate     | Std. Err.    | 95.0% Wald Confidence Interval |                   |
|----------|--------------|--------------|--------------------------------|-------------------|
|          |              |              | Lower Conf. Limit              | Upper Conf. Limit |
| c        | 5.5329       | 0.997498     | 3.57784                        | 7.48796           |
| t_0      | 37.8608      | 5.78378      | 26.5248                        | 49.1968           |
| beta_0   | 9.5028e-013  | 4.45516e-012 | -7.78167e-012                  | 9.68223e-012      |
| beta_1   | 1.28255e-013 | 5.8095e-013  | -1.01039e-012                  | 1.2669e-012       |

Log(likelihood) # Param AIC  
 Fitted Model -245.823 4 499.646

Data Summary

| CONTEXT  |    |    |    |       |          |          |
|----------|----|----|----|-------|----------|----------|
| C        | F  | I  | U  | Total | Expected | Response |
| DOSE     |    |    |    |       |          |          |
| 0        | 45 | 0  | 5  | 0     | 50       | 5.17     |
| 66       | 15 | 1  | 34 | 0     | 50       | 31.50    |
| 2.8e+002 | 9  | 9  | 32 | 0     | 50       | 42.74    |
| 9.6e+002 | 4  | 29 | 17 | 0     | 50       | 45.04    |

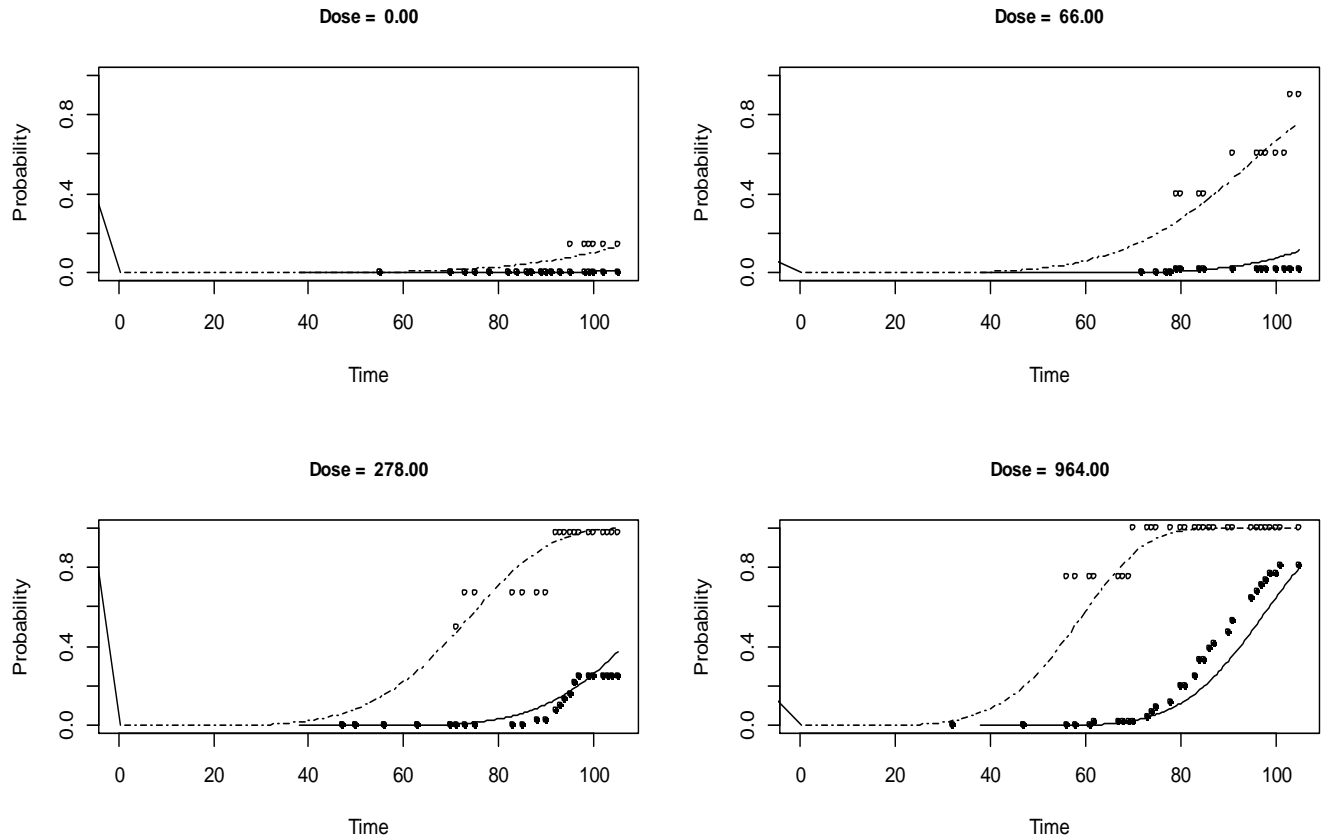
Minimum observation time for F tumor context = 62

Benchmark Dose Computation  
 Risk Response = Incidental  
 Risk Type = Extra  
 Specified effect = 0.5

Confidence level = 0.9  
Time = 105

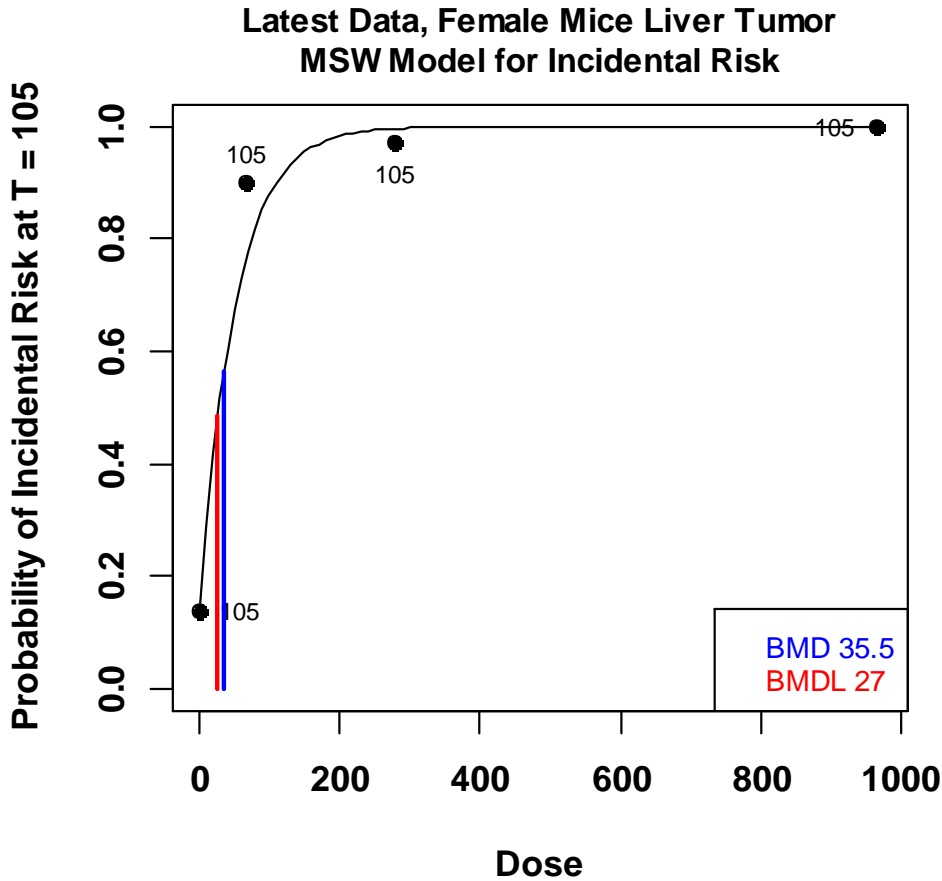
BMD = 35.4583  
BMDL = 27.0033  
BMDU = 46.9785

**Incidental Risk: Latest Data, Female Mice Liver Tumor**  
points show nonparam. est. for Incidental (unfilled) and Fatal (filled)



**Figure 1: Probability vs. Time Plot for MSW Time-to-tumor Models with Hepatocellular Carcinoma and/or Adenoma in Female Mice, [Kano et al. \(2009\)](#)**

BMD for Incidental Risk at T = 105, Extra Risk level = 0.5, conf. level = 0.9  
points show nonparametric estimate for nearest times at obsvd. doses



**Figure 2: Dose-response Plot for MSW Time-to-tumor Models with Hepatocellular Carcinoma and/or Adenoma in Female Mice, [Kano et al. \(2009\)](#)**

### K.28.2 BMDS Modeling with Poly3 Adjusted Data

The poly-3 adjustment ([Portier and Bailer, 1989](#); [Bailer and Piegorsch, 1997](#)) technique was used to adjust the tumor incidence denominators based on the individual animal survival times. The poly-3 adjustment ([Portier and Bailer, 1989](#); [Bailer and Piegorsch, 1997](#)) technique was used to adjust the tumor incidence denominators based on the individual animal survival times. Each tumor-free animal was weighted by its fractional survival time (survival time divided by the duration of the bioassay) raised to the power of 3 to reflect the fact that animals are at greater risk of cancer at older ages. Animals with tumors were given a weight of 1. The sum of the weights of all of the animals in the exposure group yielded the effective survival-adjusted denominator as the sample size in Table 4. The default

power of 3 (thus, the name "poly-3") was assumed, which was found to be representative for a large number of cancer types ([Portier et al., 1986](#)). Algebraically,

$$N_{adj} = \sum_i w_i$$

Where

$i$  indicates the animal number

$w_i = 1$  if tumor is present

$w_i = (t_i/T)^3$  if tumor is absent at time of death ( $t_i$ )

$T$  indicates the duration of study

Benchmark dose software version 3.1.1 (BMDS 3.1.1) was used to analyze the poly-3 adjusted data (Table 4). This analysis was conducted using maximum likelihood optimization and profile likelihood-based confidence intervals. Standard forms of these models<sup>31</sup> (defined below) were run in BMDS 3.1.1, applying EPA model selection procedures [U.S. EPA \(2012b\)](#). See Table 5 for results.

Standard Dichotomous Models Applied to Poly3 Adjusted Liver Tumor Data:

Gamma-restricted

Log-Logistic-restricted

Multistage-restricted; from degree = 1 to degree = # dose groups - 1

Weibull-restricted

Dichotomous Hill-unrestricted

Logistic

Log-Probit-unrestricted

Probit

General Model Options Used for Poly3 Adjusted Liver Tumor Data:

Benchmark Response (BMR): 10%, 20%, 30%, 40% and 50% Extra Risk

Confidence Level: 0.95

Background: Estimated

Model Restrictions and Model Selection

Restrictions for BMDS 3.1.1 models are defined in the BMDS 3.1.1 User Guide and are applied in accordance with EPA BMD Technical Guidance [U.S. EPA \(2012b\)](#). For each BMD analysis, a single preferred model was chosen from among the preferred standard set of models (noting instances where consideration of non-standard models may be justified) in accordance with EPA BMD Technical Guidance [U.S. EPA \(2012b\)](#).

This process led to the selection of log-logistic (restricted) as providing the preferred BMDS model suite estimates, with BMD and BMDL of 22 and 13 mg/kg-d respectively, and with a BMDL based human oral cancer slope factor of 0.26 per mg/kg-d.

#### **Table 4: Poly3 adjusted data**

---

<sup>31</sup> The set of standard models are identified in accordance with EPA BMD technical guidance (EPA, 2012) and are the default models in BMDS 3.1.1.



| Administered Dose<br>(mg/kg/day) | Poly3 Adjusted Sample<br>Size | Tumor Incidence |
|----------------------------------|-------------------------------|-----------------|
| 0                                | 41.98                         | 5               |
| 66                               | 44.69                         | 35              |
| 278                              | 44.33                         | 41              |
| 964                              | 46.66                         | 46              |

**Table 5: BMDS Modeling results with poly3 adjusted Hepatocellular Carcinoma and/or Adenoma in Female Mice, [Kano et al. \(2009\)](#)**

| Model               | Restriction       | BMR          | BMD          | BMDL         | BMDU         | P Value      | AIC           | Scaled Residual near BMD | BMDS Recommendation Notes                                                                                                                                                                        |
|---------------------|-------------------|--------------|--------------|--------------|--------------|--------------|---------------|--------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Gamma               | Restricted        | ER50%        | 66.86        | 50.56        | 92.38        | <0.0001      | 128.17        | 2.71                     | Questionable<br>Goodness of fit p-value < 0.1<br> Residual for Dose Group Near BMD  > 2                                                                                                          |
| <b>Log-Logistic</b> | <b>Restricted</b> | <b>ER50%</b> | <b>22.38</b> | <b>12.90</b> | <b>46.52</b> | <b>0.692</b> | <b>114.15</b> | <b>0.00</b>              | <b>Viable - Recommended<br/>Lowest AIC<br/>BMDL 3x lower than lowest non-zero dose</b>                                                                                                           |
| Multistage Degree 3 | Restricted        | ER50%        | 66.86        | 50.56        | 92.39        | <0.0001      | 128.17        | 2.71                     | Questionable<br>Goodness of fit p-value < 0.1<br> Residual for Dose Group Near BMD  > 2                                                                                                          |
| Multistage Degree 2 | Restricted        | ER50%        | 66.86        | 50.56        | 92.39        | <0.0001      | 128.17        | 2.71                     | Questionable<br>Goodness of fit p-value < 0.1<br> Residual for Dose Group Near BMD  > 2                                                                                                          |
| Multistage Degree 1 | Restricted        | ER50%        | 66.86        | 50.56        | 92.38        | <0.0001      | 128.17        | 2.71                     | Questionable<br>Goodness of fit p-value < 0.1<br> Residual for Dose Group Near BMD  > 2                                                                                                          |
| Weibull             | Restricted        | ER50%        | 66.86        | 50.56        | 92.39        | <0.0001      | 128.17        | 2.71                     | Questionable<br>Goodness of fit p-value < 0.1<br> Residual for Dose Group Near BMD  > 2                                                                                                          |
| Dichotomous Hill    | Unrestricted      | ER50%        | 22.38        | 2.65         | 46.52        | NA           | 116.15        | 0.00                     | Questionable<br>BMD/BMDL ratio > 3<br>BMDL 3x lower than lowest non-zero dose<br>BMDL 10x lower than lowest non-zero dose<br>d.f.=0, saturated model (Goodness of fit test cannot be calculated) |
| Logistic            | Unrestricted      | ER50%        | 116.27       | 88.79        | 157.57       | <0.0001      | 142.49        | 3.25                     | Questionable<br>Goodness of fit p-value < 0.1<br> Residual for Dose Group Near BMD  > 2<br> Residual at control  > 2                                                                             |
| Log-Probit          | Unrestricted      | ER50%        | 18.13        | 1.62         | 43.10        | 0.810        | 114.05        | 0.00                     | Questionable<br>BMD/BMDL ratio > 3<br>BMD 3x lower than lowest non-zero dose<br>BMDL 3x lower than lowest non-zero dose<br>BMDL 10x lower than lowest non-zero dose                              |
| Probit              | Unrestricted      | ER50%        | 167.86       | 132.96       | 227.20       | <0.0001      | 151.63        | 3.27                     | Questionable<br>Goodness of fit p-value < 0.1<br> Residual for Dose Group Near BMD  > 2<br> Residual at control  > 2                                                                             |

**Output2: Log-Logistic Modeling Output with Poly3 Adjusted Hepatocellular Carcinoma and/or Adenoma in Female Mice, [Kano et al. \(2009\)](#)**

| User Input              |                                                                               |
|-------------------------|-------------------------------------------------------------------------------|
| <b>Info</b>             |                                                                               |
| Model                   | frequentist Log-Logistic v1.1                                                 |
| Dataset Name            | DataSet Name1                                                                 |
| User notes              | [Add user notes here]                                                         |
| Dose-Response Model     | $P[\text{dose}] = g + (1 - g) / [1 + \exp(-a - b * \text{Log}(\text{dose}))]$ |
| <b>Model Options</b>    |                                                                               |
| Risk Type               | Extra Risk                                                                    |
| BMR                     | 0.5                                                                           |
| Confidence Level        | 0.95                                                                          |
| Background              | Estimated                                                                     |
| <b>Model Data</b>       |                                                                               |
| Dependent Variable      | [Dose]                                                                        |
| Independent Variable    | [Incidence]                                                                   |
| Total # of Observations | 4                                                                             |

| Model Results           |             |
|-------------------------|-------------|
| <b>Benchmark Dose</b>   |             |
| BMD                     | 22.37990188 |
| BMDL                    | 12.89695219 |
| BMDU                    | 46.52457822 |
| AIC                     | 114.1506984 |
| P-value                 | 0.692090927 |
| D.O.F.                  | 1           |
| Chi <sup>2</sup>        | 0.156831139 |
| <b>Model Parameters</b> |             |
| # of Parameters         | 3           |
| Variable                | Estimate    |

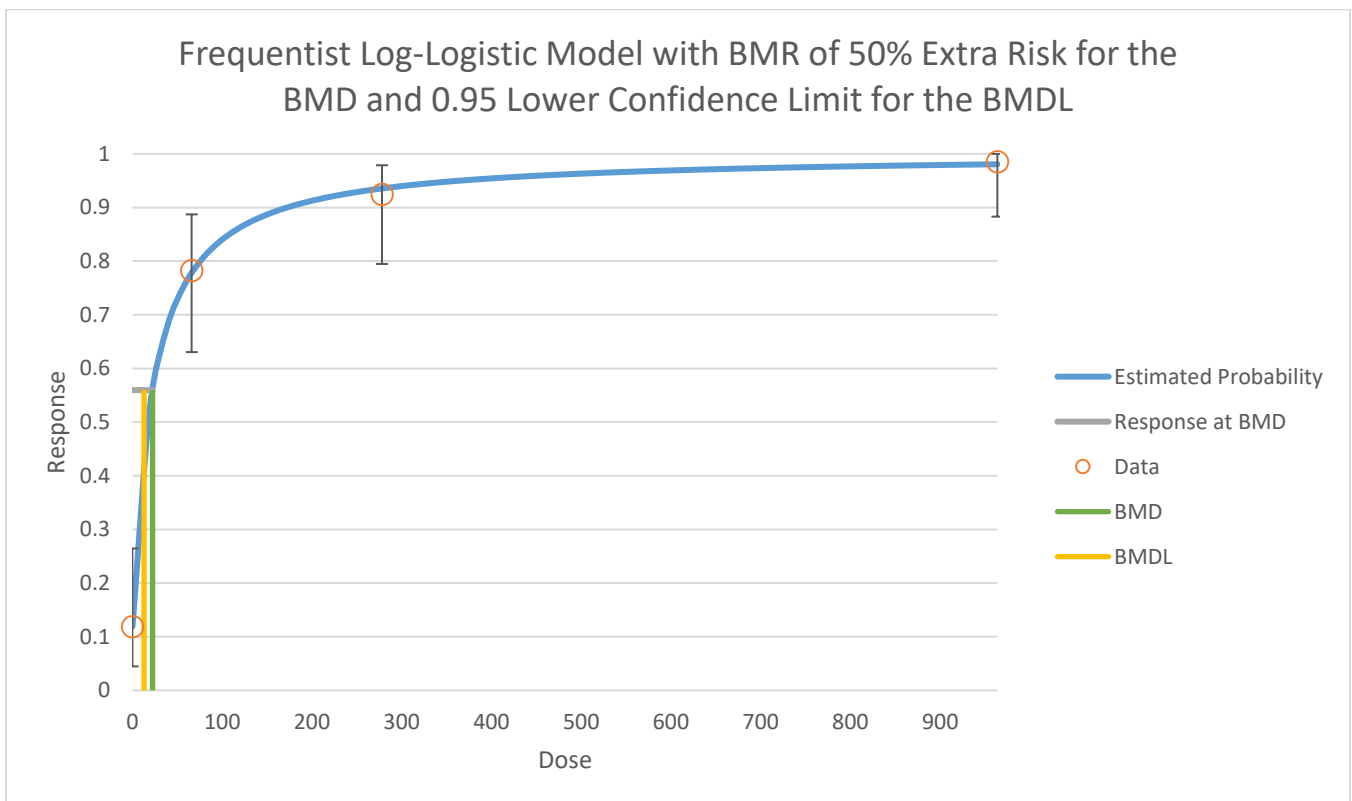
|   |              |
|---|--------------|
| g | 0.119231882  |
| a | -3.128607576 |
| b | 1.006577601  |

**Goodness of Fit**

| Dose | Estimated Probability | Expected    | Observed | Size       | Scaled Residual |
|------|-----------------------|-------------|----------|------------|-----------------|
| 0    | 0.119231882           | 5.004814738 | 5        | 41.9754739 | -0.002293231    |
| 66   | 0.778151202           | 34.77721655 | 35       | 44.6921067 | 0.080206021     |
| 278  | 0.935377478           | 41.46629827 | 41       | 44.3310848 | -0.284855247    |
| 964  | 0.980494043           | 45.75140244 | 46       | 46.6615813 | 0.263154636     |

**Analysis of Deviance**

| Model         | Log Likelihood | # of Parameters | Deviance    | Test d.f. | P Value     |
|---------------|----------------|-----------------|-------------|-----------|-------------|
| Full Model    | -53.99521585   | 4               | -           | -         | -           |
| Fitted Model  | -54.07534919   | 3               | 0.160266692 | 1         | 0.688911098 |
| Reduced Model | -106.1971175   | 1               | 104.4038034 | 3         | <0.0001     |



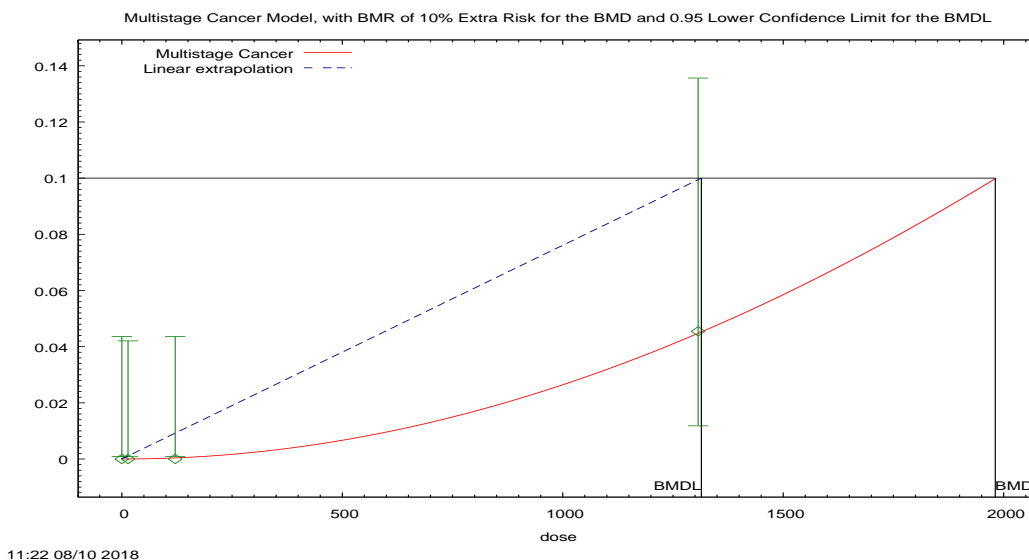
**Figure 3: Dose-Response Plot for Log-Logistic Model with Poly3 Adjusted Hepatocellular Carcinoma and/or Adenoma in Female Mice, [Kano et al. \(2009\)](#)**

## K.29 BMD5 Summary of Nasal cavity tumors in Sherman rats [Kociba et al. \(1974\)](#)

**Table K-22. Summary of BMD Modeling Results for Nasal cavity tumors in Sherman rats [Kociba et al. \(1974\)](#)**

| Model <sup>a</sup> | Goodness of fit |               | BMD <sub>10Pct</sub><br>(mg/kg-d) | BMDL <sub>10Pct</sub><br>(mg/kg-d) | Basis for model selection                                   |
|--------------------|-----------------|---------------|-----------------------------------|------------------------------------|-------------------------------------------------------------|
|                    | p-value         | AIC           |                                   |                                    |                                                             |
| One                | 0.916           | 27.352        | 3465                              | 1525                               | Lowest BMDL. Both models have some parameter values of zero |
| <b>Two</b>         | <b>0.998</b>    | <b>26.493</b> | <b>1981</b>                       | <b>1314</b>                        |                                                             |

<sup>a</sup> Selected model in bold; scaled residuals for selected model for doses 0, 14, 121, and 1307 mg/kg-d were 0, -0.02, -0.2, 0.02, respectively.



**Figure K-22. Plot of incidence rate by dose with fitted curve for Multistage-Cancer 2<sup>o</sup> model for Nasal cavity tumors in Sherman rats [Kociba et al. \(1974\)](#); dose shown in mg/kg-d.**

**Multistage Model.** (Version: 3.4; Date: 05/02/2014)

The form of the probability function is:  $P[\text{response}] = \text{background} + (1-\text{background}) * [1 - \text{EXP}(-\text{beta1} * \text{dose}^1 - \text{beta2} * \text{dose}^2)]$

The parameter betas are restricted to be positive

**Benchmark Dose Computation.**

BMR = 10% Extra risk

BMD = 1980.96

BMDL at the 95% confidence level = 1314.37

BMDU at the 95% confidence level = 8538.89

Taken together, (1314.37, 8538.89) is a 90% two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.0000760821

**Parameter Estimates**

| Variable   | Estimate   | Default Initial Parameter Values |
|------------|------------|----------------------------------|
| Background | 0          | 0                                |
| Beta(1)    | 0          | 0                                |
| Beta(2)    | 2.6849E-08 | 2.7310E-08                       |

**Analysis of Deviance Table**

| Model         | Log(likelihood) | # Param's | Deviance  | Test d.f. | p-value |
|---------------|-----------------|-----------|-----------|-----------|---------|
| Full model    | -12.2           | 4         |           |           |         |
| Fitted model  | -12.25          | 1         | 0.0850948 | 3         | 0.99    |
| Reduced model | -17.58          | 1         | 10.7433   | 3         | 0.01    |

AIC: = 26.4929

**Goodness of Fit Table**

| Dose | Est. Prob. | Expected | Observed | Size | Scaled Resid |
|------|------------|----------|----------|------|--------------|
| 0    | 0          | 0        | 0        | 106  | 0            |
| 14   | 0          | 0.001    | 0        | 110  | -0.02        |
| 121  | 0.0004     | 0.042    | 0        | 106  | -0.2         |
| 1307 | 0.0448     | 2.959    | 3        | 66   | 0.02         |

Chi<sup>2</sup> = 0.04 d.f = 3 P-value = 0.9977

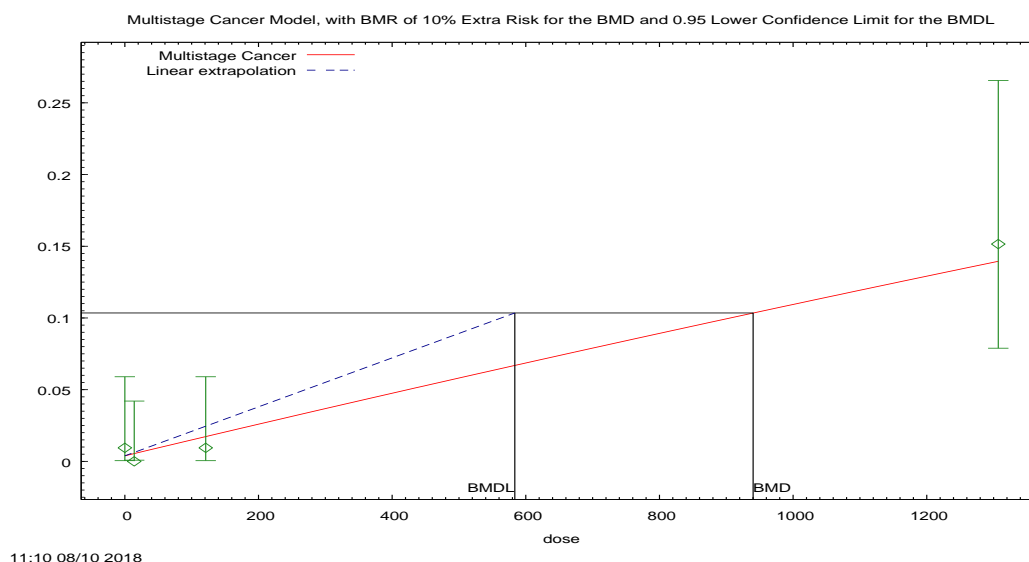
**K.30 BMDS Summary of Liver tumors in Sherman rats (male and female combined) [Kociba et al. \(1974\)](#)**

---

**Table K-23. Summary of BMD Modeling Results for Liver tumors in Sherman rats (male and female combined) [Kociba et al. \(1974\)](#)**

| Model <sup>a</sup> | Goodness of fit |               | BMD <sub>10Pct</sub><br>(mg/kg-d) | BMDL <sub>10Pct</sub><br>(mg/kg-d) | Basis for model selection                                           |
|--------------------|-----------------|---------------|-----------------------------------|------------------------------------|---------------------------------------------------------------------|
|                    | p-value         | AIC           |                                   |                                    |                                                                     |
| <b>One</b>         | <b>0.384</b>    | <b>85.119</b> | <b>940</b>                        | <b>584</b>                         | <b>Lowest AIC. All parameter estimates positive in both models.</b> |
| Two                | 0.311           | 86.287        | 1042                              | 629                                |                                                                     |

<sup>a</sup> Selected model in bold; scaled residuals for selected model for doses 0, 14, 121, and 1307 mg/kg-d were 0.92, -0.78, -0.62, 0.28, respectively.



**Figure K-23. Plot of incidence rate by dose with fitted curve for Multistage-Cancer 1<sup>o</sup> model for Liver tumors in Sherman rats (male and female combined) [Kociba et al. \(1974\)](#); dose shown in mg/kg-d.**

**Multistage Model.** (Version: 3.4; Date: 05/02/2014)

The form of the probability function is:  $P[\text{response}] = \text{background} + (1-\text{background}) * [1 - \text{EXP}(-\text{beta1} * \text{dose}^1 - \text{beta2} * \text{dose}^2)]$

The parameter betas are restricted to be positive

**Benchmark Dose Computation.**

BMR = 10% Extra risk

BMD = 940.125

BMDL at the 95% confidence level = 583.576

BMDU at the 95% confidence level = 1685.88

Taken together, (583.576, 1685.88) is a 90% two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.000171357

**Parameter Estimates**

| Variable   | Estimate    | Default Initial Parameter Values |
|------------|-------------|----------------------------------|
| Background | 0.00386835  | 0.000925988                      |
| Beta(1)    | 0.000112071 | 0.000124518                      |

**Analysis of Deviance Table**

| Model         | Log(likelihood) | # Param's | Deviance | Test d.f. | p-value |
|---------------|-----------------|-----------|----------|-----------|---------|
| Full model    | -39.39          | 4         |          |           |         |
| Fitted model  | -40.56          | 2         | 2.34056  | 2         | 0.31    |
| Reduced model | -53.53          | 1         | 28.2732  | 3         | <.0001  |

AIC: = 85.1187

**Goodness of Fit Table**

| Dose | Est. Prob. | Expected | Observed | Size | Scaled Resid |
|------|------------|----------|----------|------|--------------|
| 0    | 0.0039     | 0.41     | 1        | 106  | 0.92         |
| 14   | 0.0054     | 0.597    | 0        | 110  | -0.78        |
| 121  | 0.0173     | 1.832    | 1        | 106  | -0.62        |
| 1307 | 0.1396     | 9.213    | 10       | 66   | 0.28         |

Chi<sup>2</sup> = 1.92 d.f = 2 P-value = 0.3838

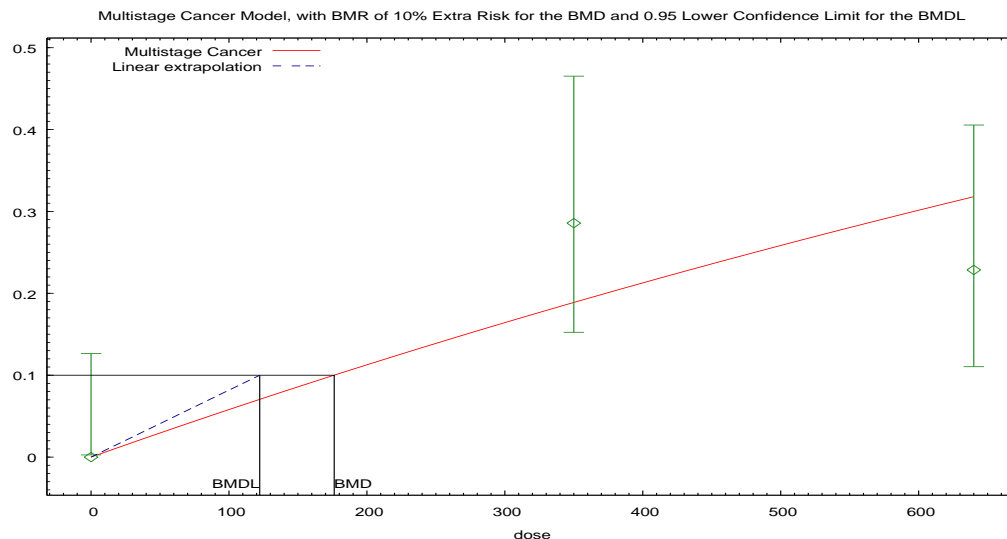
**K.31 BMDS Summary of Nasal squamous cell carcinomas in female OM rats (MS models) [NCI \(1978\)](#)**

---

**Table K-24. Summary of BMD Modeling Results for Nasal squamous cell carcinomas in female OM rats (MS models) [NCI \(1978\)](#)**

| Model <sup>a</sup> | Goodness of fit |               | BMD <sub>10Pct</sub><br>(mg/kg-d) | BMDL <sub>10Pct</sub><br>(mg/kg-d) | Basis for model selection      |
|--------------------|-----------------|---------------|-----------------------------------|------------------------------------|--------------------------------|
|                    | p-value         | AIC           |                                   |                                    |                                |
| <b>One</b>         | <b>0.180</b>    | <b>84.800</b> | <b>176</b>                        | <b>122</b>                         | <b>Model has adequate fit.</b> |

<sup>a</sup> Selected model in bold; scaled residuals for selected model for doses 0, 350, and 640 were 0, 1.47, -1.13, respectively.



17:08 08/08 2018

**Figure K-24. Plot of incidence rate by dose with fitted curve for Multistage-Cancer 1° model for Nasal squamous cell carcinomas in female OM rats (MS models) [NCI \(1978\)](#); dose shown in mg/kg-d.**



**Multistage Model.** (Version: 3.4; Date: 05/02/2014)

The form of the probability function is:  $P[\text{response}] = \text{background} + (1-\text{background}) * [1 - \text{EXP}(-\text{beta1} * \text{dose} - \text{beta2} * \text{dose}^2)]$

The parameter betas are restricted to be positive

**Benchmark Dose Computation.**

BMR = 10% Extra risk

BMD = 176.281

BMDL at the 95% confidence level = 122.274

BMDU at the 95% confidence level = 271.474

Taken together, (122.274, 271.474) is a 90% two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.000817837

**Parameter Estimates**

| Variable   | Estimate    | Default Initial Parameter Values |
|------------|-------------|----------------------------------|
| Background | 0           | 0.0569154                        |
| Beta(1)    | 0.000597685 | 0.00042443                       |

**Analysis of Deviance Table**

| Model         | Log(likelihood) | # Param's | Deviance | Test d.f. | p-value |
|---------------|-----------------|-----------|----------|-----------|---------|
| Full model    | -39.75          | 3         |          |           |         |
| Fitted model  | -41.4           | 1         | 3.29259  | 2         | 0.19    |
| Reduced model | -47.92          | 1         | 16.3252  | 2         | 0       |

AIC: = 84.7996

**Goodness of Fit Table**

| Dose | Est. Prob. | Expected | Observed | Size | Scaled Resid |
|------|------------|----------|----------|------|--------------|
| 0    | 0          | 0        | 0        | 34   | 0            |
| 350  | 0.1888     | 6.607    | 10       | 35   | 1.47         |
| 640  | 0.3179     | 11.125   | 8        | 35   | -1.13        |

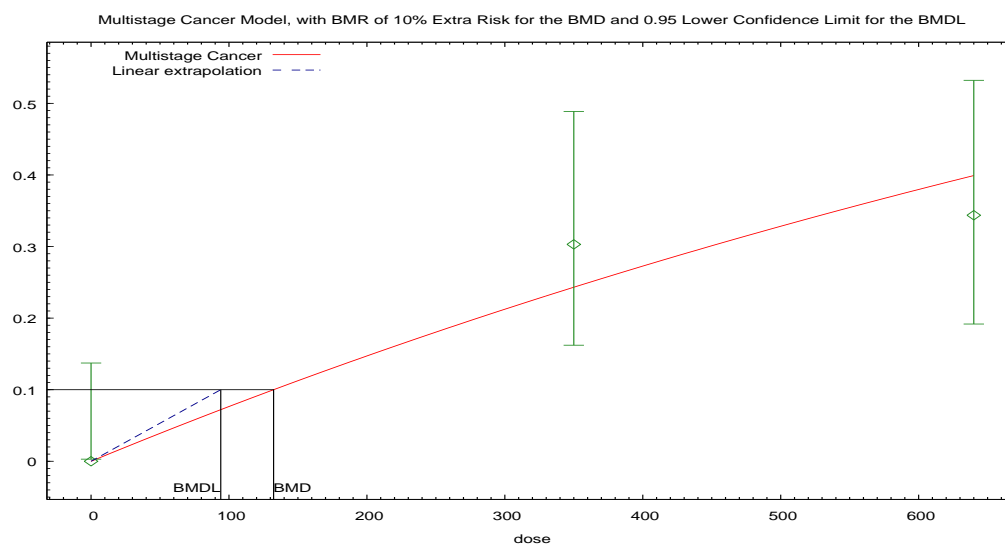
Chi<sup>2</sup> = 3.44 d.f = 2 P-value = 0.1795

## K.32 BMDs Summary of Hepatocellular adenoma in female OM rats NCI (1978)

**Table K-25. Summary of BMD Modeling Results for Hepatocellular adenoma in female OM rats  
NCI (1978)**

| Model <sup>a</sup> | Goodness of fit |               | BMD <sub>10Pct</sub><br>(mg/kg-d) | BMDL <sub>10Pct</sub><br>(mg/kg-d) | Basis for model selection      |
|--------------------|-----------------|---------------|-----------------------------------|------------------------------------|--------------------------------|
|                    | p-value         | AIC           |                                   |                                    |                                |
| <b>One</b>         | <b>0.591</b>    | <b>84.697</b> | <b>132</b>                        | <b>94.1</b>                        | <b>Model has adequate fit.</b> |

<sup>a</sup> Selected model in bold; scaled residuals for selected model for doses 0, 350, and 640 mg/kg-d were 0, 0.8, -0.64, respectively.



**Figure K-25. Plot of incidence rate by dose with fitted curve for Multistage-Cancer 1<sup>o</sup> model for Hepatocellular adenoma in female OM rats NCI (1978); dose shown in mg/kg-d.**

**Multistage Model.** (Version: 3.4; Date: 05/02/2014)

The form of the probability function is:  $P[\text{response}] = \text{background} + (1-\text{background}) * [1 - \text{EXP}(-\text{beta1} * \text{dose} - \text{beta2} * \text{dose}^2)]$

The parameter betas are restricted to be positive

**Benchmark Dose Computation.**

BMR = 10% Extra risk

BMD = 132.359

BMDL at the 95% confidence level = 94.0591

BMDU at the 95% confidence level = 194.33

Taken together, (94.0591, 194.33) is a 90% two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.00106316

**Parameter Estimates**

| Variable   | Estimate   | Default Initial Parameter Values |
|------------|------------|----------------------------------|
| Background | 0          | 0.0385912                        |
| Beta(1)    | 0.00079602 | 0.000670869                      |

**Analysis of Deviance Table**

| Model         | Log(likelihood) | # Param's | Deviance | Test d.f. | p-value |
|---------------|-----------------|-----------|----------|-----------|---------|
| Full model    | -40.83          | 3         |          |           |         |
| Fitted model  | -41.35          | 1         | 1.02868  | 2         | 0.6     |
| Reduced model | -50.43          | 1         | 19.1932  | 2         | <.0001  |

AIC: = 84.6972

**Goodness of Fit Table**

| Dose | Est. Prob. | Expected | Observed | Size | Scaled Resid |
|------|------------|----------|----------|------|--------------|
| 0    | 0          | 0        | 0        | 31   | 0            |
| 350  | 0.2432     | 8.024    | 10       | 33   | 0.8          |
| 640  | 0.3992     | 12.774   | 11       | 32   | -0.64        |

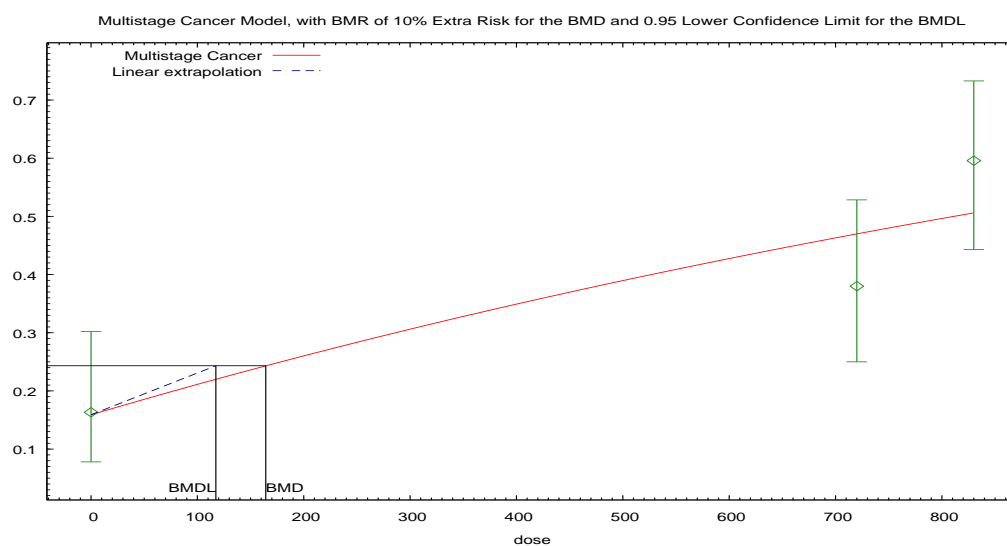
Chi<sup>2</sup> = 1.05 d.f = 2 P-value = 0.5908

### K.33 BMDs Summary of Hepatocellular adenomas or carcinomas in male B6C3F1 mice [NCI \(1978\)](#)

**Table K-26. Summary of BMD Modeling Results for Hepatocellular adenomas or carcinomas in male B6C3F1 mice [NCI \(1978\)](#)**

| Model <sup>a</sup> | Goodness of fit |               | BMD <sub>10Pct</sub><br>(mg/kg-d) | BMDL <sub>10Pct</sub><br>(mg/kg-d) | Basis for model selection      |
|--------------------|-----------------|---------------|-----------------------------------|------------------------------------|--------------------------------|
|                    | p-value         | AIC           |                                   |                                    |                                |
| <b>One</b>         | <b>0.0762</b>   | <b>180.62</b> | <b>164</b>                        | <b>117</b>                         | <b>Model has adequate fit.</b> |

<sup>a</sup> Selected model in bold; scaled residuals for selected model for doses 0, 720, and 830 mg/kg-d were 0.08, -1.28, 1.23, respectively.



**Figure K-26. Plot of incidence rate by dose with fitted curve for Multistage-Cancer 1° model for Hepatocellular adenomas or carcinomas in male B6C3F1 mice [NCI \(1978\)](#); dose shown in mg/kg-d.**

**Multistage Model.** (Version: 3.4; Date: 05/02/2014)

The form of the probability function is:  $P[\text{response}] = \text{background} + (1 - \text{background}) * [1 - \text{EXP}(-\text{beta1} * \text{dose}^1 - \text{beta2} * \text{dose}^2)]$

The parameter betas are restricted to be positive

**Benchmark Dose Computation.**

BMR = 10% Extra risk

BMD = 164.285

BMDL at the 95% confidence level = 117.371

BMDU at the 95% confidence level = 265.631

Taken together, (117.371, 265.631) is a 90% two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.000851999

**Parameter Estimates**

| Variable   | Estimate    | Default Initial Parameter Values |
|------------|-------------|----------------------------------|
| Background | 0.15914     | 0.142253                         |
| Beta(1)    | 0.000641327 | 0.000710746                      |

**Analysis of Deviance Table**

| Model         | Log(likelihood) | # Param's | Deviance | Test d.f. | p-value |
|---------------|-----------------|-----------|----------|-----------|---------|
| Full model    | -86.72          | 3         |          |           |         |
| Fitted model  | -88.31          | 2         | 3.17505  | 1         | 0.07    |
| Reduced model | -96.72          | 1         | 19.9875  | 2         | <.0001  |

AIC: = 180.618

**Goodness of Fit Table**

| Dose | Est. Prob. | Expected | Observed | Size | Scaled Resid |
|------|------------|----------|----------|------|--------------|
| 0    | 0.1591     | 7.798    | 8        | 49   | 0.08         |
| 720  | 0.4701     | 23.505   | 19       | 50   | -1.28        |
| 830  | 0.5062     | 23.792   | 28       | 47   | 1.23         |

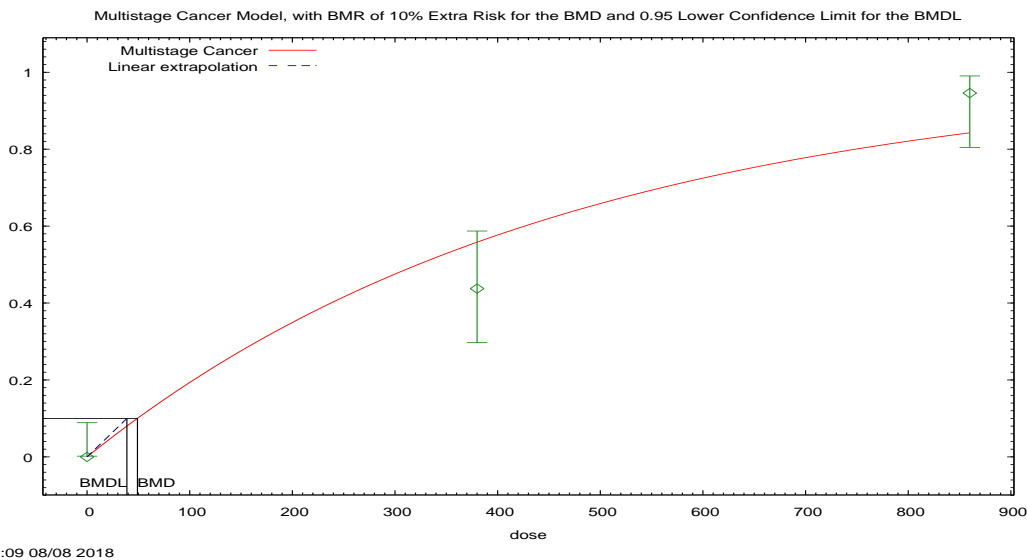
Chi<sup>2</sup> = 3.14 d.f = 1 P-value = 0.0762

## K.34 BMDs Summary of Hepatocellular adenomas or carcinomas in female B6C3F1 mice [NCI \(1978\)](#)

**Table K-27. Summary of BMD Modeling Results for Hepatocellular adenomas or carcinomas in female B6C3F1 mice [NCI \(1978\)](#)**

| Model <sup>a</sup> | Goodness of fit |               | BMD <sub>10Pct</sub><br>(mg/kg-d) | BMDL <sub>10Pct</sub><br>(mg/kg-d) | Basis for model selection      |
|--------------------|-----------------|---------------|-----------------------------------|------------------------------------|--------------------------------|
|                    | p-value         | AIC           |                                   |                                    |                                |
| <b>One</b>         | <b>0.0548</b>   | <b>89.986</b> | <b>49.1</b>                       | <b>38.8</b>                        | <b>Model has adequate fit.</b> |

<sup>a</sup> Selected model in bold; scaled residuals for selected model for doses 0, 380, and 860 mg/kg-d were 0, -1.67, 1.73, respectively.



**Figure K-27. Plot of incidence rate by dose with fitted curve for Multistage-Cancer 1<sup>o</sup> model for Hepatocellular adenomas or carcinomas in female B6C3F1 mice [NCI \(1978\)](#); dose shown in mg/kg-d.**

**Multistage Model.** (Version: 3.4; Date: 05/02/2014)

The form of the probability function is:  $P[\text{response}] = \text{background} + (1-\text{background}) * [1 - \text{EXP}(-\text{beta1} * \text{dose}^1 - \text{beta2} * \text{dose}^2)]$

The parameter betas are restricted to be positive

**Benchmark Dose Computation.**

BMR = 10% Extra risk

BMD = 49.1018

BMDL at the 95% confidence level = 38.8015

BMDU at the 95% confidence level = 62.9223

Taken together, (38.8015, 62.9223) is a 90% two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.00257722

**Parameter Estimates**

| Variable   | Estimate   | Default Initial Parameter Values |
|------------|------------|----------------------------------|
| Background | 0          | 0                                |
| Beta(1)    | 0.00214576 | 0.00345682                       |

**Analysis of Deviance Table**

| Model         | Log(likelihood) | # Param's | Deviance | Test d.f. | p-value |
|---------------|-----------------|-----------|----------|-----------|---------|
| Full model    | -40.68          | 3         |          |           |         |
| Fitted model  | -43.99          | 1         | 6.63483  | 2         | 0.04    |
| Reduced model | -91.61          | 1         | 101.861  | 2         | <.0001  |

AIC: = 89.986

**Goodness of Fit Table**

| Dose | Est. Prob. | Expected | Observed | Size | Scaled Resid |
|------|------------|----------|----------|------|--------------|
| 0    | 0          | 0        | 0        | 50   | 0            |
| 380  | 0.5575     | 26.762   | 21       | 48   | -1.67        |
| 860  | 0.842      | 31.155   | 35       | 37   | 1.73         |

Chi<sup>2</sup> = 5.81 d.f = 2 P-value = 0.0548

**K.35 MS-Combo Result [Kano et al. \(2009\)](#), Male F344/ DuCrj rats, excluding liver**

| Output information                 |                                                      |
|------------------------------------|------------------------------------------------------|
| Tumor Output Directory             | C:\Users\ \Documents\MODELS\14dioxane\oral\kano_MSC\ |
| Tumor Output File Name             | Kano_M_nasal_perit_subcut.out                        |
| Combined BMD and BMDL Calculations |                                                      |
| Combined Log-Likelihood            | -150.6683784                                         |
| Combined Log-likelihood Constant   | 135.326183                                           |
| Benchmark Dose Computation         |                                                      |
| Specified effect                   | 0.1                                                  |
| Risk Type                          | Extra risk                                           |
| Confidence level                   | 0.95                                                 |
| BMD                                | 55.1605                                              |
| BMDL                               | 28.1197                                              |
| Multistage Cancer Slope Factor     | 0.00355622                                           |

\*\*\*\* Start of combined BMD and BMDL Calculations.\*\*\*\*

Combined Log-Likelihood                    -150.66837843809108

Combined Log-likelihood Constant        135.32618295034047

Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =    Extra risk

Confidence level =        0.95

BMD =        55.1605

BMDL =       28.1197

BMDU =       88.9926

Multistage Cancer Slope Factor =    0.00355622

**K.36 MS-Combo Result [Kano et al. \(2009\)](#), Male F344/ DuCrj rats, including liver**

| Output information     |                                                      |
|------------------------|------------------------------------------------------|
| Tumor Output Directory | C:\Users\ \Documents\MODELS\14dioxane\oral\kano_MSC\ |



|                                           |                |
|-------------------------------------------|----------------|
| Tumor Output File Name                    | Kano_M_all.out |
| <b>Combined BMD and BMDL Calculations</b> |                |
| Combined Log-Likelihood                   | -222.5755927   |
| Combined Log-likelihood Constant          | 200.3198288    |
| <b>Benchmark Dose Computation</b>         |                |
| Specified effect                          | 0.1            |
| Risk Type                                 | Extra risk     |
| Confidence level                          | 0.95           |
| BMD                                       | 35.099         |
| BMDL                                      | 17.8487        |
| Multistage Cancer Slope Factor            | 0.00560264     |

\*\*\*\* Start of combined BMD and BMDL Calculations.\*\*\*\*

Combined Log-Likelihood                    -222.57559271275764  
 Combined Log-likelihood Constant        200.31982880189281

**Benchmark Dose Computation**

Specified effect =        0.1  
 Risk Type        =    Extra risk  
 Confidence level =        0.95  
  
       BMD =        35.099  
       BMDL =       17.8487  
       BMDU =       55.9726  
  
 Multistage Cancer Slope Factor =    0.00560264

**K.37 MS-Combo Result [Kano et al. \(2009\)](#), Female F344/ DuCrj rats, excluding liver**

|                                           |                                                      |
|-------------------------------------------|------------------------------------------------------|
| <b>Output information</b>                 |                                                      |
| Tumor Output Directory                    | C:\Users\ \Documents\MODELS\14dioxane\oral\kano_MSC\ |
| Tumor Output File Name                    | Kano_Frat_mam_nas.out                                |
| <b>Combined BMD and BMDL Calculations</b> |                                                      |
| Combined Log-Likelihood                   | -116.9411818                                         |
| Combined Log-likelihood Constant          | 105.6980867                                          |

| Benchmark Dose Computation     |            |
|--------------------------------|------------|
| Specified effect               | 0.1        |
| Risk Type                      | Extra risk |
| Confidence level               | 0.95       |
| BMD                            | 120.172    |
| BMDL                           | 76.5303    |
| Multistage Cancer Slope Factor | 0.00130667 |

\*\*\*\* Start of combined BMD and BMDL Calculations.\*\*\*\*

Combined Log-Likelihood                    -116.94118175960915

Combined Log-likelihood Constant        105.69808670837932

#### Benchmark Dose Computation

Specified effect =        0.1

Risk Type        =    Extra risk

Confidence level =        0.95

      BMD =        120.172

      BMDL =       76.5303

      BMDU =       231.101

Multistage Cancer Slope Factor =    0.00130667

### K.38 MS-Combo Result [Kano et al. \(2009\)](#), Female F344/ DuCrj rats, including liver

---

| Output information                 |                                                      |
|------------------------------------|------------------------------------------------------|
| Tumor Output Directory             | C:\Users\ \Documents\MODELS\14dioxane\oral\kano_MSC\ |
| Tumor Output File Name             | kano_F_all.out                                       |
| Combined BMD and BMDL Calculations |                                                      |
| Combined Log-Likelihood            | -160.736061                                          |
| Combined Log-likelihood Constant   | 143.1853353                                          |
| Benchmark Dose Computation         |                                                      |
| Specified effect                   | 0.1                                                  |

|                                |            |
|--------------------------------|------------|
| Risk Type                      | Extra risk |
| Confidence level               | 0.95       |
| BMD                            | 57.6028    |
| BMDL                           | 41.6426    |
| Multistage Cancer Slope Factor | 0.00240139 |

\*\*\*\* Start of combined BMD and BMDL Calculations.\*\*\*\*

Combined Log-Likelihood                    -160.73606100858856

Combined Log-likelihood Constant        143.18533527241118

Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =    Extra risk

Confidence level =        0.95

      BMD =        57.6028

      BMDL =      41.6426

      BMDU =      70.5585

Multistage Cancer Slope Factor = 0.00240139

**ATTACHMENT B**

In addition to publishing the full text of this document in the **Federal Register**, the Commission provides all interested persons an opportunity to view and/or print the contents of this document via the internet through the Commission's Home Page (<http://ferc.gov>) using the "eLibrary" link. Enter the docket number excluding the last three digits in the docket number field to access the document. At this time, the Commission has suspended access to the Commission's Public Reference Room, due to the proclamation declaring a National Emergency concerning the Novel Coronavirus Disease (COVID-19), issued by the President on March 13, 2020. For assistance, contact the Federal Energy Regulatory Commission at [FERCOnlineSupport@ferc.gov](mailto:FERCOnlineSupport@ferc.gov) or call toll-free, (886) 208-3676 or TTY, (202) 502-8659.

Dated: January 4, 2021.

**Nathaniel J. Davis, Sr.,**  
Deputy Secretary.

[FR Doc. 2021-00128 Filed 1-7-21; 8:45 am]

**BILLING CODE 6717-01-P**

## ENVIRONMENTAL PROTECTION AGENCY

[EPA-HQ-OPPT-2019-0238; FRL-10017-46]

### 1,4-Dioxane; Final Toxic Substances Control Act (TSCA) Risk Evaluation; Notice of Availability

**AGENCY:** Environmental Protection Agency (EPA).

**ACTION:** Notice.

**SUMMARY:** The Environmental Protection Agency (EPA) is announcing the availability of the final Toxic Substances Control Act (TSCA) risk evaluation of 1, 4-dioxane. The purpose of conducting risk evaluations under TSCA is to determine whether a chemical substance presents an unreasonable risk of injury to health or the environment under the conditions of use, including an unreasonable risk to a relevant potentially exposed or susceptible subpopulation, without consideration of costs or other nonrisk factors. EPA has determined that specific conditions of use of 1, 4-dioxane present an unreasonable risk of injury to health or the environment. For those conditions of use for which EPA has found an unreasonable risk, EPA must take regulatory action to address that unreasonable risk through risk management measures enumerated in TSCA. EPA has also determined that specific conditions of use do not present

an unreasonable risk of injury to health or the environment. For those conditions of use for which EPA has found no unreasonable risk of injury to health or the environment, the Agency's determination is a final Agency action and is issued via order in the risk evaluation.

**ADDRESSES:** The docket for this action, identified by docket identification (ID) number EPA-HQ-OPPT-2019-0238, is available online at <http://www.regulations.gov> or in-person at the Office of Pollution Prevention and Toxics Docket (OPPT Docket), Environmental Protection Agency Docket Center (EPA/DC), West William Jefferson Clinton Bldg., Rm. 3334, 1301 Constitution Ave. NW, Washington, DC. The Public Reading Room is open from 8:30 a.m. to 4:30 p.m., Monday through Friday, excluding legal holidays. The telephone number for the Public Reading Room is (202) 566-1744, and the telephone number for the OPPT Docket is (202) 566-0280.

Due to the public health concerns related to COVID-19, the EPA Docket Center (EPA/DC) and Public Reading Room are closed to visitors with limited exceptions. The EPA/DC staff continue to provide remote customer service via email, phone, and webform. For the latest status information on EPA/DC services and docket access, visit <https://www.epa.gov/dockets>.

**FOR FURTHER INFORMATION CONTACT:** For technical information contact: Yvette Selby-Mohamadu, Office of Pollution Prevention and Toxics (7403M), Environmental Protection Agency, 1200 Pennsylvania Ave. NW, Washington, DC 20460-0001; telephone number: (202) 564-5245; email address: [selby-mohamadu.yvette@epa.gov](mailto:selby-mohamadu.yvette@epa.gov).

For general information contact: The TSCA-Hotline, ABVI-Goodwill, 422 South Clinton Ave., Rochester, NY 14620; telephone number: (202) 554-1404; email address: [TSCA-Hotline@epa.gov](mailto:TSCA-Hotline@epa.gov).

#### SUPPLEMENTARY INFORMATION:

##### I. General Information

###### A. Does this action apply to me?

This action is directed to the public in general. This action may be of interest to persons who are or may be interested in risk evaluations of chemical substances under TSCA, 15 U.S.C. 2601 *et seq.* Since other entities may also be interested in this final risk evaluation, the EPA has not attempted to describe all the specific entities that may be affected by this action.

###### B. What is EPA's authority for taking this action?

TSCA section 6, 15 U.S.C. 2605, requires EPA to conduct risk evaluations to "determine whether a chemical substance presents an unreasonable risk of injury to health or the environment, without consideration of costs or other nonrisk factors, including an unreasonable risk to a potentially exposed or susceptible subpopulation identified as relevant to the risk evaluation by the Administrator, under the conditions of use." 15 U.S.C. 2605(b)(4)(A). TSCA sections 6(b)(4)(A) through (H) enumerate the deadlines and minimum requirements applicable to this process, including provisions that provide instruction on chemical substances that must undergo evaluation, the minimum components of a TSCA risk evaluation, and the timelines for public comment and completion of the risk evaluation. TSCA also requires that EPA operate in a manner that is consistent with the best available science, make decisions based on the weight of the scientific evidence and consider the reasonably available information. 15 U.S.C. 2625(h), (i), and (k). TSCA section 6(i) directs that a determination of "no unreasonable risk" shall be issued by order and considered to be a final Agency action, while a determination of "unreasonable risk" is not considered to be a final Agency action. 15 U.S.C. 2605(i).

The statute identifies the minimum components for all chemical substance risk evaluations. For each risk evaluation, EPA must publish a document that outlines the scope of the risk evaluation to be conducted, which includes the hazards, exposures, conditions of use, and the potentially exposed or susceptible subpopulations that EPA expects to consider. 15 U.S.C. 2605(b)(4)(D). The statute further provides that each risk evaluation must also: (1) Integrate and assess available information on hazards and exposures for the conditions of use of the chemical substance, including information that is relevant to specific risks of injury to health or the environment and information on relevant potentially exposed or susceptible subpopulations; (2) describe whether aggregate or sentinel exposures were considered and the basis for that consideration; (3) take into account, where relevant, the likely duration, intensity, frequency, and number of exposures under the conditions of use; and (4) describe the weight of the scientific evidence for the identified hazards and exposures. 15 U.S.C. 2605(b)(4)(F)(i) through (ii) and (iv) through (v). Each risk evaluation

must not consider costs or other nonrisk factors. 15 U.S.C. 2605(b)(4)(F)(iii).

The statute requires that the risk evaluation process be completed within a specified timeframe and provide an opportunity for public comment on a draft risk evaluation prior to publishing a final risk evaluation. 15 U.S.C. 2605(b)(4).

Subsection 5.4.1 of the final risk evaluation for 1, 4-dioxane constitutes the order required under TSCA section 6(i)(1), and the “no unreasonable risk” determinations in that subsection are considered to be a final Agency action effective on the date of issuance of the order. In conducting risk evaluations, “EPA will determine whether the chemical substance presents an unreasonable risk of injury to health or the environment under each condition of use within the scope of the risk evaluation . . . .” 40 CFR 702.47. Under EPA’s implementing regulations, “[a] determination by EPA that the chemical substance, under one or more of the conditions of use within the scope of the risk evaluation, does not present an unreasonable risk of injury to health or the environment will be issued by order and considered to be a final Agency action, effective on the date of issuance of the order.” 40 CFR 702.49(d). For purposes of TSCA section 19(a)(1)(A), the date of issuance of the TSCA section 6(i)(1) order for 1, 4-dioxane shall be at 1:00 p.m. Eastern time (standard or daylight, as appropriate) on the date that is two weeks after the date when this notice is published in the **Federal Register**, which is in accordance with 40 CFR 23.5.

#### C. What action is EPA taking?

EPA is announcing the availability of the risk evaluation of the chemical substance identified in Unit II. In this risk evaluation, EPA has made unreasonable risk determinations on some of the conditions of use within the scope of the risk evaluation for this chemical. For those conditions of use for which EPA has found an unreasonable risk of injury to health or the environment, EPA must initiate regulatory action to address those risks through risk management measures enumerated in 15 U.S.C. 2605(a).

EPA also is announcing the availability of the information required to be provided publicly with each risk evaluation, which is available online at <http://www.regulations.gov> in the dockets identified. 40 CFR 702.51. Specifically, EPA has provided:

- The scope document and problem formulation (in Docket ID No. EPA-HQ-OPPT-2016-0723);

- Draft risk evaluation, supplemental analysis to the draft risk evaluation, and final risk evaluation (in Docket ID No. EPA-HQ-OPPT-2019-0238);

- All notices, determinations, findings, consent agreements, and orders (in Docket ID No. EPA-HQ-OPPT-2019-0238);

- Any information required to be provided to the Agency under 15 U.S.C. 2603 (in Docket ID No. EPA-HQ-OPPT-2016-0723 and Docket ID No. EPA-HQ-OPPT-2019-0238);

- A nontechnical summary of the risk evaluation (in Docket ID No. EPA-HQ-OPPT-2019-0238);

- A list of the studies, with the results of the studies, considered in carrying out each risk evaluation (Risk Evaluation for 1, 4-dioxane) in Docket ID No. EPA-HQ-OPPT-2019-0238);

- The final peer review report, including the response to peer review and public comments received during peer review (in Docket ID No. EPA-HQ-OPPT-2019-0238); and

- Response to public comments received on the draft scope, the draft risk evaluation and the supplemental analysis to the draft risk evaluation (in Docket ID No. EPA-HQ-OPPT-2019-0238).

## II. TSCA Risk Evaluation

### A. What is EPA’s risk evaluation process for existing chemicals under TSCA?

The risk evaluation process is the second step in EPA’s existing chemical review process under TSCA, following prioritization and before risk management. As this chemical is one of the first ten chemical substances undergoing risk evaluation, the chemical substance was not required to go through prioritization (81 FR 91927, December 19, 2016) (FRL-9956-47). The purpose of conducting risk evaluations is to determine whether a chemical substance presents an unreasonable risk of injury to health or the environment under the conditions of use, including an unreasonable risk to a relevant potentially exposed or susceptible subpopulation. As part of this process, EPA must evaluate both hazard and exposure, not consider costs or other nonrisk factors, use reasonably available information and approaches in a manner that is consistent with the requirements in TSCA for the use of the best available science, and ensure decisions are based on the weight of the scientific evidence.

The specific risk evaluation process that EPA has established by rule to implement the statutory process is set out in 40 CFR part 702 and summarized on EPA’s website at <http://>

[www.epa.gov/assessing-and-managing-chemicals-under-tsca/risk-evaluations-existing-chemicals-under-tsca](http://www.epa.gov/assessing-and-managing-chemicals-under-tsca/risk-evaluations-existing-chemicals-under-tsca). As explained in the preamble to EPA’s final rule on procedures for risk evaluation (82 FR 33726, July 20, 2017) (FRL-9964-38), the specific regulatory process set out in 40 CFR part 702, subpart B is being followed for the first ten chemical substances undergoing risk evaluation to the maximum extent practicable.

Prior to the publication of this final risk evaluation, a draft risk evaluation was subject to peer review and public comment and a supplemental analysis to the draft risk evaluation was subject to public comment. EPA reviewed the report from the peer review committee and public comments and has amended the risk evaluation in response to these comments as appropriate. The public comments, peer review report, and EPA’s response to comments is in Docket ID No. EPA-HQ-OPPT-2019-0238. Prior to the publication of the draft risk evaluation, EPA made available the scope and problem formulation, and solicited public input on uses and exposure. EPA’s documents and the public comments are in Docket ID No. EPA-HQ-OPPT-2016-0723. Additionally, information about the scope, problem formulation, and draft risk evaluation phases of the TSCA risk evaluation for this chemical is available at EPA’s website at <https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/risk-evaluation-14-dioxane>.

### B. What is 1, 4-dioxane?

1,4-dioxane is used primarily as a solvent in a variety of commercial and industrial applications like in the manufacture of other chemicals, as a processing aid, a laboratory chemical, and in adhesives and sealants. 2016 CDR data shows that there were two manufacturers producing or importing 1,059,980 pounds of 1,4-dioxane in the U.S. in 2015.

**Authority:** 15 U.S.C. 2601 *et seq.*

**Andrew Wheeler,**  
Administrator.

[FR Doc. 2021-00114 Filed 1-7-21; 8:45 am]

**BILLING CODE 6560-50-P**

**CERTIFICATE OF SERVICE**

I hereby certify that on March 22, 2021, I electronically filed the foregoing Petition for Review with the Clerk of the Court for the United States Court of Appeals for the Ninth Circuit using the Appellate Electronic Filing system.

I further certify that on March 22, 2021, the foregoing Petition for Review will be sent via email and first-class mail to the following counsel for the

Respondents:

Joseph E. Cole, Associate General Counsel  
Pesticides and Toxic Substances Law Office  
Office of General Counsel  
U.S. Environmental Protection Agency  
1200 Pennsylvania Avenue, N.W.  
Mail Code: 2333A  
Washington, DC 20460  
cole.josephe@epa.gov

*/s/ Sarah K. Kam*  
Sarah K. Kam