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Problem Formulation of the Risk Evaluation for 1,4-Dioxane

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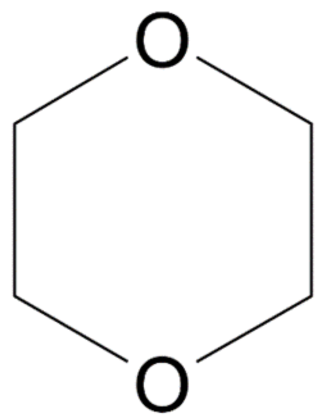

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Docket

Supporting information can be found in public docket: EPA-HQ-OPPT-2016-0723.

Disclaimer

ABBREVIATIONS

°C	Degrees Celsius
AAL	Allowable Ambient Level
ACGIH	American Conference of Government Industrial Hygienists
AEGL	Acute Exposure Guideline Level
AES	Alkyl Ethyl Sulphates
AMA	Ambient Monitoring Archive
AQS	Air Quality System
atm	Atmosphere(s)
ATSDR	Agency for Toxic Substances and Disease Registries
BAF	Bioaccumulation Factor
BCF	Bioconcentration Factor
BSER	Best System of Emission Reduction
CAA	Clean Air Act
CASRN	Chemical Abstracts Service Registry Number
CBI	Confidential Business Information
CCL	Candidate Contaminant List
CDR	Chemical Data Reporting
CERCLA	Comprehensive Environmental Response, Compensation and Liability Act
cm^3	Cubic Centimeter(s)
COC	Concentration of Concern
COU	Conditions of Use
cP	Centipoise
CPCat	Chemical and Product Categories
CSCL	Chemical Substances Control Law
EC	European Commission
EPA	Environmental Protection Agency
EPCRA	Emergency Planning and Community Right-to-Know Act
EU	European Union
FDA	Food and Drug Administration
FFDCA	Federal Food, Drug and Cosmetic Act
g	Gram(s)
GACT	Generally Available Control Technology
HAP	Hazardous Air Pollutant
HHE	Health Hazard Evaluation
HPV	High Production Volume
IARC	International Agency for Research on Cancer
IRIS	Integrated Risk Information System
ISHA	Industrial Safety and Health Act
kg	Kilogram(s)
kPa	Kilopascal(s)
L	Liter(s)
lb	Pound
Log K_{oc}	Logarithmic Soil Organic Carbon:Water Partitioning Coefficient
Log K_{ow}	Logarithmic Octanol:Water Partition Coefficient
m^3	Cubic Meter(s)
MACT	Maximum Achievable Control Technology
mg	Milligram(s)

µg	Microgram(s)
mmHg	Millimeter(s) of Mercury
MSDS	Material Safety Data Sheet
NAC	National Advisory Committee
NAICS	North American Industry Classification System
NATA	National Air Toxics Assessment
NCEA	National Center for Environmental Assessment
NEI	National Emissions Inventory
NESHAP	National Emission Standards for Hazardous Air Pollutants
NICNAS	National Industrial Chemicals Notification and Assessment Scheme
NIH	National Institute of Health
NIOSH	National Institute of Occupational Safety and Health
NOAEL	No-Observed-Adverse-Effect Level
NPRI	National Pollutant Release Inventory
NSPS	New Source Performance Standards
NTP	National Toxicology Program
OCSPP	Office of Chemical Safety and Pollution Prevention
OECD	Organisation for Economic Co-operation and Development
ONU	Occupational Non-User
OPPT	Office of Pollution Prevention and Toxics
OSHA	Occupational Safety and Health Administration
PBPK	Physiologically Based Pharmacokinetic
PEL	Permissible Exposure Limit
PESS	Potentially Exposed or Susceptible Subpopulations
PET	Polyethylene Terephthalate
POD	Point of Departure
POTW	Publicly Owned Treatment Works
ppm	Part(s) per Million
PWS	Public Water System
RCRA	Resource Conservation and Recovery Act
REL	Recommended Exposure Level
SDS	Safety Data Sheet
SDWA	Safe Drinking Water Act
SIDS	Screening Information Data Set
TCA	1,1,1-Trichloroethane
TCCR	Transparent, Clear, Consistent and Reasonable
TLV	Threshold Limit Value
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	Time-Weighted Average
UCMR	Unregulated Contaminant Monitoring Rule
U.S.	United States
UV	Ultraviolet
VCCEP	Voluntary Children’s Chemical Evaluation Program
VOC	Volatile Organic Compound
WHO	World Health Organisation

EXECUTIVE SUMMARY

TSCA § 6(b)(4) requires the United States Environmental Protection Agency (U.S. EPA) to establish a risk evaluation process. In performing risk evaluations for existing chemicals, EPA is directed to "determine whether a chemical substance presents an unreasonable risk of injury to health or the environment, without consideration of costs 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." In December of 2016, EPA published a list of 10 chemical substances that are the subject of the Agency's initial chemical risk evaluations (81 FR 91927), as required by TSCA § 6(b)(2)(A). 1,4-Dioxane was one of these chemicals.

TSCA § 6(b)(4)(D) requires that EPA publish the scope of the risk evaluation to be conducted, including the hazards, exposures, conditions of use and potentially exposed or susceptible subpopulations that the Administrator expects to consider. In June 2017, EPA published the Scope of the Risk Evaluation for 1,4-Dioxane. As explained in the scope document, because there was insufficient time for EPA to provide an opportunity for comment on a draft of the scope, as EPA intends to do for future scope documents, EPA is publishing and taking public comment on a problem formulation document to refine the current scope, as an additional interim step prior to publication of the draft risk evaluation for 1,4-dioxane. Comments received on this problem formulation document will inform development of the draft risk evaluation.

This problem formulation document refines the conditions of use, exposures and hazards presented in the scope of the risk evaluation for 1,4-dioxane and presents refined conceptual models and analysis plans that describe how EPA expects to evaluate the risk for 1,4-dioxane.

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 a reportable 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 listed as a waste 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).

Information on domestic manufacture, processing and use of 1,4-dioxane is available to EPA through its Chemical Data Reporting (CDR) Rule, issued under TSCA. In 2016, approximately 1 million pounds per year was reported to be manufactured in the U.S. (U.S. EPA, 2016c). 1,4-Dioxane is currently used in industrial processes and for industrial and commercial uses. Industrial processing uses include use as a processing aid and in functional fluids in open and closed systems. 1,4-Dioxane has uses as a laboratory chemical reagent, in adhesives and sealants and several other identified uses. Historically, 90% of 1,4-dioxane produced was used as a stabilizer in chlorinated solvents such as 1,1,1-trichloroethane (TCA). Use of 1,4-dioxane has decreased since TCA was phased out by the Montreal Protocol in 1996.

The most recent data on environmental releases, according to the Toxics Release Inventory (TRI), indicate that approximately 675,000 pounds of 1,4-dioxane were released to the environment in 2015 (U.S. EPA, 2017d). Releases are reported to all types of environmental media: air, water and land. The environmental fate of 1,4-dioxane is characterized by partitioning to the atmosphere, surface water and groundwater, and degradation by atmospheric oxidation or biodegradation. It is expected to be moderately persistent in the environment and has a low bioaccumulation potential.

This document presents the potential exposures that may result from the conditions of use of 1,4-dioxane. Workers and occupational non-users may be exposed to 1,4-dioxane during industrial and commercial conditions of use such as manufacturing, processing, distribution, use and disposal. EPA plans to further analyze inhalation exposures to vapors and mists for workers and occupational non-users and dermal exposures for skin contact with liquids in occluded situations for workers in the risk evaluation. For environmental release pathways, EPA plans to include surface water exposure to aquatic vertebrates, invertebrates and aquatic plants, exposure to sediment organisms and exposure to 1,4-dioxane in land-applied biosolids in the risk evaluation.

1,4-Dioxane has been the subject of numerous human health reviews including EPA's Integrated Risk Information System (IRIS) Toxicological Review, Agency for Toxic Substances and Disease Registry's (ATSDR's) Toxicological Profile, Health Canada Screening Assessment, and Interim Acute Exposure Guideline Levels (AEGL). Many targets of toxicity from exposures to 1,4-dioxane have been identified in animal and human studies for both oral and inhalation exposures. EPA plans to evaluate all potential hazards for 1,4-dioxane, including any found in recent literature. Hazard endpoints identified in previous assessments include acute toxicity, non-cancer effects and cancer. Non-cancer effects include irritation of the eyes and respiratory tract, liver toxicity and kidney toxicity. Animals exposed to 1,4-dioxane by inhalation and oral exposure have also developed multiple types of cancer. If additional hazard concerns are identified during the systematic review of the literature, these will also be considered. These hazards will be evaluated based on the specific exposure scenarios identified.

The revised conceptual models presented in this problem formulation identify conditions of use; exposure pathways (e.g., media); exposure routes (e.g., inhalation, dermal, oral); potentially exposed or susceptible subpopulations; and hazards EPA expects to further analyze in the risk evaluation. The initial conceptual models provided in the scope document (U.S. EPA, 2017c) were revised during problem formulation based on evaluation of reasonably available information for physical and chemical properties, fate, exposures and hazards to indicate conditions of use, exposure pathways, exposure routes, and hazards, conditions of use and consideration of other statutory and regulatory authorities. In each problem formulation document for the first 10 chemical substances, EPA also refined the activities, hazards and exposure pathways that will be included in and excluded from the risk evaluation.

EPA's overall objectives in the risk evaluation process are to conduct timely, relevant, high-quality, and scientifically credible risk evaluations within the statutory deadlines, and to evaluate the conditions of use that raise greatest potential for risk 82 FR 33726, 33728 (July 20, 2017).

1 INTRODUCTION

This document presents for comment the problem formulation of the risk evaluation to be conducted 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 (TSCA), the Nation's primary chemicals management law, on June 22, 2016. The new law includes statutory requirements and deadlines for actions related to conducting risk evaluations of existing chemicals.

In December of 2016, EPA published a list of 10 chemical substances that are the subject of the Agency's initial chemical risk evaluations (81 FR 91927), as required by TSCA § 6(b)(2)(A). These 10 chemical substances were drawn from the 2014 update of EPA's TSCA Work Plan for Chemical Assessments, a list of chemicals that EPA identified in 2012 and updated in 2014 (currently totaling 90 chemicals) for further assessment under TSCA. EPA's designation of the first 10 chemical substances constituted the initiation of the risk evaluation process for each of these chemical substances, pursuant to the requirements of TSCA § 6(b)(4).

TSCA § 6(b)(4)(D) requires that EPA publish the scope of the risk evaluation to be conducted, including the hazards, exposures, conditions of use and potentially exposed or susceptible subpopulations that the Administrator expects to consider, within 6 months after the initiation of a risk evaluation. The scope documents for all first 10 chemical substances were issued on June 22, 2017. The first 10 problem formulation documents are a refinement of what was presented in the first 10 scope documents. TSCA § 6(b)(4)(D) does not distinguish between scoping and problem formulation, and requires EPA to issue scope documents that include information about the chemical substance, such as the hazards, exposures, conditions of use, and the potentially exposed or susceptible subpopulations that the Administrator expects to consider in the risk evaluation. In the future, EPA expects scoping and problem formulation to be completed prior to the issuance of scope documents and intends to issue scope documents that include problem formulation.

As explained in the scope document, because there was insufficient time for EPA to provide an opportunity for comment on a draft of the scope, as EPA intends to do for future scope documents, EPA is publishing and taking public comment on a problem formulation document to refine the current scope, as an additional interim step prior to publication of the draft risk evaluation for 1,4-dioxane. Comments received on this problem formulation document will inform development of the draft risk evaluation.

The Agency defines problem formulation as the analytical phase of the risk assessment in which "the purpose for the assessment is articulated, the problem is defined, and a plan for analyzing and characterizing risk is determined" (see section 2.2 of the *Framework for Human Health Risk Assessment to Inform Decision Making*, (U.S. EPA, 2014c). The outcome of problem formulation is a conceptual model(s) and an analysis plan. The conceptual model describes the linkages between stressors and adverse human health effects, including the stressor(s), exposure pathway(s), exposed life stage(s) and population(s), and endpoint(s) that will be addressed in the risk evaluation (U.S. EPA, 2014c). The analysis plan follows the development of the conceptual model(s) and is intended to describe the approach for conducting the risk evaluation, including its design, methods and key inputs and intended outputs as described in the EPA *Human Health Risk Assessment Framework* (U.S. EPA, 2014c). The problem formulation documents refine the initial conceptual models and analysis plans that were provided in the scope documents.

First, EPA has removed from the risk evaluation any activities and exposure pathways that EPA has concluded do not warrant inclusion in the risk evaluation. For example, for some activities that were listed as "conditions of use" in the scope document, EPA has insufficient information following the further investigations during problem formulation to find they are circumstances under which the chemical is actually "intended, known, or reasonably foreseen to be manufactured, processed, distributed in commerce, used, or disposed of."

Second, EPA also identified certain exposure pathways that are under the jurisdiction of regulatory programs and associated analytical processes carried out under other EPA-administered environmental statutes – namely, the Clean Air Act (CAA), the Safe Drinking Water Act (SDWA), the Clean Water Act (CWA), and the Resource Conservation and Recovery Act (RCRA) – and which EPA does not expect to include in the risk evaluation.

As a general matter, EPA believes that certain programs under other Federal environmental laws adequately assess and effectively manage the risks for the covered exposure pathways. To use Agency resources efficiently under the TSCA program, to avoid duplicating efforts taken pursuant to other Agency programs, to maximize scientific and analytical efforts, and to meet the three-year statutory deadline, EPA is planning to exercise its discretion under TSCA 6(b)(4)(D) to focus its analytical efforts on exposures that are likely to 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.[1] EPA does not expect to include any such excluded pathways in the risk evaluation as further explained below. The provisions of various EPA-administered environmental statutes and their implementing regulations represent the judgment of Congress and the Administrator, respectively, as to the degree of health and environmental risk reduction that is sufficient under the various environmental statutes.

Third, EPA identified any conditions of use, hazards, or exposure pathways which were included in the scope document and that EPA expects to include in the risk evaluation but which EPA does not expect to further analyze in the risk evaluation. EPA expects to be able to reach conclusions about particular conditions of use, hazards or exposure pathways without further analysis and therefore plans to conduct no further analysis on those conditions of use, hazards or exposure pathways in order to focus the Agency's resources on more extensive or quantitative analyses. Each risk evaluation will be "fit-for-purpose," meaning not all conditions of use will warrant the same level of evaluation and the Agency may be able to reach some conclusions without comprehensive or quantitative risk evaluations. 82 FR 33726, 33734, 33739 (July 20, 2017).

EPA received comments on the published scope document for 1,4-dioxane and has considered the comments specific to 1,4-dioxane in this problem formulation document. EPA is soliciting public comments on this problem formulation document and when the draft risk evaluation is issued the Agency intends to respond to comments that are submitted. In its draft risk evaluation, EPA may revise the conclusions and approaches contained in this problem formulation, including the conditions of use and pathways covered and the conceptual models and analysis plans, based on comments received.

[1]As explained in the final rule for chemical risk evaluation procedures, "EPA may, on a case-by case basis, exclude certain activities that EPA has determined to be conditions of use in order to focus its analytical efforts on those exposures that are likely to present the greatest concern, and consequently merit an unreasonable risk determination." [82 FR 33726, 33729 (July 20, 2017)].

1.1 Regulatory 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. As noted in public comments to the scope document, the NESHAP for Rubber Manufacturing does not apply to 1,4-dioxane and has been removed from Table_Apx A-1. EPA evaluated and considered the impact of existing laws and regulations in the problem formulation step to determine what, if any further analysis might be necessary as part of the risk evaluation. Consideration of the nexus between these existing regulations and TSCA uses may additionally be made as detailed/specific conditions of use and exposure scenarios are developed in conducting the analysis phase of the risk evaluation.

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 implemented by state agencies or departments. 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.

1.2 Assessment History

EPA has identified assessments conducted by other EPA Programs and other organizations (see Table 1-1). Depending on the source, these assessments may include information on conditions of use, hazards, exposures and potentially exposed or susceptible subpopulations. Table 1-1 shows the assessments that have been conducted. EPA found no additional assessments beyond those listed in the Scope document.

In addition to using this information, EPA intends to conduct a full review of the relevant data/information collected in the initial comprehensive search (see *1,4-Dioxane (CASRN 123-91-1) Bibliography: Supplemental File for the TSCA Scope Document*, EPA-HQ-OPPT-2016-0723) following the literature search and screening strategies documented in the *Strategy for Conducting Literature Searches for 1,4-Dioxane: Supplemental File for the TSCA Scope Document*, EPA-HQ-OPPT-2016-0723. This will ensure that EPA considers data/information that has been made available since these assessments were conducted.

Table 1-1. 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) (2015c)
EPA, National Center for Environmental Assessment (NCEA)	Toxicological Review of 1,4-Dioxane (With Inhalation Update) (CASRN 123-91-1) (2013c)
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)
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)

Authoring Organization	Assessment
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)

1.3 Data and Information Collection

EPA/OPPT generally applies a systematic review process and workflow that includes: (1) data collection, (2) data evaluation and (3) data integration of the scientific data used in risk evaluations developed under TSCA. Scientific analysis is often iterative in nature as new knowledge is obtained. Hence, EPA/OPPT expects that multiple refinements regarding data collection may occur during the process of risk evaluation.

Data Collection: Data Search

EPA/OPPT conducted chemical-specific searches for data and information on: physical and chemical properties; environmental fate and transport; conditions of use information; environmental exposures, human exposures, including potentially exposed or susceptible subpopulations; ecological hazard, human health hazard, including potentially exposed or susceptible subpopulations.

EPA/OPPT designed its initial data search to be broad enough to capture a comprehensive set of sources containing data and/or information potentially relevant to the risk evaluation. Generally, the search was not limited by date and was conducted on a wide range of data sources, including but not limited to: peer-reviewed literature and gray literature (e.g., publicly-available industry reports, trade association resources, government reports). For human health hazard, EPA/OPPT relied on the search strategies from recent assessments, such as EPA Integrated Risk Information System (IRIS) assessments and the NTP *Report on Carcinogens*, to identify relevant information published after the end date of the previous search to capture more recent literature. The *Strategy for Conducting Literature Searches for 1,4-Dioxane: Supplemental File for the TSCA Scope Document* (EPA-HQ-OPPT-2016-0723) provides details about the data and information sources and search terms that were used in the literature search.

Data Collection: Data Screening

Following the data search, references were screened and categorized using selection criteria outlined in the *Strategy for Conducting Literature Searches for 1,4-Dioxane: Supplemental File for the TSCA Scope Document* (EPA-HQ-OPPT-2016-0723). Titles and abstracts were screened against the criteria as a first step with the goal of identifying a smaller subset of the relevant data to move into the subsequent data extraction and data evaluation steps. Prior to full-text review, EPA/OPPT anticipates refinements to the search and screening strategies, as informed by an evaluation of the performance of the initial title/abstract screening and categorization process.

The categorization scheme (or tagging structure) used for data screening varies by scientific discipline (i.e., physical and chemical properties; environmental fate and transport; chemical use/conditions of use information; environmental exposures, human exposures, including potentially exposed or susceptible subpopulations identified by virtue of greater exposure; human health hazard, including potentially exposed or susceptible subpopulations identified by virtue of greater susceptibility; and ecological hazard). However, within each data set, there are two broad categories or data tags: (1) o*n-topic* references or (2) *off-topic* references. *On-topic* references are those that may contain data and/or information relevant to the risk evaluation. O*ff-topic* references are those that do not appear to contain data or information relevant to the risk evaluation. The supplemental document, *Strategy for Conducting Literature Searches for 1,4-Dioxane: Supplemental File for the TSCA Scope Document* (EPA-HQ-OPPT-2016-0723) discusses the inclusion and exclusion criteria that EPA/OPPT used to categorize references as *on-topic* or *off-topic*.

Additional data screening using sub-categories (or sub-tags) was also performed to facilitate further sorting of data/information. For example, identifying references by source type (e.g., published peer-reviewed journal article, government report); data type (e.g., primary data, review article); human health hazard (e.g., liver toxicity, cancer, reproductive toxicity); or chemical-specific and use-specific data or information. These sub-categories are described in the supplemental document, *Strategy for Conducting Literature Searches for 1,4-Dioxane: Supplemental File for the TSCA Scope Document* (EPA-HQ-OPPT-2016-0723) and will be used to organize the different streams of data during the stages of data evaluation and data integration steps of systematic review.

Results of the initial search and categorization can be found in the *1,4-Dioxane* (*CASRN 123-91-1) Bibliography: Supplemental File for the TSCA Scope Document* (EPA-HQ-OPPT-2016-0723). This document provides a comprehensive list (bibliography) of the sources of data identified by the initial search and the initial categorization for *on-topic* and *off-topic* references. Because systematic review is an iterative process, EPA/OPPT expects that some references may move from the *on-topic* to the *off-topic* categories, and vice versa. Moreover, targeted supplemental searches may also be conducted to address specific needs for the analysis phase (e.g., to locate specific data needed for modeling); hence, additional *on-topic* references not initially identified in the initial search may be identified as the systematic review process proceeds.

1.4 Data Screening During Problem Formulation

EPA/OPPT is in the process of completing the full text screening of the on-topic references identified in the *1,4-Dioxane* (*CASRN 123-91-1) Bibliography: Supplemental File for the TSCA Scope Document* (EPA-HQ-OPPT-2016-0723). The screening process at the full-text level is described in the *Application of Systematic Review in TSCA Risk Evaluations* (U.S. EPA, 2018a). Appendix F provides the inclusion and exclusion criteria applied at the full text screening. The eligibility criteria are guided by the analytical considerations in the revised conceptual models and analysis plan, as discussed in the problem formulation document. Thus, it is expected that the number of data/information sources entering evaluation is reduced to those that are relevant to address the technical approach and issues described in the analysis plan of this document. Following the screening process, the quality of the included data/information sources will be assessed using the evaluation strategies that are described in the *Application of Systematic Review in TSCA Risk Evaluations* (U.S. EPA, 2018a).

2 PROBLEM FORMULATION

As required by TSCA, the scope of the risk evaluation identifies the conditions of use, hazards, exposures and potentially exposed or susceptible subpopulations that the Administrator expects to consider. To communicate and visually convey the relationships between these components, EPA included in the scope document a life cycle diagram and conceptual models that describe the actual or potential relationships between 1,4-dioxane and human and ecological receptors. During the problem formulation, EPA revised the conceptual models based on further data gathering and analysis as presented in this Problem Formulation document. An updated analysis plan is also included which identifies, to the extent feasible, the approaches and methods that EPA may use to assess exposures, effects (hazards) and risks under the conditions of use of 1,4-dioxane.

2.1 Physical and Chemical Properties

Physical-chemical properties influence the environmental behavior and the toxic properties of a chemical, thereby informing the potential conditions of use, exposure pathways and routes and hazards that EPA intends to consider. For scope development, EPA considered the measured or estimated physical-chemical properties set forth in Table 2-1 and EPA found no additional information during problem formulation that would change these values.

Table 2-1. Physical and Chemical Properties of 1,4-Dioxane

Property	Value [a]	References
Molecular formula	$C_4H_8O_2$	
Molecular weight	88.1 g/mole	(Howard, 1990)
Physical form	Clear liquid	(O'Neil et al., 2001)
Melting point	11.75°C	(Haynes, 2014)
Boiling point	101.1°C	(O'Neil et al., 2006)
Density	1.0329 g/cm^3	(O'Neil et al., 2006)
Vapor pressure	40 mm Hg at 25°C	(Lewis, 2000)
Vapor density	Not readily available	
Water solubility	>8.00 × 10^2 g/L	(Yalkowsky et al., 2010)
Octanol:water partition	-0.27 (estimated)	(Hansch et al., 1995)
Henry's Law constant	4.8 × 10^{-6} atm-m^3/mole at 25°C	(Sander, 2017); (Howard, 1990); (Atkins, 1986)
Flash point	18.3°C (open cup)	(Lewis, 2012)
Autoflammability	Not readily available	
Viscosity	0.0120 cP at 25°C	(O'Neil, 2013)
Refractive index	1.4224 at 20°C	(Haynes, 2014)
Dielectric constant	2.209	(Bruno and Svoronos, 2006)
[a] Measured unless otherwise noted		

2.2 Conditions of Use

TSCA § 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."

2.2.1 Data and Information Sources

In the scope documents, EPA identified, based on reasonably available information, the conditions of use for the subject chemicals. As further described in this document, EPA searched a number of available data sources (e.g. *Use and Market Profile for 1,4-Dioxane*, (EPA-HQ-OPPT-2016-0723). Based on this search, EPA published a preliminary list of information and sources related to chemical conditions of use (see *Preliminary Information on Manufacturing, Processing, Distribution, Use, and Disposal: 1,4-Dioxane*, EPA-HQ-OPPT-2017-0723-0003) prior to a February 2017 public meeting on scoping efforts for risk evaluations convened to solicit comment and input from the public. EPA also convened meetings with companies, industry groups, chemical users and other stakeholders to aid in identifying conditions of use and verifying conditions of use identified by EPA. The information and input received from the public and stakeholder meetings has been incorporated into this problem formulation document to the extent appropriate. Thus, EPA believes the identified manufacture, processing, distribution, use and disposal activities constitute the intended, known, and reasonably foreseeable activities associated with the subject chemical, based on reasonably available information.

2.2.2 Identification of Conditions of Use

To determine the current conditions of use of 1,4-dioxane and inversely, conditions of use that are no longer ongoing, EPA conducted extensive research and outreach. This included EPA's review of published literature and online databases including the most recent data available from EPA's Chemical Data Reporting program (CDR) and Safety Data Sheets (SDSs). EPA also conducted online research by reviewing company websites of potential manufacturers, importers, distributors, retailers, or other users of 1,4-dioxane and queried government and commercial trade databases. EPA also received comments on the Scope of the Risk Evaluation for 1,4-Dioxane (EPA-HQ-OPPT-2016-0723) that were used to determine the current conditions of use. In addition, EPA convened meetings with companies, industry groups, chemical users, states, environmental groups, and other stakeholders to aid in identifying conditions of use and verifying conditions of use identified by EPA. Those meetings included a February 14, 2017 public meeting with such entities and a September 15, 2017 meeting with several representatives from trade associations.

EPA has removed from the risk evaluation activities that EPA concluded do not constitute conditions of use – for example because EPA has insufficient information to find certain activities are circumstances under which the chemical is actually "intended, known, or reasonably foreseen to be manufactured, processed, distributed in commerce, used or disposed of." EPA has also identified any conditions of use that EPA does not plan to include in the risk evaluation. As explained in the final rule for Procedures for Chemical Risk Evaluation Under the Amended Toxic Substances Control Act, TSCA section 6(b)(4)(D) requires EPA to identify "the hazards, exposures, conditions of use and the potentially exposed or susceptible subpopulations that the Agency expects to consider in a risk evaluation," suggesting that EPA may exclude certain activities that EPA has determined to be conditions of use on a case-by-case basis (82 FR 33736, 33729; July 20, 2017). For example, EPA may exclude conditions of use that the Agency has sufficient basis to conclude would present only de minimis exposures or otherwise insignificant risks (such as use in a closed system that effectively precludes exposure or as an intermediate).

The activities that EPA no longer believes are conditions of use or were otherwise excluded during problem formulation are described in Section 2.2.2.1. The conditions of use included in the scope of the risk evaluation are summarized in Section 2.2.2.2.

2.2.2.1 Categories and Subcategories Determined Not to be Conditions of Use During Problem Formulation

For 1,4-dioxane, EPA has reviewed reasonably available information about 1,4-dioxane conditions of use. EPA did not find evidence of any current consumer uses (U.S. EPA, 2016c) for 1,4-dioxane and is excluding consumer uses from the scope of the risk evaluation as explained in the Scope document (U.S. EPA, 2017c). As described in the Scope, contamination of industrial, commercial and consumer products are not intended conditions of use for 1,4-dioxane and will not be evaluated. For fuels and fuel additives (Other uses category), EPA contacted several racing authorities that indicated that their organizations banned the use of dioxane in competitions. The organizations also could not provide credible information on whether or how often dioxane was used prior to their bans nor whether it is currently used at all. Based on the lack of information confirming that 1,4-dioxane is currently used as a fuel or fuel additive and the fact that racing authorities have prohibited this use, use in fuels and fuel additives is not a condition of use under which EPA will evaluate 1,4-dioxane.

Table 2-2. Categories and Subcategories Determined Not to Be Conditions of Use During Problem Formulation

Life Cycle Stage	Category	Subcategory	References
Industrial use, potential commercial use	Other Uses	Fuels and fuel additives	Use document, EPA-HQ-OPPT-2016-0723-0003

2.2.2.2 Categories and Subcategories of Conditions of Use Included in the Scope of the Risk Evaluation

For 1,4-dioxane, EPA has conducted public outreach and literature searches to collect information about conditions of use and has reviewed reasonably available information obtained or possessed by EPA concerning activities associated with 1,4-dioxane.

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). Industrial processing uses included in the scope include processing as a reactant or intermediate, non-incorporative processing, repackaging and recycling. Uses include processing aids (not otherwise listed), functional fluids in open and closed systems, laboratory chemicals, adhesives and sealants, other uses (spray polyurethane foam, printing and printing compositions) and disposal. Note that during problem formulation, EPA determined that some subcategories, such as cutting and tapping fluid, may also be used in open systems and is including these uses. Activities related to distribution (e.g., loading, unloading) will be considered throughout the 1,4-dioxane life cycle, rather than as a single distribution scenario. Also included in the scope are 1,4-dioxane use as a laboratory chemical reagent and use in adhesives and sealants in industrial and/or commercial settings and use in laboratory reference materials or standards containing 1,4-dioxane. Searches identified two products with greater than 5% of 1,4-dioxane that are included: a professional film cement and a chemiluminescent laboratory reagent. Other uses included are spray polyurethane foam; and printing and printing compositions.

Table 2-3 summarizes each life cycle stage and the corresponding categories and subcategories of conditions of use for 1,4-dioxane that EPA is including in the scope of the risk evaluation. Using the 2016 CDR (U.S. EPA, 2016c), EPA identified industrial processing or use activities, industrial function categories and commercial use product categories. EPA identified the subcategories by supplementing CDR data with other published literature and information obtained through stakeholder consultations. For this risk evaluation, EPA intends to consider each life cycle stage (and corresponding use categories and subcategories) and assess certain relevant potential sources of release and human exposure associated with that life cycle stage.

Beyond the uses identified in the *Scope of the Risk Evaluation for 1,4-Dioxane* (U.S. EPA, 2017c), EPA has received no additional information identifying additional current conditions of use for 1,4-dioxane from public comment and stakeholder meetings.

Table 2-3. 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
Processing	Processing as a reactant	Pharmaceutical intermediate	Use document, EPA-HQ-OPPT-2016-0723-0003
		Polymerization catalyst	Use document, EPA-HQ-OPPT-2016-0723-0003
	Non-incorporative	Pharmaceutical and medicine manufacturing (process solvent)	Public Comment, EPA-HQ-OPPT-2016-0723-0012
		Basic organic chemical manufacturing (process solvent)	Public Comment, EPA-HQ-OPPT-2016-0723-0012
	Repackaging	Bulk to packages, then distribute	Public Comment, EPA-HQ-OPPT-2016-0723-0012
	Recycling	Recycling	(U.S. EPA, 2017d)
Distribution in commerce	Distribution	Distribution	Use document, EPA-HQ-OPPT-2016-0723-0003
Industrial use	Intermediate use	Agricultural chemical intermediate	Use document, EPA-HQ-OPPT-2016-0723-0003
		Plasticizer intermediate	Use document, EPA-HQ-OPPT-2016-0723-0003
		Catalysts and reagents for anhydrous acid reactions,	Use document, EPA-HQ-OPPT-2016-0723-0003

Life Cycle Stage	Category [a]	Subcategory [b]	References
		brominations and sulfonations	
	Processing aids, not otherwise listed	Wood pulping	Use document, EPA-HQ-OPPT-2016-0723-0003
		Extraction of animal and vegetable oils	Use document, EPA-HQ-OPPT-2016-0723-0003
		Wetting and dispersing agent in textile processing	Use document, EPA-HQ-OPPT-2016-0723-0003
		Polymerization catalyst	Use document, EPA-HQ-OPPT-2016-0723-0003
		Purification of pharmaceuticals	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); refer to section 2.5.1 below for details	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
		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

Life Cycle Stage	Category [a]	Subcategory [b]	References
		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	Use document, EPA-HQ-OPPT-2016-0723-0003; Public Comment, EPA-HQ-OPPT-2016-0723-0012
Disposal	Disposal	Industrial pre-treatment	(U.S. EPA, 2017d)
		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 initial life cycle diagram, reflect CDR codes and broadly represent conditions of use for 1,4-dioxane in industrial and/or commercial settings.
[b] These subcategories reflect more specific uses of 1,4-dioxane.

2.2.2.3 Overview of Conditions of Use and Lifecycle Diagram

The life cycle diagram provided in Figure 2-1 depicts the conditions of use that are considered within the scope of the risk evaluation during various life cycle stages including manufacturing, processing, distribution, use (industrial, commercial; when distinguishable) and disposal. Additions or changes to conditions of use based on additional information gathered or analyzed during problem formulation were described in Section 2.2.2.1 and 2.2.2.2. The activities that EPA determined are out of scope during problem formulation are not included in the life cycle diagram. The information is grouped according to Chemical Data Reporting (CDR) processing codes and use categories (including functional use codes for industrial uses and product categories for commercial and consumer uses), in combination with other data sources (e.g., published literature and consultation with stakeholders), to provide an overview of conditions of use. EPA notes that some subcategories may be grouped under multiple CDR categories.

Use categories include the following: "industrial use" means use at a site at which one or more chemicals or mixtures are manufactured (including imported) or processed. "Commercial use" means the use of a chemical or a mixture containing a chemical (including as part of an article) in a commercial enterprise providing saleable goods or services (U.S. EPA, 2016c).

To understand conditions of use relative to one another and associated potential exposures under those conditions of use, the life cycle diagram includes the production volume associated with each stage of the life cycle, as reported in the 2016 CDR reporting (U.S. EPA, 2016c), when the volume was not claimed confidential business information (CBI).

The 2016 CDR reporting data for 1,4-dioxane are provided in Table 2-4 for 1,4-dioxane from EPA's CDR database (U.S. EPA, 2016c). This information has not changed from that provided in the scope document.

Table 2-4. 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). Because of an ongoing CBI substantiation process required by amended TSCA, the CDR data available in the scope document is more specific than currently in ChemView.

According to data collected in EPA's 2016 Chemical Data Reporting (CDR) Rule, over one million pounds of 1,4-dioxane were produced or imported in the U.S. in 2015 (U.S. EPA, 2016c). Data reported indicate that there was one manufacturer of 1,4-dioxane in the U.S. in 2015. The total volume (in lbs) of 1,4-dioxane manufactured (including imported) in the U.S. from 2012 to 2015 indicates that production has varied over that time period. Historically, the main use (90%) of 1,4-dioxane was as a stabilizer of chlorinated solvents such as 1,1,1 trichloroethane (TCA) (ATSDR, 2012). Use of TCA was phased out under the 1995 Montreal Protocol and the use of 1,4-dioxane as a solvent stabilizer was terminated (NTP, 2011; ECJRC, 2002). Lack of recent reports for other previously reported uses (Sapphire Group, 2007) suggest that many other industrial, commercial and consumer uses were also stopped.

Descriptions of the industrial, commercial and consumer use categories identified from the 2016 CDR (U.S. EPA, 2016a) and included in the life cycle diagram . Descriptions in Appendix B contain detailed descriptions (e.g., process descriptions, worker activities, process flow diagrams, equipment illustrations) for each manufacture, processing, distribution, use and disposal category. The descriptions are primarily based on the corresponding industrial function category and/or commercial and consumer product category descriptions from the 2016 CDR and can be found in EPA's *Instructions for Reporting 2016 TSCA Chemical Data Reporting* (U.S. EPA, 2016b).

Figure 2-1 depicts the life cycle diagram of 1,4-dioxane from manufacture to the point of disposal. Activities related to distribution (e.g., loading, unloading) will be considered throughout the 1,4-dioxane life cycle, rather than using a single distribution scenario.

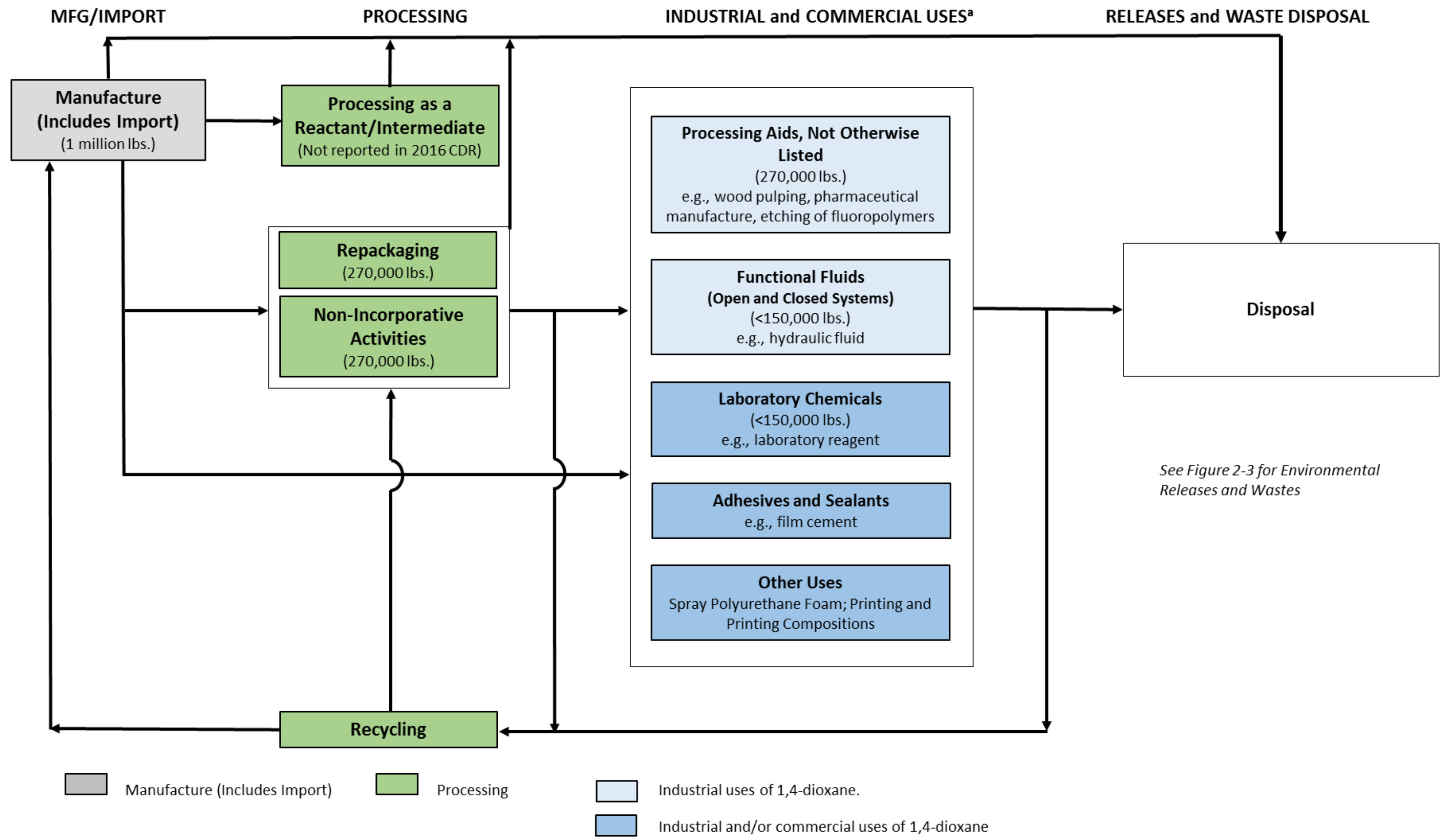

Figure 2-1. 1,4-Dioxane Life Cycle Diagram

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). Activities related to distribution (e.g., loading, unloading) will be considered throughout the 1,4-dioxane life cycle, rather than using a single distribution scenario.

[a] See Table 2-3 for additional uses not mentioned specifically in this diagram.

2.3 Exposures

For TSCA exposure assessments, EPA expects to evaluate exposures and releases to the environment resulting from the conditions of use applicable to 1,4-dioxane. Post-release pathways and routes will be described to characterize the relationship between the conditions of use of 1,4-dioxane and the exposure to human receptors, including potentially exposed or susceptible subpopulations, and ecological receptors. EPA will take into account, where relevant, the duration, intensity (concentration), frequency and number of exposures in characterizing exposures to 1,4-dioxane.

2.3.1 Fate and Transport

Environmental fate includes both transport and transformation processes. Environmental transport is the movement of the chemical within and between environmental media. Transformation occurs through the degradation or reaction of the chemical with other species in the environment. Hence, knowledge of the environmental fate of the chemical informs the determination of the specific exposure pathways and potential human and environmental receptors EPA expects to consider in the risk evaluation. Table 2-5 provides environmental fate data that EPA identified and considered in developing the scope for 1,4-dioxane. This information has not changed from that provided in the scope document.

Fate data including volatilization during wastewater treatment, volatilization from lakes and rivers, biodegradation rates, and organic carbon:water partition coefficient (log K_{OC}) were used when considering changes to the conceptual models. Systematic literature review is currently underway, so model results and basic principles were used to support the fate data used in problem formulation.

EPI Suite™ (U.S. EPA, 2012c) modules were used to predict volatilization of 1,4-dioxane from wastewater treatment plants, lakes, and rivers and to confirm the data showing slow biodegradation. The EPI Suite™ module that estimates chemical removal in sewage treatment plants ("STP" module) was run using default settings to evaluate the potential for 1,4-dioxane to volatilize to air or adsorb to sludge during wastewater treatment. The STP module estimates that 0.27% of 1,4-dioxane in wastewater will be removed by volatilization while 1.75% of 1,4-dioxane will be removed by adsorption.

The EPI Suite™ module that estimates volatilization from lakes and rivers ("Volatilization" module) was run using default settings to evaluate the volatilization half-life of 1,4-dioxane in surface water. The volatilization module estimates that the half-life of 1,4-dioxane in a model river will be 4.8 days and the half-life in a model lake will be 56 days.

The EPI Suite™ module that predicts biodegradation rates ("BIOWIN" module) was run using default settings to estimate biodegradation rates of 1,4-dioxane in soil and sediment. Three of the models built into the BIOWIN module (BIOWIN 1, 2, and 5) estimate that 1,4-dioxane will not rapidly biodegrade in aerobic environments, while a fourth (BIOWIN 6) estimates that 1,4-dioxane will rapidly biodegrade in aerobic environments. These results support the biodegradation data presented in the 1,4-dioxane scope document, which demonstrate slow biodegradation under aerobic conditions. The model that estimates anaerobic biodegradation (BIOWIN 7) predicts that 1,4-dioxane will not rapidly biodegrade under anaerobic conditions. Further, previous assessments of 1,4-dioxane found that biodegradation was slow or negligible (ATSDR, 2012; NTP, 2011; Health Canada, 2010; ECJRC, 2002; NICNAS, 1998).

The log K_{OC} reported in the 1,4-dioxane scoping document was predicted using EPI Suite™. That value (0.4) is supported by the basic principles of environmental chemistry which states that the K_{OC} is typically within one order of magnitude (one log unit) of the octanol:water partition coefficient (K_{OW}).

Indeed, the log K_{OW} reported for 1,4-dioxane in the scoping document was -0.27, which is within the expected range. Further, the K_{OC} could be approximately one order of magnitude larger than predicted by EPI Suite™ before sorption would be expected to significantly impact the mobility of 1,4-dioxane in groundwater. The log K_{OC} reported in previous assessments of 1,4-dioxane were in the range of 0.4 – 1.23 (U.S. EPA, 2013b; ATSDR, 2012; U.S. EPA, 2010; ECJRC, 2002; NICNAS, 1998) and all values within that range would be associated with low sorption to soil and sediment (ECJRC, 2002; NICNAS, 1998), and all values within that range would be associated with low sorption to soil and sediment.

Table 2-5. Environmental Fate Characteristics of 1,4-Dioxane

Property or Endpoint	Value [a]	References
Direct photodegradation	Not expected to undergo direct photolysis	(U.S. EPA, 2015c)
Indirect photodegradation	4.6 hours (estimated for atmospheric degradation)	(U.S. EPA, 2015c)
Hydrolysis half-life	Does not undergo hydrolysis	(U.S. EPA, 2015c)
Biodegradation	<10% in 29 days (aerobic in water, OECD 301F) <5% in 60 days (aerobic in water, OECD 310) 0% in 120 days, 60% in 300 days (aerobic in soil microcosm)	(U.S. EPA, 2015c)
Bioconcentration factor (BCF)	0.2-0.7 (OECD 305C)	(U.S. EPA, 2015c)
Bioaccumulation factor (BAF)	0.93 (estimated)	(U.S. EPA, 2015c)
Organic carbon:water partition coefficient (log K_{oc})	0.4 (estimated)	(U.S. EPA, 2015c)

[a] Measured unless otherwise noted.

1,4-Dioxane is expected to volatilize from dry surfaces and dry soil due to its vapor pressure of 40 mm Hg at 25°C (Table 2-1). It reacts with hydroxyl radicals (OH•) in the atmosphere with an estimated indirect photolysis half-life on the order of hours. 1,4-Dioxane is not expected to be susceptible to direct photolysis under environmental conditions since this compound lacks functional groups that absorb light at visible-ultraviolet (UV) light wavelengths.

Due to its water solubility (>800 g/L; Table 2-1) and Henry's Law constant (4.8×10^{-6} atm-m^3/mole at 25°C; Table 2-1), 1,4-dioxane is expected to demonstrate limited volatility from water surfaces and moist soil. Once it enters the environment, 1,4-dioxane is expected to be mobile in soil based on its organic carbon partition coefficient (estimated log K_{oc} = 0.4) and may therefore migrate to surface waters and groundwater. 1,4-Dioxane will not hydrolyze in water because it does not have functional hydrolyzable groups.

In experimental studies, 1,4-dioxane has been demonstrated to be not readily biodegradable but was subject to biodegradation after acclimation in a soil microcosm. Measured bioconcentration factors for 1,4-dioxane are 0.7 or below and the estimated bioaccumulation factor is 0.93. Therefore, 1,4-dioxane has low bioaccumulation potential.

2.3.2 Releases to the Environment

Releases to the environment from conditions of use (e.g., industrial and commercial processes, commercial or consumer uses resulting in down-the-drain releases) 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 rule, 1,4-dioxane is a TRI-reportable substance effective January 1, 1987. During problem formulation EPA further analyzed the TRI data and examined the definitions of elements in the TRI data to determine the level of confidence that a release would result from certain types of disposal to land (i.e. RCRA Subtitle C hazardous landfill and Class I underground Injection wells) and incineration. EPA also examined how many facilities recycle 1,4 dioxane, and how it is treated at industrial facilities.

Table 2-6 provides production-related waste managed data (also referred to as waste managed) for 1,4-dioxane reported by industrial facilities to the TRI program for 2015. Table 2-7 provides more detailed information on the quantities released to air or water or disposed of on land.

Table 2-6. Summary of 1,4-Dioxane TRI Production-Related Waste Managed in 2015 (lbs)

Number of Facilities	Recycling	Energy Recovery	Treatment	Releases [a,b,c]	Total Production Related Waste
49	4,292	1,591,064	1,923,623	705,691	4,224,670

Data source: 2015 TRI Data (updated March 2017) (U.S. EPA, 2017d).
[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] Does not include releases due to one-time event not associated with production such as remedial actions or earthquakes.
[c] Counts all releases including release quantities transferred and release quantities disposed of by a receiving facility reporting to TRI.

Table 2-7. 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 Under-ground 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, 2017d).
[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.

Facilities are required to report if they manufacture (including import) or process more than 25,000 pounds of 1,4-dioxane, or if they otherwise use more than 10,000 pounds of 1,4-dioxane. In 2015, 49 facilities reported a total of 4.2 million pounds of 1,4-dioxane waste managed. Of this total, over 4 thousand pounds were recycled, 1.6 million pounds were recovered for energy, 1.9 million pounds were treated and 700 thousand pounds were released to the environment. No TRI facilities reported recycling

1,4-dioxane on-site, but one reported transferring it off-site for recycling, specifically for solvents/organics recovery.

Of the almost 700 thousand pounds of total releases, there were stack and fugitive air releases, water releases, Class I underground injection, release to Resource Conservation and Recovery Act (RCRA) Subtitle C landfills and other land disposal (Table 2-7). For stack releases, multiple types of facilities report on incineration destruction, including hazardous waste facilities, and facilities that perform other industrial activities and may be privately or publically (i.e., federal, state or municipality) owned or operated. Approximately 46,000 lbs of 1,4-dioxane releases were reported to TRI as on-site stack releases, and account for any incineration destruction. Stack releases reported to TRI represent the total amount of 1,4 dioxane being released to the air at the facility from stacks, confined vents, ducts, pipes or other confined air streams.

In 2015, 205,725 pounds of 1,4-dioxane were released on-site, and 469,674 pounds were released off-site. Of the on-site releases, 52% (107,726 pounds) went to land disposal, 30% (62,596 pounds) went to air, including stack and fugitive releases, and 17% (35,402 pounds) was discharged to water. Of the on-site land disposal, most went to Class I underground injection wells or RCRA Subtitle C Landfills. Just 47 pounds went to on-site landfills other than RCRA Subtitle C Landfills, and none was disposed of in on-site Class II-V underground injection wells, on-site land treatment, or on-site surface impoundments. Of the off-site releases, the vast majority (469,672 lb) went to Class I underground injection wells. Very small amounts were transferred off-site to RCRA Subtitle C Landfills (0.31 lb), landfills other than RCRA Subtitle C Landfills (0.1 lb), and other types of land disposal (1.65 lb) and are considered of negligible concern for exposure.

While most 1, 4-dioxane going to land disposal went to highly regulated land disposal units in 2015, in past years, the TRI data show 1,4-dioxane going to other types of land disposal as well. From 1989 to 2002 the data show thousands of pounds of 1,4-dioxane disposed of via on-site land treatment. From 2009 to 2011, hundreds of pounds were disposed of in on-site landfills other than RCRA Subtitle C Landfills. There was also off-site disposal, with thousands of pounds disposed of off-site in landfills other than RCRA Subtitle C from 2002 to 2005. The volumes then decreased from hundreds, to tens, to almost no pounds disposed of off-site in landfills other than RCRA Subtitle C from 2006 to 2015.

While the volume of production-related waste managed shown in Table 2-6 excludes any quantities reported as catastrophic or one-time releases (TRI section 8 data), release quantities shown in Table 2-7 includes both production-related and non-routine quantities (TRI section 5 and 6 data). As a result, release quantities may differ slightly and may reflect differences in TRI calculation methods for reported release range estimates (U.S. EPA, 2017d).

EPA's *Compilation of Air Pollutant Emission Factors*, AP-42 section 6.13 on pharmaceuticals production provides general process and emissions information and the ultimate disposition of 1,4-dioxane (air, sewer, incineration, solid waste, product) by pharmaceutical manufacturers. Other sources of information provide evidence of releases of 1,4-dioxane, including National Emission Standards for Hazardous Air Pollutants (NESHAPs) promulgated under the Clean Air Act (CAA) or other EPA standards and regulations that set legal limits on the amount of 1,4-dioxane that can be emitted to a particular media.

2.3.3 Presence in the Environment and Biota

Monitoring studies or a collection of relevant and reliable monitoring studies provide(s) information that can be used in an exposure assessment. Monitoring studies that measure environmental concentrations or concentrations of chemical substances in biota provide evidence of exposure. Monitoring data were identified in EPA's data search for 1,4-dioxane.

Monitoring data (measured) from EPA's Air Quality System (AQS) and the open literature, as well as modeled estimates based on the National Air Toxics Assessment (NATA) and TRI emissions data suggest that 1,4-dioxane is present in ambient air. Monitored and modeled air concentrations from these sources suggest that many air concentrations may be low (i.e., <1 μg/m^3) and appear to have been higher in the past, possibly reflecting past uses (U.S. EPA, 2015a, 2011a). Recent (2015) air monitoring data). Recent (2015) air monitoring data were extracted from the Ambient Monitoring Archive (AMA). Of a total of 1397 collected samples, there were 948 non-detects (68%) and 449 detections (32%), which ranged from 0.005 to 0.96 ppb. All non-detects and detections for this chemical were sampled in four states: MI, OH, NC, and IN.

Indoor air monitoring data are available. One recent study reported annual average concentrations of 1,4-dioxane ranging from 0.01 to 0.11 μg/m^3 in several hundred homes in Germany (Wissenbach et al., 2016). Older indoor air monitoring studies are summarized in the U.S. EPA Voluntary Children's Chemical Evaluation Program (VCCEP) submission and report slightly higher concentrations, possibly reflecting past uses (Sapphire Group, 2007).

EPA's third Unregulated Contaminant Monitoring Rule (UCMR 3), published in 2012, required monitoring for 1,4-dioxane, along with 29 other contaminants. Over 28,000 drinking water samples were collected for chemicals suspected to be present in drinking water that lack health-based standards under the Safe Drinking Water Act.

Reported levels of 1,4-dioxane in groundwater range from 3 to 31,000 μg/L (ATSDR, 2012; USGS, 2002). Such instances of ground water contamination with 1,4-dioxane are documented in the states of California and Michigan. These data provide a basis for including groundwater in the scope of the 1,4dioxane risk evaluation from manufacturing, processing, distribution and use unless otherwise regulated or managed.

There are relatively fewer data available on 1,4-dioxane levels in surface water, though some studies of groundwater contamination also reported levels in nearby surface water. 1,4-Dioxane is released into surface water and some studies have examined 1,4-dioxane levels in sewage treatment or chemical plant effluent, combined collection treatments from apartment homes, and in river basin systems (ATSDR, 2012). 1,4-Dioxane has also been detected in landfill leachate (ATSDR, 2012).

1,4-Dioxane has not been measured and is unlikely to be present at elevated levels in sediment, sludge, soil or dust, based on its physical and chemical properties. Note, 1,4 dioxane is expected to be present in the water within the biosolids and the porewater within the soil. 1,4-Dioxane has a low bioaccumulation potential for accumulation in aquatic organisms and is short-lived in humans and few biomonitoring data are available.

2.3.4 Environmental Exposures

The manufacturing, processing, use and disposal of 1,4-dioxane can result in releases to the environment. In this section, EPA presents exposures to aquatic and terrestrial organisms.

Aquatic Environmental Exposures

EPA identified and reviewed national scale monitoring data to support this problem formulation. Based on national-scale monitoring data from EPA's STOrage and RETreival (STORET) and National Water Information System (NWIS) for the past ten years, 1,4-dioxoane is detected in surface water. The data points showed a detection rate of approximately 6% for this media, with detections ranging from 0.568 to 100 μg/L.

While recent monitoring data on ambient surface water levels indicate relatively low levels, EPA has used release estimates and measured effluent concentrations from EPA's Toxic Release Inventory (TRI) and Discharge Monitoring Report (DMR) Pollutant Loading Tool, respectively, to predict surface water concentrations near such discharging facilities for this problem formulation. To examine whether near-facility surface water concentrations could approach 1,4-dioxane's concentrations of concern, EPA employed a conservative approach, using readily-available modeling tools and data, as well as conservative assumptions. EPA's Exposure and Fate Assessment Screening Tool (U.S. EPA, 2014b) was used to estimate site-specific surface water concentrations based on estimated loadings of 1,4-Dioxane into receiving water bodies or reported on-site releases to surface waters for DMR and TRI facilities. The estimated loadings for the DMR facilities are calculated by the DMR Tool by combining the reported effluent concentrations with facility effluent flows. For TRI, the reported releases are based on monitoring, emission factors, mass balance and/or other engineering calculations. E-FAST 2014 incorporates stream dilution using stream flow information contained within the model. E-FAST also incorporates wastewater treatment removal efficiencies. Wastewater treatment removal is assumed to be 0% for this exercise, as reported loadings/releases are assumed to account for any treatment. To ensure this effort was likely to capture high-end surface water concentrations, loading data from the top ten dischargers from each data source were modeled for the last two years of complete datasets (2014-2015 for TRI sites and 2015-2016 for DMR facilities). Furthermore, as days of release and operation are not reported in these sources, EPA assumed a range of possible release days (i.e., 1, 20, and 250 days/year for facilities and 250 days/year for wastewater treatment plants or POTWs). Refer to the E-FAST 2014 Documentation Manual for equations used in the model to estimate surface water concentrations (U.S. EPA, 2007). Based on availability of site-specific flow data within E-FAST 2014 and scenario results, refinements were made to clarify or confirm the receiving water body and/or likely days of release.

High-end surface water concentrations (i.e., those obtained assuming low receiving water body stream flows) from all E-FAST 2014 runs ranged from 0.006 μg/L to 11,500 μg/L, with the minimum of 0.006 μg/L associated with a chronic release scenario (i.e., more than 20 days of release per year assumed) and the maximum of 11,500 μg/L associated with an acute release scenario (i.e., fewer than 20 days of release per year assumed). The maximum acute scenario high-end concentration was 11,500 μg/L and the maximum chronic scenario high-end concentration was 5,762 μg/. Results based on TRI release estimates were within the same range as those based on DMR annual loading values for the top ten dischargers and the reporting years covered. For a full table of results, see Appendix E.

Terrestrial Environmental Exposures

Based on its fate properties, 1,4-dioxane is not expected to reside in soil because it will either volatilize from dry surfaces and dry soil or move through the soil column with pore water.

2.3.5 Human Exposures

In this section, EPA presents occupational and general population exposures. Subpopulations, including potentially exposed and susceptible subpopulations, within these exposure categories are also presented.

2.3.5.1 Occupational Exposures

Exposure pathways and exposure routes are listed below for worker activities under the various conditions of use described in Section 2.2. In addition, exposures to occupational non-users who do not directly handle the chemical but perform work in an area where the chemical is present are listed. Engineering controls and/or personal protective equipment may impact the occupational exposure levels.

Workers and occupational non-users may be exposed to 1,4-dioxane when performing activities associated with the conditions of use described in Section 2.2, including, but not limited to:

- Unloading and transferring 1,4-dioxane to and from storage containers to process vessels.
- Using 1,4-dioxane in process equipment.
- Cleaning and maintaining equipment.
- Sampling chemical, formulations or products containing 1,4-dioxane for quality control.
- Repackaging chemicals, formulations or products containing 1,4-dioxane.
- Handling, transporting and disposing waste containing 1,4-dioxane.
- Performing other work activities in or near areas where 1,4-dioxane is used.

Key Data

Key data that inform occupational exposure assessment include: the OSHA Chemical Exposure Health Data (CEHD) and NIOSH Health Hazard Evaluation (HHE) program data. OSHA data are workplace monitoring data from OSHA inspections. The inspections can be random or targeted, or can be the result of a worker complaint. OSHA data can be obtained through the OSHA Integrated Management Information System (IMIS) at https://www.osha.gov/oshstats/index.html. Table_Apx B-1 in Appendix B.1.3 provides a summary of industry sectors with 1,4-dioxane personal monitoring air samples obtained from OSHA inspections conducted between 2002 and 2016. NIOSH HHEs are conducted at the request of employees, union officials, or employers and help inform potential hazards at the workplace. HHEs can be downloaded at https://www.cdc.gov/niosh/hhe/.

Inhalation

Based on these activities, inhalation exposure to vapors and mists are expected for workers and occupational non-users. There is potential for spray application of some products containing 1,4-dioxane so exposures to mists are also expected for workers and will be incorporated into the worker inhalation exposure. See section 2.5.1 for additional details on the pathways EPA expects to analyze for occupational exposures.

The United States has several regulatory and non-regulatory exposure limits for 1,4-dioxane: An Occupational Safety and Health Administration (OSHA) Permissible Exposure Limit (PEL) of 100 ppm 8-hour time-weighted average (TWA) (360 mg/m^3) with a skin notation, a National Institute of Occupational Safety and Health (NIOSH) Recommended Exposure Limit (REL) of 1 ppm (3.6 mg/m^3) as a 30-minute ceiling and an American Conference of Government Industrial Hygienists (ACGIH) Threshold Limit Value (TLV) of 20 ppm TWA (72 mg/m^3) (OSHA, 2005). The influence of these exposure limits on occupation exposures will be considered in the occupational exposure assessment.

Dermal

Based on the conditions of use, EPA expects dermal exposure for workers and occupational non-users, including skin contact with vapors, liquids and mists. Occupational non-users do not handle the chemical directly, so dermal exposure from liquids containing 1,4-dioxane are not expected.

Oral
Worker exposure via the oral route is not expected. For some uses (described in Section 2.5.1), there are potential worker exposures through mists that deposit in the upper respiratory tract. Based on physical chemical properties, mists of 1,4-dioxane will likely be rapidly absorbed in the respiratory tract and will be considered as an inhalation exposure.

2.3.5.2 Consumer Exposures

As stated in the Scope document (U.S. EPA, 2017c) and Section 2.2.2.1, there are no current consumer uses for 1,4-dioxane in the U.S.

2.3.5.3 General Population Exposures

Wastewater/liquid wastes, solid wastes or air emissions of 1,4-dioxane could result in potential pathways for oral, dermal or inhalation exposure to the general population.

Inhalation
The general population may be exposed to 1,4-dioxane through inhalation of ambient air and indoor air. Ambient air exposures may occur from releases from industrial/commercial sources. Indoor air exposures may occur from infiltration from ambient air or emissions from tap water during activities such as showering and bathing. Based on the relatively high water solubility and relatively low Henry's law constant for 1,4-dioxane, EPA expects that volatilization would be low for many indoor uses. However, increased water temperature during bathing and showering can increase volatilization. The Henry's Law constant for 1,4-dioxane is appreciably higher at 40°C (4.9×10^{-4} atm-m^3/mole) than 25°C (4.8×10^{-6} atm-m^3/mole). Furthermore, smaller droplets of water created by some indoor uses (e.g., showering) have a larger surface area from which 1,4-dioxane may volatize.

Vapor intrusion and volatilization from wastewater treatment are not considered significant sources of exposure to the general population because the Henry's Law constant (4.8×10^{-6} atm-m^3/mole) and high water solubility of 1,4-dioxane (>800 g/L) indicate that 1,4-dioxane will primarily remain in the aqueous phase (wastewater or groundwater) and that volatilization from water to air will be limited. Estimated volatilization from the sewage treatment plant (STP) module in EPI Suite™ found that 0.27% of 1,4-dioxane in wastewater would be removed by volatilization during wastewater treatment.

Oral
The general population may ingest 1,4-dioxane via contaminated drinking water. Based on reported uses, down-the-drain sources may contribute to surface water and drinking water levels. Therefore, there is potential oral exposure to 1,4-dioxane by ingestion of drinking water from surface water and ground water sources to municipal drinking water.

Dermal
Dermal exposure via water may occur through extended contact with tap water containing 1,4-dioxane during washing and bathing. The source of the contaminated water may be either contaminated surface or ground waters used as a source of municipal drinking water.

2.3.5.4 Potentially Exposed or Susceptible Subpopulations

TSCA requires that the determination of whether a chemical substance presents an unreasonable risk to "a potentially exposed or susceptible subpopulation identified as relevant to the risk evaluation" by EPA. 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." General population is "the total of individuals inhabiting an area or making up a whole group" and refers here to the U.S. general population (U.S. EPA, 2011a).

As part of the Problem Formulation, EPA identified potentially exposed and susceptible subpopulations for further analysis during the development and refinement of the life cycle, conceptual models, exposure scenarios and analysis plan. In this section, EPA addresses the potentially exposed or susceptible subpopulations identified as relevant based on greater exposure. EPA will address the subpopulations identified as relevant based on greater susceptibility in the hazard section.

EPA identifies the following as potentially exposed or susceptible subpopulations due to their *greater exposure*:

- Workers and occupational non-users.
- Other groups of individuals within the general population who may experience greater exposures due to their proximity to conditions of use identified in Section 2.2 that result in releases to the environment and subsequent exposures (e.g., individuals who live or work near manufacturing, processing, distribution, use or disposal sites).

In developing exposure scenarios, EPA will analyze available data to ascertain whether some human receptor groups may be exposed via exposure pathways that may be distinct to a particular subpopulation or lifestage and whether some human receptor groups may have higher exposure via identified pathways of exposure due to unique characteristics (e.g., activities, duration or location of exposure) when compared with the general population (U.S. EPA, 2006).

In summary, in the risk evaluation for 1,4-dioxane, EPA plans to analyze the following potentially exposed groups of human receptors: workers, occupational non-users and the general population. EPA may also identify additional potentially exposed or susceptible subpopulations that will be considered based on greater exposure.

2.4 Hazards (Effects)

For scoping, EPA conducted comprehensive searches for data on hazards of 1,4-dioxane, as described in *Strategy for Conducting Literature Searches for 1,4-Dioxane: Supplemental File for the TSCA Scope Document* (EPA-HQ-OPPT-2016-0723). Based on initial screening, EPA plans to analyze the hazards of 1,4-dioxane identified in this problem formulation document. However, when conducting the risk evaluation, the relevance of each hazard within the context of a specific exposure scenario will be judged for appropriateness. For example, hazards that occur only as a result of chronic exposures may not be applicable for acute exposure scenarios. This means that it is unlikely that every identified hazard will be analyzed for every exposure scenario.

2.4.1 Environmental Hazards

During problem formulation, EPA analyzed potential environmental health hazards associated with 1,4-dioxane. EPA identified the following sources of environmental hazard data for 1,4-dioxane: (Health

Canada, 2010; ECJRC, 2002; OECD, 1999; NICNAS, 1998); and the European Chemicals Agency (ECHA) Database. Studies published since 2003 were identified in the literature search for 1,4-dioxane (*1,4-Dioxane (CASRN 123-91-1) Bibliography: Supplemental File for the TSCA Scope Document*, EPA-HQ-OPPT-2016-0723) and were reviewed as described in *Application of Systematic Review in TSCA Risk Evaluations* (U.S. EPA, 2018a) and *Strategy for Assessing Data Quality in TSCA Risk Evaluations* (U.S. EPA, 2018b). Only the *on-topic* references listed in the Ecological Hazard Literature Search Results were considered as potentially relevant data/information sources for the risk evaluation. Inclusion criteria were used to screen the results of the ECOTOX literature search (as explained in the *Strategy for Conducting Literature Searches for 1-4-Dioxane: Supplemental Document to the TSCA Scope Document, CASRN:123-91-1*). Data from the screened literature are summarized below (Table 2-8) as ranges (min-max). EPA plans to complete review of these 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, 2018a).

Toxicity to Aquatic Organisms

EPA identified 1,4-dioxane environmental hazard data for fish, aquatic invertebrates and aquatic plants exposed under acute and chronic exposure conditions. Aquatic toxicity studies are summarized in Table 2-8.

Table 2-8. Ecological Hazard Characterization of 1,4-Dioxane

Duration	Test organism	Endpoint	Hazard value(s)[a]	Units	Effect(s)	Citation(s)
Aquatic Organisms						
Acute	Fish	LC_{50}	>100 – 67,000	mg/L	Mortality	(Geiger et al., 1990)
	Aquatic invertebrates	EC_{50}	>299 - >1,000	mg/L	Immobilization	(Dow Chemical Company, 1989) as cited in (ECJRC, 2002)
	Algae	EC_{50}	575 - 5600	mg/L	Inhibition	(Bringman and Kuhn, 1977)
			580	mg/L	Biomass	(ECHA, 2014b)
			>1,000	mg/L	Biomass	(ECHA, 2014b)
	Acute COC = 60 mg/L					
Chronic	Fish	NOEC[b]	565	mg/L	Carcinogenicity	(Johnson et al., 1993)
		MATC[c]	>145		Development, Hatching, Survival	(TSCATS, 1989) as cited in (ECJRC, 2002)
	Aquatic invertebrates	NOEC	1,000	mg/L	Reproduction	(ECHA, 2014a)
	Chronic COC = 15 mg/L					
Terrestrial Organisms						
Chronic	Terrestrial Plant	EC_{50}	1,450	mg/L	Germination/Root Elongation	(Reynolds, 1989)

[a]Values in the tables are presented as reported by the study authors.
[b]NOEC: No Observable Effect Concentration,
[c]MATC, Maximum Acceptable Toxicant Concentration; Calculated using the geometric mean of LOEC and NOEC values (as described in (U.S. EPA, 2013a)

The acute 96-hour LC_{50} values for fish range from >100 mg/L (highest concentration tested) for fathead minnow (*Pimephales promelas*) to 67,000 mg/L for inland silversides (*Menidia beryllina*). Two studies on the acute ecotoxicity to aquatic invertebrates (*Daphnia magna* and *Ceridodaphnia dubia*) indicate that the 48-hour EC_{50} is >1,000 mg/L (highest concentration tested) (ECJRC, 2002) and >299 mg/L (highest concentration tested; (Dow Chemical Company, 1989)).

In a chronic study, Medaka (*Oryzias latipes*) were exposed to measured concentrations of 1,4-dioxane ranging from 565 to 6,933 mg/L for 28 days under flow-through conditions. There were effects on growth and survival (Johnson et al., 1993). A no observed effect concentration (NOEC) 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 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. A NOEC of >103 mg/L based on larval survival and a maximum acceptable toxicant concentration (MATC) of 145 mg/L was calculated ($NOEC=MATC/\sqrt{2}$) (ECJRC, 2002).

In a study on the chronic toxicity of 1,4-dioxane to aquatic invertebrates, water fleas (*D. magna*) were exposed to unspecified concentrations of 1,4-dioxane in a 21-day reproduction test. The exposure conditions were not reported. The highest exposure concentration tested was 1,000 mg/L. No effects on reproduction, survival, or growth were reported. A 21-day NOEC of >1,000 mg/L was reported (ECHA, 2014a).

Three studies have characterized the toxicity of 1,4-dioxane to aquatic plants. In one study, green algae (*Pseudokirchnerella subcapitata*) were exposed to unspecified concentrations of 1,4-dioxane for 72-hours under static conditions. No effects were observed on growth rate or biomass at 1,000 mg/L, the highest concentration tested. A 72-hour EC_{50} (growth rate and biomass) of > 1,000 mg/L was reported. A NOEC (biomass) of 580 mg/L and a NOEC (growth rate) of 1,000 mg/L was reported (ECHA, 2014b). Also, two short-term toxicity studies in *Microcystis aeruginosa* and *Scenedesmus quadricauda* reported EC_{50} cell inhibition of 575 and 5,600 mg/L after eight days of exposure to 1,4-dioxane (Bringman and Kuhn, 1977).

Toxicity to Sediment and Terrestrial Organisms

In one study, lettuce (*Actuca sativa*) were exposed to 1,4-dioxane in a germination/root elongation toxicity test for 3-days. An EC50 of 1,450 mg/L was reported for germination (Reynolds, 1989).

There are no available acute or chronic toxicity studies that characterize the hazard of 1,4-dioxane to sediment organisms. However, available hazard, fate and exposure characteristics (Sections 2.3.1 and 2.3.3) suggest that sediment organisms are not at risk from 1,4-dioxane exposures.

Concentrations of Concern (COC)

The concentrations of concern (COCs) for aquatic species were calculated based on the summarized environmental hazard data for 1,4-dioxane. The analysis of the environmental COCs are described in Appendix C and are based on EPA/OPPT methods (U.S. EPA, 2013a, 2012d). The acute and chronic COC for 1,4-dioxane are based on the lowest toxicity value in the dataset. For a particular environment (e.g., aquatic environment), the COC is based on the most sensitive species or the species with the lowest toxicity value reported in that environment.

The acute concentration of concern for 1,4-dioxane is based on a 96-hour fish toxicity study where the LC_{50} is >100 mg/L (ECHA, 2014a; Geiger et al., 1990) and the chronic COC is based on a 32-day MATC fish toxicity value of 145 mg/L (Brooke, 1987). The acute and chronic COCs for 1,4-dioxane are 59,800 ppb and 14,500 ppb, respectively.

2.4.2 Human Health Hazards

1,4-Dioxane has an existing EPA IRIS Assessment (U.S. EPA, 2013c, 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); hence, many of the hazards of 1,4-dioxane have been previously compiled and reviewed. EPA expects to use these previous analyses as a starting point for identifying key and supporting studies to inform the human health hazard assessment, including dose-response analysis. The relevant studies will be evaluated using the data quality criteria in the *Application of Systematic Review in TSCA Risk Evaluations* (U.S. EPA, 2018a). EPA also plans to analyze other studies (e.g., more recently published, alternative test data) that have been published since these reviews, as identified in the literature search conducted by the Agency for 1,4-dioxane (*1,4-Dioxane* (*CASRN 123-91-1*) *Bibliography: Supplemental File for the TSCA Scope Document*, EPA-HQ-OPPT-2016-0723). Based on reasonably available information, the following sections describe the potential hazards associated with 1,4-dioxane.

2.4.2.1 Non-Cancer Hazards

Acute Toxicity

Effects following acute exposures were evaluated (U.S. EPA, 2005b). The Interim AEGLs (U.S. EPA, 2005b) evaluated the data on acute toxicity and irritation and concluded that, in animals, acute toxic effects of 1,4-dioxane include central nervous system depression, kidney and liver damage and irritation. Humans acutely exposed to 1,4-dioxane experienced irritation of the eyes, nose and throat, nausea and vomiting, coma and death. Also, 1,4-dioxane can cause narcosis in animals inhaling very high concentrations (U.S. EPA, 2005b).

Irritation

Acute inhalation studies in human volunteers noted irritation of the eyes, nose and throat (U.S. EPA, 2005b). In rats, 2 years of inhalation exposure to 1,4-dioxane, resulted in metaplasia, hyperplasia, atrophy, hydropic change, vacuolic change and preneoplastic cell proliferation in the nasal cavity (U.S. EPA, 2013c).

Liver Toxicity

In subchronic and chronic repeated exposure studies conducted in rats and mice by the oral (via drinking water) and inhalation routes, evidence shows that 1,4-dioxane is toxic to the liver (U.S. EPA, 2013c). Chronic administration of 1,4-dioxane via the drinking water resulted in hepatocellular degeneration and preneoplastic changes. Inhalation exposure to 1,4-dioxane resulted in necrosis of the centrilobular region and preneoplastic changes in the liver.

Kidney Toxicity

In subchronic and chronic repeated exposure studies conducted in rats and mice by the oral (via drinking water) and inhalation routes, evidence shows that 1,4-dioxane is toxic to the kidney (U.S. EPA, 2013c). Kidney damage following drinking water exposure to 1,4-dioxane includes degeneration of cortical tubule cells, necrosis with hemorrhage and glomerulonephritis.

2.4.2.2 Genotoxicity and Cancer Hazards

U.S. EPA (2013c) concluded that overall, the available literature indicates that 1,4-dioxane is nongenotoxic or weakly genotoxic. Per EPA's Cancer Guidelines (U.S. EPA, 2005a), EPA concluded "there is insufficient biological support for potential key events and to have reasonable confidence in the sequence of events and how they relate to the development of nasal tumors following exposure to 1,4-dioxane". No single mode of action (MOA) accounts for the formation of liver, nasal, peritoneal (mesotheliomas), and mammary gland tumors seen in laboratory animals exposed to 1,4-dioxane. Some data support a non-linear MOA for liver tumorigenesis, but currently available data do not support non-linearity for the remaining tumor types.

EPA evaluated the weight of the evidence for cancer in humans and animals and concluded that 1,4-dioxane is "likely to be carcinogenic to humans" based on evidence of carcinogenicity in several 2-year bioassays (oral and inhalation) conducted in four strains of rats, two strains of mice and in guinea pigs (U.S. EPA, 2013c). The National Toxicology Program classified 1,4-dioxane as "reasonably anticipated to be a human carcinogen" (NTP, 2016), and NIOSH has classified it as a "potential occupational carcinogen" (ATSDR, 2012). Human occupational studies into 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.

2.4.2.3 Potentially Exposed or Susceptible Subpopulations

TSCA requires that the determination of whether a chemical substance presents an unreasonable risk include consideration of unreasonable risk to "a potentially exposed or susceptible subpopulation identified as relevant to the risk evaluation" by EPA. 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." In developing the hazard assessment, EPA will analyze available data to ascertain whether some human receptor groups may have greater susceptibility than the general population to the chemical's hazard(s).

2.5 Conceptual Models

EPA risk assessment guidance ((U.S. EPA, 2014c, 1998)), defines Problem Formulation as the part of the risk assessment framework that identifies the factors to be considered in the assessment. It draws from the regulatory, decision-making and policy context of the assessment and informs the assessment's technical approach.

A conceptual model describes the actual or predicted relationships between the chemical substance and receptors, either human or environmental. These conceptual models are integrated depictions of the conditions of use, exposures (pathways and routes), hazards and receptors. The initial conceptual models describing the scope of the assessment for 1,4-dioxane, have been refined during problem formulation. The changes to the conceptual models in this problem formulation are described along with the rationales.

In this section EPA outlines those pathways that will be included and further analyzed in the risk evaluation; will be included but will not be further analyzed in risk evaluation; and will not be included in the TSCA risk evaluation and the underlying rationale for these decisions.

EPA determined as part of problem formulation that it is not necessary to conduct further analysis on certain exposure pathways that were identified in the 1,4-dioxane scope document and that remain in the risk evaluation. Each risk evaluation will be "fit-for-purpose," meaning not all conditions of use will warrant the same level of evaluation and the Agency may be able to reach some conclusions without comprehensive risk evaluations. 82 FR 33726, 33734, 33739 (July 20, 2017).

As part of this problem formulation, EPA also identified t exposure pathways under other environmental statutes, administered by EPA, which adequately assess and effectively manage exposures and for which long-standing regulatory and analytical processes already exist, i.e., the Clean Air Act (CAA), the Safe Drinking Water Act (SDWA), the Clean Water Act (CWA) and the Resource Conservation and Recovery Act (RCRA). OPPT worked closely with the offices within EPA that administer and implement the regulatory programs under these statutes. In some cases, EPA has determined that chemicals present in various media pathways (i.e., air, water, land) fall under the jurisdiction of existing regulatory programs and associated analytical processes carried out under other EPA-administered statutes and have been assessed and effectively managed under those programs. EPA believes that the TSCA risk evaluation should focus on those exposure pathways associated with TSCA uses that are not subject to the regulatory regimes discuss above because these pathways are likely to represent the greatest areas of concern to EPA. As a result, EPA does not plan to include in the risk evaluation certain exposure pathways identified in the 1,4-dioxane scope document.

2.5.1 Conceptual Model for Industrial and Commercial Activities and Uses: Potential Exposures and Hazards

The revised conceptual model (Figure 2-2) describes the pathways of exposure from industrial and commercial activities and uses of 1,4-dioxane that EPA plans to include in the risk evaluation. There are exposures to workers and occupational non-users via dermal and inhalation routes during manufacturing, processing, use and disposal of 1,4-dioxane for all uses identified in the scope, except for distribution in commerce. During distribution, 1,4-dioxane is contained in closed systems (e.g. drums, pails, bottles) so releases and exposures are not expected. Any associated open system loading and unloading activities into these containers will be analyzed for the condition of use.

The description for uses of 1,4-dioxane as Functional Fluids has been refined to include both open and closed systems. When the scope of the risk evaluation was determined, the information available to EPA suggested that 1,4-dioxane was used as Functional Fluids only in closed systems. However, during problem formulation, EPA determined that some of the subcategories of uses, such as cutting and tapping fluid, may also include uses in open systems. This change is reflected in the conceptual model (Figure 2-2).

Inhalation

EPA expects that for workers and occupational non-users, exposure via inhalation will be the most significant route of exposure for most exposure scenarios. EPA plans to further analyze inhalation exposures to vapors and mists for workers and occupational non-users in the risk evaluation.

EPA reviewed the potential for occupational exposures associated with subcategories of conditions of use where a mist may be generated. EPA determined that most subcategories will not produce a mist during their typical use and, for these, EPA concludes that exposure to 1,4-dioxane would be negligible and does not plan further analysis. For subcategories of uses where either a spray application or rotary equipment is likely, EPA determined that these conditions of use may produce a mist that could result in exposures for workers when the mist is inhaled and subsequently swallowed and EPA plans to analyze exposures associated with these uses. EPA will also evaluate subcategories of uses where EPA is uncertain whether a mist is likely to be produced during use. EPA expects to further evaluate exposure via a mist for the uses listed in Table 2-9.

Table 2-9. 1,4-Dioxane Conditions of Use that May Produce a Mist

Life Cycle Stage	Category	Subcategory
Processing	Recycling	Recycling
Industrial use	Processing aids, not otherwise listed	Wood pulping Extraction of animal and vegetable oils Wetting and dispersing agent in textile processing Etching of fluoropolymers
Industrial use	Functional fluids (open and closed system)	Polyalkylene glycol lubricant Synthetic metalworking fluid Cutting and tapping fluid Hydraulic fluid
Industrial use, potential commercial use	Other uses	Spray polyurethane foam Printing and printing compositions

Dermal

There is the potential for dermal exposures to 1,4-dioxane in many worker scenarios. Dermal exposure from contact with liquids containing 1,4-dioxane are expected primarily for workers, such as operators, directly involved in working with these liquids. Where workers may be exposed to 1,4-dioxane, the OSHA standard requires that workers are protected from contact (e.g. gloves) (29 CFR 1910.1052). Occupational non-users are not directly handling 1,4-dioxane; therefore, skin contact with liquid 1,4-dioxane is not expected for occupational non-users and will not be further analyzed in the risk evaluation. EPA plans to further analyze dermal exposures for skin contact with liquids in occluded situations for workers.

Workers and occupational non-users can have skin contact with 1,4-dioxane vapor concurrently with inhalation exposures. The parameters determining the absorption of 1,4-dioxane vapor are based on the concentration of the vapor, the duration of exposure and absorption. The concentration of the vapor and the duration of exposure are the same for concurrent dermal and inhalation exposures. Therefore, the differences between dermal and inhalation exposures depend on the absorption. The dermal absorption can be estimated from the skin permeation coefficient (0.00043 cm/hr from a water solution; (Bronaugh, 1982)) and exposed skin surface area (on the order of 0.2 m^2, (U.S. EPA, 2011a)). The absorption of inhaled vapors can be estimated from the volumetric inhalation rate (approximately 1.25 m^3/hr for a person performing light activity, (U.S. EPA, 2011a)) adjusted by a retention factor such as 0.75. Based on these parameters the absorption of 1,4-dioxane vapor via skin will be orders of magnitude lower than via inhalation and will not be further analyzed.

Oral

There are potential worker exposures through mists that deposit in the upper respiratory tract. Based on physical chemical properties, mists of 1,4-dioxane will likely be rapidly absorbed in the respiratory tract or evaporate and contribute to the amount of 1,4-dioxane vapor in the air. Furthermore, if 1,4-dioxane mists were ingested orally the available toxicological data do not suggest significantly different toxicity from considering the mists as an inhalation exposure.

Waste Handling, Treatment and Disposal

Figure 2-2 shows that waste handling, treatment and disposal is expected to lead to the same pathways as other industrial and commercial activities and uses. The path leading from the “Waste Handling, Treatment and Disposal” box to the “Hazards Potentially Associated with Acute and/or Chronic Exposures See Section 2.4.2” box was re-routed to accurately reflect the expected exposure pathways, routes, and receptors associated with these conditions of use of 1,4-dioxane.

For each condition of use identified in Table 2-3, a determination was made as to whether each unique combination of exposure pathway, route, and receptor will be evaluated further in the risk evaluation. The results of that analysis along with the supporting rationale are presented in Appendix D and Appendix E.

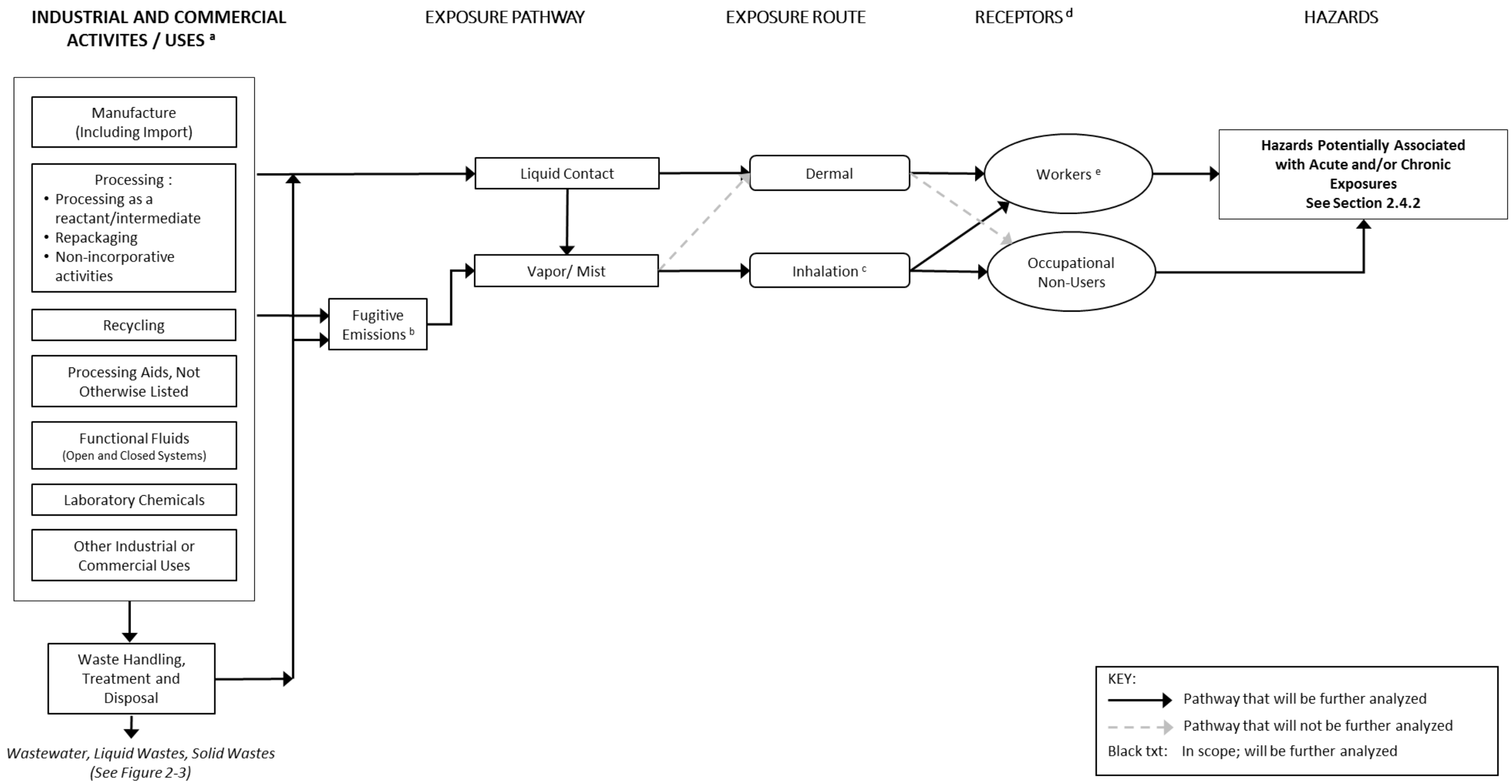

Figure 2-2. 1,4-Dioxane Conceptual Model for Industrial and Commercial Activities and Uses: Potential Exposures and Hazards

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 plans to analyze.

[a] Additional uses of 1,4-dioxane are included in Table 2-3.

[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 may be considered an inhalation exposure.

[d] Receptors include potentially exposed or susceptible subpopulations.

[e] When data and information are available to support the analysis, EPA also considers the effect that engineering controls and/or personnel protective equipment have on occupational exposure levels.

2.5.2 Conceptual Model for Consumer Activities and Uses: Potential Exposures and Hazards

The 1,4-dioxane life cycle diagram (Figure 2-1) indicates that no uses of 1,4-dioxane were identified in consumer products. EPA did not receive data, information or comments that informed a change was necessary to the scope. Therefore, EPA does not plan to evaluate use of 1,4-dioxane in consumer products and there is no conceptual model provided for consumer activities and uses.

2.5.3 Conceptual Model for Environmental Releases and Wastes: Potential Exposures and Hazards

The revised conceptual model (Figure 2-2) illustrates the expected exposure pathways to human and ecological receptors from environmental releases and waste stream associated with industrial and commercial activities for 1,4-dioxane. The pathways that EPA plans to include but not analyze further in risk evaluation are described in Section 2.5.3.2 and shown in the conceptual model. The pathways that EPA does not plan to include in the risk evaluation are described in Section 2.5.3.2.

2.5.3.1 Pathways That EPA Plans to Include and Further Analyze in the Risk Evaluation

There are no environmental release and waste pathways for the environment or general populations that EPA plans to include and further analyze in the risk evaluation (see Figure 2-3).

2.5.3.2 Pathways that EPA Plans to Include in the Risk Evaluation But Not Further Analyze

The pathways that EPA plans to include in the risk evaluation but not further analyze are ambient water exposure to aquatic vertebrates, invertebrates and aquatic plants, sediment and land-applied biosolids.

Aquatic Pathways

EPA analyzed risks to aquatic organisms exposed to 1,4-dioxane in surface water based on the relatively high potential for release, fate properties, and the availability of environmental monitoring data and hazard data. Based on 2015 TRI reporting, an estimated 35,402 lb of 1,4-dioxane was released to water from industrial sources. 1,4-Dioxane has high water solubility and slow removal from surface water due lack of hydrolysis (no hydrolyzable groups) and slow biodegradation (< 10% degradation in 29 days). Monitored concentrations in surface water from STORET/NWIS are as high as 100 µg/L and predicted concentrations in surface water for acute and chronic scenarios are up to 11,500 µg/L and 5,762 µg/L, respectively (Section 2.3.4). Measured and estimated levels of 1,4-dioxane in the environment are sufficiently below the acute and chronic aquatic COCs of 20,000 µg/L and 14,500 µg/L (See Environmental Hazards, Section 2.4.1 and Analysis of the Environmental Concentrations of Concern, Appendix C). EPA is including the analysis of risks to aquatic invertebrates and aquatic plants from exposures to 1,4-dioxane in surface waters in the evaluation, but will not further analyze the data.

Sediment Pathways

EPA does not plan to further analyze 1,4-dioxane pathways to sediment. 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 KOC = 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 KOC = 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. While no ecotoxicity studies were available for sediment organisms, the toxicity of 1,4-dioxane to sediment invertebrates is expected to be similar to the toxicity to aquatic invertebrates.

Land-Applied Biosolids Pathway

EPA does not plan to further analyze other releases to land during risk evaluation, including biosolids application to soil. EPA expects releases of 1,4-dioxane to wastewater treatment plants (WWTP), resulting in biosolids that can be land-applied. Species in the environment including aquatic organisms, amphibians and terrestrial organisms may come into contact with 1,4-dioxane-contaminated biosolids and soil pore water when the biosolids are land applied. However, the release of 1,4-dioxane from land-applied biosolids represents a negligible fraction of its overall environmental release, due to its physical-chemical properties.

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 ≥ 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 approximately 2% will be removed via adsorption to sludge or volatilization to air, < 2% will be removed with biosolids-associated water, and > 95% will be present in the effluent (see Section 2.3.1, 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, and therefore exposures of aquatic organisms from surface water due to land-applied biosolids will not be further analyzed.

2.5.3.3 Pathways That EPA Does Not Plan to Include in the Risk Evaluation

Exposures to receptors (i.e. general population) may occur from industrial and/or commercial uses; industrial releases to air, water or land; and other conditions of use. As described in section 2.5, pathways under other environmental statutes, administered by EPA, which adequately assess and effectively manage exposures and for which long-standing regulatory and analytical processes already exist will not be included in the risk evaluation. These pathways are described below.

Ambient Air Pathway

The Clean Air Act (CAA) contains a list of hazardous air pollutants (HAP), including 1,4-dioxane, 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 HAP.

1,4-Dioxane is a HAP. EPA has issued a number of technology-based standards for source categories that emit 1,4-dioxane to ambient air and, as appropriate, has reviewed, or is in the process of reviewing remaining risks. Because stationary source releases of 1,4-dioxane to ambient air are adequately assessed and any risks effectively managed when under the jurisdiction of the CAA, EPA does not plan to evaluate emission pathways to ambient air from commercial and industrial stationary sources or associated inhalation exposure of the general population or terrestrial species in this TSCA evaluation.

Drinking Water Pathway
EPA has regular analytical processes to identify and evaluate drinking water contaminants of potential regulatory concern for public water systems under the Safe Drinking Water Act (SDWA). Under SDWA, EPA must also review and revise "as appropriate" existing drinking water regulations every 6 years.

The Contaminant Candidate List (CCL) is a list of unregulated contaminants that are known or anticipated to occur in public water systems and that may require regulation. EPA must publish a CCL every 5 years and make Regulatory Determinations (RegDet) to regulate (or not) at least five CCL contaminants every 5 years. To regulate a contaminant EPA must conclude 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.

Currently, there is no National Primary Drinking Water regulation for 1,4-Dioxane under SDWA. 1,4-dioxane released to surface water can contribute to levels of the chemical in drinking water. EPA's Office of Water has established a Health Advisory level of 35 μg/L (which corresponds to a 1 in ten thousand lifetime cancer risk) for 1,4-Dioxane. 1,4-Dioxane is also currently listed on EPA's Fourth Contaminant Candidate List (CCL 4) and was subject to occurrence monitoring in public water systems under the third Unregulated Contaminants Monitoring Rule (UMCR 3). Under UMCR 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. None of the systems measured levels greater than the Health Advisory level, however, 341 systems (6.9%) had results at or above 0.35 μg/L (which corresponds to a 1 in a million-lifetime cancer risk). In accordance with EPA-OW's process, 1,4-dioxane is currently being evaluated under the fourth Regulatory Determination process under SDWA.

Hence, because the drinking water exposure pathway for 1,4-dioxane is being addressed under the regular analytical processes to identify and evaluate drinking water contaminants of potential regulatory concern for public water systems under SDWA, EPA does not plan to include this pathway in the risk evaluation for 1,4-dioxane under TSCA. EPA's Office of Water and Office of Pollution Prevention and Toxics will continue to work together providing understanding and analysis of the SDWA regulatory analytical processes for public water systems and to exchange information related to toxicity and occurrence data on chemicals undergoing risk evaluation under TSCA.

Ambient Water Pathways
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 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.

EPA has not developed CWA section 304(a) recommended water quality criteria for the protection of aquatic life for 1,4-dioxane, so there are no national recommended criteria for this use available for adoption into state water quality standards and available for use in NPDES permits. Currently, only one state (Colorado) includes human health criteria for 1,4-dioxane in their water quality standards and none include aquatic life criteria for 1,4-dioxane. As a result, this pathway will undergo aquatic life risk evaluation under TSCA (see Section 2.5.3.2). EPA may publish CWA section 304(a) aquatic life criteria for 1,4-dioxane in the future if it is identified as a priority under the CWA.

Disposal Pathways

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 RCRA standard in section 3004(a) for the technical (regulatory) criteria that govern the management (treatment, storage, and disposal) of hazardous waste (i.e., Subtitle C) 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 Clean Air Act (CAA) hazardous waste combustion MACT) or injected into UIC Class I hazardous waste wells (subject to joint control under Subtitle C and the Safe Drinking Water Act (SDWA)).

Emissions to ambient air from municipal and industrial waste incineration and energy recovery units will not be included in the risk evaluation, as they are regulated under section 129 of the Clean Air Act. CAA section 129 also requires EPA to review and, if necessary, add provisions to ensure the standards adequately protect public health and the environment. Thus, combustion by-products from incineration treatment of 1,4 dioxane wastes (the majority of the 46,000 lbs identified as treated in Table 2-6) would be subject to these regulations, as would 1,4 dioxane burned for energy recovery (1.6 million lbs).

EPA does not plan to include on-site releases to land that go to underground injection in its risk evaluation. TRI data (U.S. EPA, 2015b) indicate that 94,304 lb of 1,4-dioxane was disposed of on-site to Class I underground injection wells and no releases to underground injection wells of Classes II-VI. Environmental disposal of 1,4-dioxane injected into Class I well types are managed and prevented from further environmental release by RCRA and SDWA regulations. Therefore, disposal of 1,4-dioxane via underground injection is not likely to result in environmental and general population exposures.

EPA does not plan to include on-site releases to land that go to RCRA Subtitle C hazardous waste landfills or RCRA Subtitle D municipal solid waste (MSW) landfills in its risk evaluation. TRI data (U.S. EPA, 2015b) indicate that RCRA Subtitle C Landfills received 13,375 lb of 1,4-dioxane, with a small amount of 1,4-dioxane (47 lb) reported to on-site landfills other than RCRA Subtitle C 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 must also meet RCRA waste treatment standards before disposal. Given these controls, general population exposure to 1,4-dioxane in groundwater from Subtitle C landfill leachate is not expected to be a significant pathway.

EPA does not plan to include on-site releases to land from RCRA Subtitle C hazardous waste landfills or RCRA Subtitle D municipal solid waste landfills or exposures of the general population (including susceptible populations) or terrestrial species from such releases in the TSCA evaluation. While permitted and managed by the individual states, municipal solid waste (MSW) 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.

EPA does not expect to include on-site releases to land from industrial non-hazardous and construction/demolition waste landfills. Industrial non-hazardous and construction/demolition waste landfills are primarily regulated under 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 requirement such as for liners, post-closure and financial assurance, but are not required to do so. Therefore, EPA does not expect to include this pathway in the risk evaluation.

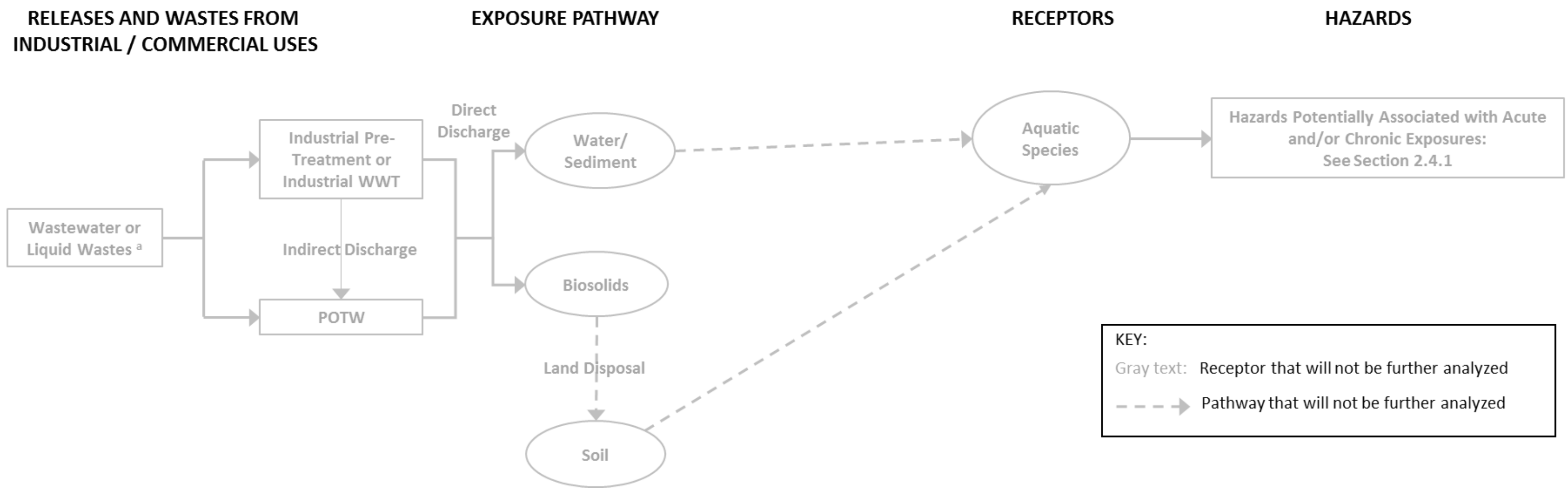

Figure 2-3. 1,4-Dioxane Conceptual Model for Environmental Releases and Wastes: Potential Exposures and Hazards
The conceptual model presents the exposure pathways, exposure routes and hazards to human and environmental receptors from environmental releases and wastes of 1,4-dioxane that EPA plans to analyze.
[a] Industrial wastewater or liquid wastes may be treated on-site and then released to surface water (direct discharge), or pre-treated and released to POTW (indirect discharge). Drinking water will undergo further treatment in drinking water treatment plants. Ground water may also be a source of drinking water.

2.6 Analysis Plan

The analysis plan presented in the problem formulation elaborates on the initial analysis plan that was published in the *Scope of the Risk Evaluation for 1,4-Dioxane* (U.S. EPA, 2017c).

The analysis plan is based on the conditions of use of 1,4-dioxane, as described in Section 2.2 of this problem formulation. EPA is implementing systematic review approaches and/or methods to identify, select, assess, integrate and summarize the findings of studies supporting the TSCA risk evaluation. The analytical approaches and considerations in the analysis plan are used to frame the scope of the systematic review activities for this assessment. The supplemental document, *Application of Systematic Review in TSCA Risk Evaluations* (U.S. EPA, 2018a), provides additional information about the criteria, approaches and/or methods that have been and will be applied to the first ten chemical risk evaluations. This supplemental document will be published in early 2018.

While EPA has conducted a search for reasonably available information as described in the *Scope of the Risk Evaluation for 1,4-Dioxane* (U.S. EPA, 2017c), EPA encourages submission of additional existing data, such as full study reports or workplace monitoring from industry sources, that may be relevant for refining conditions of use, exposures, hazards and potentially exposed or susceptible subpopulations during the risk evaluation. EPA will continue to consider new information submitted by the public until the end of the public comment period in 2018.

During the risk evaluation, EPA will rely on the search results [*1, 4-Dioxane (CASRN 123-91-1) Bibliography: Supplemental File for the TSCA Scope Document*; (U.S. EPA, 2017a)] or perform supplemental searches to address specific questions. Further, EPA may consider any relevant CBI information in the risk evaluation in a manner that protects the confidentiality of the information from public disclosure. The analysis plan is based on EPA's knowledge of 1,4-dioxane to date which includes partial, but not complete review of identified information. Should additional data or approaches become available, EPA may refine its analysis plan based on this information.

2.6.1 Exposure

For 1,4-dioxane, EPA does not plan to further analyze background levels for ambient air, indoor air, groundwater, and drinking water.

2.6.1.1 Environmental Releases, Fate and Exposures

EPA does not plan to further analyze environmental releases to environmental media based on information described in Section 2.5. For the purposes of developing estimates of occupational exposure, EPA may use release related data collected under selected data sources such as the Toxics Release Inventory (TRI) and National Emissions Inventory (NEI) programs. Analyses conducted using physical and chemical properties, fate information and TRI/DMR show that TSCA-related environmental releases for 1,4-dioxane do not result in significant exposure to aquatic species through water and sediment exposure pathways (see Section 2.5.3.3). For the pathways of exposures for the general population and terrestrial species, EPA has determined that the existing regulatory programs and associated analytical processes have addressed or are in the process of addressing potential risks of chemicals that may be present in other media pathways. For these cases, EPA believes that the TSCA risk evaluation should focus not on those exposure pathways, but rather on exposure pathways associated with TSCA uses that are not subject to those regulatory processes.

EPA does not plan to further analyze the environmental fate of 1,4-dioxane based on the conceptual models described in Section 2.5.2 and Section 2.5.3.

EPA does not plan to further analyze environmental exposures to 1,4-dioxane based on the exposure assessment presented in Section 2.3.4.

2.6.1.2 Occupational Exposures

EPA expects to evaluate both worker and occupational non-user exposures as follows:

1) Review reasonably available exposure monitoring data for specific condition(s) of use.

Exposure data to be reviewed may include workplace monitoring data collected by government agencies such as OSHA and the NIOSH, and monitoring data found in published literature [e.g., personal exposure monitoring data (direct measurements) and area monitoring data (indirect measurements)]. Studies will be evaluated using the evaluation strategies laid out in the *Application of Systematic Review in TSCA Risk Evaluations* (U.S. EPA, 2018a).

EPA will evaluate applicable regulatory and non-regulatory exposure limits. Available data sources that may contain relevant monitoring data for the various conditions of use are listed in Table 2-10.

Table 2-10. Potential Sources of 1,4-Dioxane Occupational Exposure Data

The 2002 ECJRC Summary Risk Assessment Report: 1,4-Dioxane (ECJRC, 2002)
Health Canada Screening Assessment for the Challenge: 1,4-Dioxane (Health Canada, 2010)
U.S. NIOSH Health Hazard Evaluation (HHE) Program reports (NIOSH, 1987, 1982, 1980)
U.S. OSHA Chemical Exposure Health Data (CEHD) program data (OSHA, 2017b)
Industry workplace exposure monitoring data submitted to EPA by BASF Corporation and the American Chemistry Council (ACC) (BASF, 2017; ACC, 2015)
U.S. EPA Generic Scenarios (https://www.epa.gov/tsca-screening-tools/using-predictive-methods-assess-exposure-and-fate-under-tsca#fate)
OECD Emission Scenario Documents (OECD, 2015, 2011)
Buffler, P. A., Wood, S. M., Suarez, L., Kilian, D. J. Mortality follow-up of workers exposed to 1,4-dioxane. Journal of Occupational and Environmental Medicine. 1978. 20:255-259.
Jezewska, A., Szewczyńska, M., Woźnica, A. Occupational exposure to airborne chemical substances in paintings conservators. Medycyna Pracy. 2014. 65:33-41.
Kupczewska-Dobecka, M., Czerczak, S., Jakubowski, M., Maciaszek, P., Janasik, B. Application of predictive model to estimate concentrations of chemical substances in the work environment. Medycyna Pracy. 2010. 61:307-314.

2) **For conditions of use where data are limited or not available, review existing exposure models that may be applicable in estimating exposure levels.**

EPA has identified potentially relevant OECD ESDs and EPA GS corresponding to some conditions of use. For example, the GS for Synthetic Fiber Manufacture, the GS on Lubricant Additives, the ESD on the Use of Metalworking Fluid, and the ESD on the Use of Adhesives are some of the ESDs and GS's that EPA may use to estimate occupational exposures for conditions of use such as use as a wetting and dispersing agent in textile manufacturing, use in hydraulic fluids, and use in film cement. EPA will need to critically review these generic scenarios and ESDs to determine their applicability to the conditions of use assessed. EPA was not able to identify ESDs or GS's corresponding to several conditions of use, including solvent recycling, distribution, wood pulping, animal and vegetable oil extraction, fluoropolymer etching, and use as a fuel additive. EPA will perform additional targeted research, such as consulting Kirk-Othmer, in order to better understand those conditions of use, which may inform the identification of exposure scenarios. EPA may also need to perform targeted research to identify applicable models that may be used to estimate exposures for certain conditions of use.

3) **Review reasonably available data that may be used in developing, adapting or applying exposure models to the particular risk evaluation.**

If necessary, EPA will evaluate relevant data to determine whether the data can be used to develop, adapt, or apply models for specific conditions of use and corresponding exposure scenarios.

4) **Consider and incorporate applicable engineering controls and/or personal protective equipment into exposure scenarios.**

EPA will review potential data sources on engineering controls and personal protective equipment as identified in Table 2-10 to determine their applicability and incorporation into exposure scenarios during risk evaluation. Studies will be evaluated using the evaluation strategies laid out in the *Application of Systematic Review in TSCA Risk Evaluations* (U.S. EPA, 2018a).

5) **Evaluate the weight of the evidence of occupational exposure data.**

EPA will rely on the weight of the scientific evidence when evaluating and integrating occupational exposure data. The data integration strategy will be designed to be fit-for-purpose in which EPA will use systematic review methods to assemble the relevant data, evaluate the data for quality and relevance, including strengths and limitations, followed by synthesis and integration of the evidence.

6) **Map or group each condition of use to occupational exposure assessment scenario(s).**

EPA has identified release/occupational exposure scenarios and mapped them to relevant conditions of use in Appendix D. As presented in the fourth column of the table in this appendix, EPA has grouped the uses into 23 representative release/exposure scenarios each with 5-6 unique combinations of exposure pathway, route, and receptor that will be further evaluated. EPA may further refine the mapping/grouping of 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. Consumer Exposures EPA does not expect to consider and analyze consumer exposures in the risk evaluation as described in the *Scope of the Risk Evaluation for 1,4-Dioxane* (U.S. EPA, 2017c).

2.6.1.3 General Population

EPA does not expect to consider and analyze general population exposures in the risk evaluation for 1,4-dioxane based on Section 2.5.3.3. EPA has determined that the existing regulatory programs and associated analytical processes have addressed or are in the process of addressing potential risks of 1,4-dioxane that may be present in various media pathways (e.g., air, water, land) for the general population.

For these cases, EPA believes that the TSCA risk evaluation should focus not on those exposure pathways, but rather on exposure pathways associated with TSCA uses that are not subject to those regulatory processes.

2.6.2 Hazard

2.6.2.1 Environmental Hazards

EPA does not plan to further analyze environmental hazards to 1,4-dioxane based on the hazard assessment presented in Section 2.4.1.

2.6.2.2 Human Health Hazards

EPA expects to evaluate human health hazards as follows:

1) **Review reasonably available human health hazard data, including data from alternative test methods (e.g., computational toxicology and bioinformatics; high-throughput screening methods; data on categories and read-across; *in vitro* studies; systems biology).**

For the 1,4 dioxane risk evaluation, EPA will evaluate information in the IRIS assessment and human health studies using OPPT's structured process described in the document, *Application of Systematic Review in TSCA Risk Evaluations* (U.S. EPA, 2018a). Human, animal and mechanistic data will be identified and included as described in Appendix F.3. EPA plans to prioritize the evaluation of mechanistic evidence. Specifically, EPA does not plan to evaluate mechanistic studies unless needed to clarify questions about associations between 1,4-dioxane and health effects and its relevance to humans. The protocol describes how studies will be evaluated using specific data evaluation criteria and a predetermined systematic approach. Study results will be extracted and presented in evidence tables by hazard endpoint. EPA plans to evaluate key studies used in the Integrated Risk Information System (IRIS) Toxicological Review of 1,4-Dioxane (U.S. EPA, 2013c, 2010), the TSCA Work Plan Problem Formulation and Initial Assessment (U.S. EPA, 2015c) and studies published after 2010 (oral) and 2013 (inhalation) that were captured in the comprehensive literature search conducted by the Agency for 1,4 Dioxane (*1, 4-Dioxane (CASRN 123-91-1) Bibliography: Supplemental File for the TSCA Scope Document*; (U.S. EPA, 2017a)). EPA intends to review studies published after the IRIS assessment to ensure that EPA is considering information that has been made available since these assessments were conducted.

2) **In evaluating reasonably available data, determine whether particular human receptor groups may have greater susceptibility to the chemical's hazard(s) than the general population.**

Reasonably available human health hazard data will be evaluated to ascertain whether some human receptor groups may have greater susceptibility than the general population to 1,4-dioxane hazard(s). Susceptibility of particular human receptor groups to 1,4-dioxane will be determined by evaluating information on factors that influence susceptibility.

3) **Conduct hazard identification (the qualitative process of identifying non-cancer and cancer endpoints) and dose-response assessment (the quantitative relationship between hazard and exposure) for all identified human health hazard endpoints.**

Human health hazards from acute and chronic exposures will be identified by evaluating the human and animal data that meet the systematic review data quality criteria described in the *Application of Systematic Review in TSCA Risk Evaluations* document (U.S. EPA, 2018a). Data quality evaluation will be performed on key studies identified from the IRIS assessments (U.S. EPA, 2013b, 2010), the *TSCA Work Plan Problem Formulation and Initial Assessment* (U.S. EPA, 2015c) and studies published after 2010 (oral) and 2013 (inhalation) that were captured in the comprehensive literature search. Hazards identified by studies meeting data quality criteria will be grouped by routes of exposure relevant to humans (oral, dermal, inhalation) and by cancer and noncancer endpoints.

Dose-response assessment will be performed in accordance with EPA guidance (U.S. EPA, 2012b, 2011b, 1994). Dose-response analyses performed for the IRIS oral and inhalation reference dose determinations (U.S. EPA, 2013c, 2010) may be used if the data meet data quality criteria and if additional information on the identified hazard endpoints are not available or would not alter the analysis.

The cancer mode of action (MOA) determines how cancer risks can be quantitatively evaluated. EPA will evaluate information on genotoxicity and the mode of action for all tumor types to determine the appropriate approach for quantitative cancer assessment in accordance with the U.S. EPA *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a).

4) **Derive points of departure (PODs) where appropriate; conduct benchmark dose modeling depending on the available data. Adjust the PODs as appropriate to conform (e.g., adjust for duration of exposure) to the specific exposure scenarios evaluated.**

Hazard data will be evaluated to determine the type of dose-response modeling that is applicable. Where modeling is feasible, a set of dose-response models that are consistent with a variety of potentially underlying biological processes will be applied to empirically model the dose-response relationships in the range of the observed data consistent with the EPA *Benchmark Dose Technical Guidance Document* (U.S. EPA, 2012b). Where dose-response modeling is not feasible, NOAELs or LOAELs will be identified.

EPA will evaluate whether the available PBPK and empirical kinetic models are adequate for route-to-route and interspecies extrapolation of the POD, or for extrapolation of the POD to standard exposure durations (e.g., lifetime continuous exposure). If application of the PBPK model is not possible, oral PODs may be adjusted by $BW^{3/4}$ scaling in accordance with (U.S. EPA, 2011b), and inhalation PODs may be adjusted by exposure duration and chemical properties in accordance with (U.S. EPA, 1994).

5) **Consider the route(s) of exposure (oral, inhalation, dermal), available route-to-route extrapolation approaches, available biomonitoring data and available approaches to correlate internal and external exposures to integrate exposure and hazard assessment.**

EPA believes there are sufficient data to conduct dose-response analysis and/or benchmark dose modeling for both inhalation and oral routes of exposure.

If sufficient dermal toxicity studies are not identified in the literature search to assess risks from dermal exposures, then a route-to-route extrapolation from the inhalation and oral toxicity studies would be needed to assess systemic risks from dermal exposures. Without an adequate PBPK model, the approaches described in the EPA guidance document *Risk Assessment Guidance for Superfund Volume I: Human Health Evaluation Manual (Part E, Supplemental Guidance for Dermal Risk Assessment)* could be applied. These approaches may be able to further inform the relative importance of dermal exposures compared with other routes of exposure.

6) Evaluate the weight of the evidence of human health hazard data.

EPA will rely on the weight of the scientific evidence when evaluating and integrating human health hazard data. The data integration strategy will be designed to be fit-for-purpose in which EPA will use systematic review methods to assemble the relevant data, evaluate the data for quality and relevance, including strengths and limitations, followed by synthesis and integration of the evidence.

2.6.3 Risk Characterization

Risk characterization is an integral component of the risk assessment process for both ecological and human health risks. EPA will derive the risk characterization in accordance with EPA's *Risk Characterization Handbook* (U.S. EPA, 2000). As defined in EPA's Risk Characterization Policy, "the risk characterization integrates information from the preceding components of the risk evaluation and synthesizes an overall conclusion about risk that is complete, informative and useful for decision makers." Risk characterization is considered to be a conscious and deliberate process to bring all important considerations about risk, not only the likelihood of the risk but also the strengths and limitations of the assessment, and a description of how others have assessed the risk into an integrated picture.

Risk characterization at EPA assumes different levels of complexity depending on the nature of the risk assessment being characterized. The level of information contained in each risk characterization varies according to the type of assessment for which the characterization is written. Regardless of the level of complexity or information, the risk characterization for TSCA risk evaluations will be prepared in a manner that is transparent, clear, consistent and reasonable (TCCR) (U.S. EPA, 2000). EPA will also present information in this section consistent with approaches described in the *Procedures for Chemical Risk Evaluation Under the Amended Toxic Substances Control Act* (82 FR 33726). For instance, in the risk characterization summary, EPA will further carry out the obligations under TSCA section 26; for example, by identifying and assessing uncertainty and variability in each step of the risk evaluation, discussing considerations of data quality such as the reliability, relevance and whether the methods utilized were reasonable and consistent, explaining any assumptions used, and discussing information generated from independent peer review. EPA will also be guided by EPA's *Information Quality Guidelines* (U.S. EPA, 2002) as it provides guidance for presenting risk information. Consistent with those guidelines, in the risk characterization, EPA will also identify: (1) Each population addressed by an estimate of applicable risk effects; (2) the expected risk or central estimate of risk for the potentially exposed or susceptible subpopulations affected; (3) each appropriate upper-bound or lower bound estimate of risk; (4) each significant uncertainty identified in the process of the assessment of risk effects and the studies that would assist in resolving the uncertainty; and (5) peer reviewed studies known to the Agency that support, are directly relevant to, or fail to support any estimate of risk effects and the methodology used to reconcile inconsistencies in the scientific information.

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APPENDICES

Appendix A REGULATORY HISTORY

A.1 Federal Laws and Regulations

Table_Apx 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	1,4-Dioxane is a listed substance subject to reporting requirements under 40 CFR 372.65 effective as of January 01, 1987.

Statutes/Regulations	Description of Authority/Regulation	Description of Regulation
	and that manufacture, process or otherwise use a TRI-listed chemical in quantities above threshold levels.	
Federal Food, Drug, and Cosmetic Act (FFDCA) – Section 408	FFDCA governs the allowable residues of pesticides in food. Section 408 of the FFDCA provides EPA with the authority to 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.	In 1998, 1,4-dioxane was removed from the list of pesticide product inert 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	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,

Statutes/Regulations	Description of Authority/Regulation	Description of Regulation
	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 (taking into account the cost of achieving reductions and environmental impacts and energy requirements) EPA determines has been adequately demonstrated.	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 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.	1,4-Dioxane is listed as a HAP under section 112 (42 U.S.C. § 7412) of the CAA.
CAA – Section 112(d)	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	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)

Statutes/Regulations	Description of Authority/Regulation	Description of Regulation
	control technology (GACT) standards, are allowed at the Administrator's discretion for area sources.	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), 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).

Statutes/Regulations	Description of Authority/Regulation	Description of Regulation
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, taking 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.	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).
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 1,4dioxane 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	In 1989, 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

Statutes/Regulations	Description of Authority/Regulation	Description of Regulation
	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.	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 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.	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 171, 40 CFR 173.202 and 40 CFR 173.242).

A.2 State Laws and Regulations

Table_Apx 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_Apx 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 [Government of Canada (2010) *1,4-Dioxane*. 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 (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

Country/Organization	Requirements and Restrictions
	• 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. The WHO water quality guideline is 0.05 mg/L 1,4-dioxane in drinking water (WHO, 2005).

Appendix B PROCESS, RELEASE AND OCCUPATIONAL EXPOSURE INFORMATION

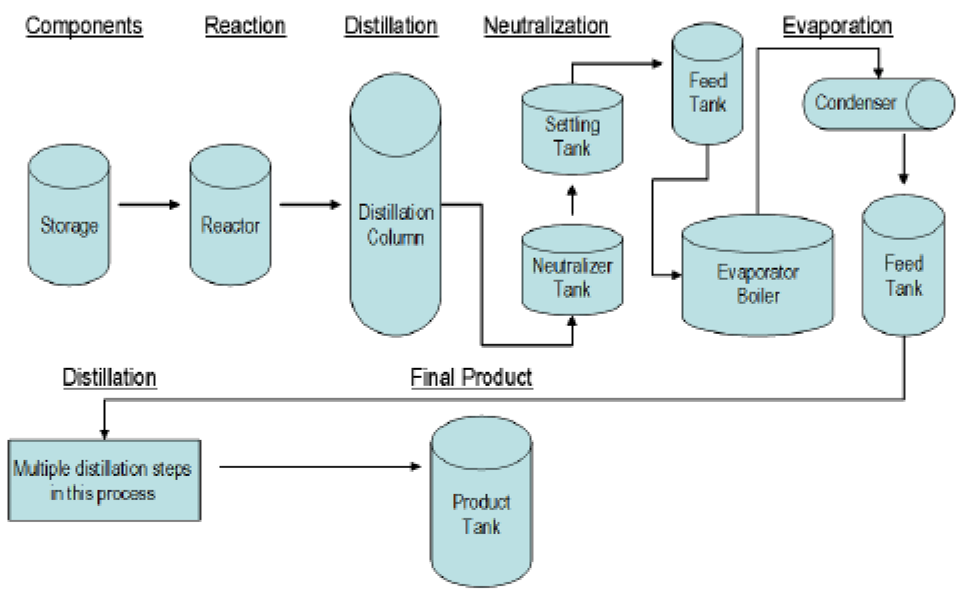
This appendix provides information and data found in preliminary data gathering for 1,4-dioxane.

B.1 Process Information

Process-related information potentially relevant to the risk evaluation may include process diagrams, descriptions and equipment. Such information may inform potential release sources and worker exposure activities for consideration.

B.1.1 Manufacture (Including Import)

The primary method for industrial production of 1,4-dioxane involves an acid-catalyzed conversion of ethylene glycol (mono-, di-, tri- and polyethylene glycol may be used) by ring closure in a closed system. The process is carried out 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). The synthesis step is performed in a heated vessel. The raw 1,4-dioxane product is then moved to a distillation column to start the purification process. Multiple steps are used to purify the 1,4-dioxane, including separation from water and volatile by-products by extractive distillation, heating with acids, salting out with NaCl, $CaCl_2$ or NaOH, and fine subsequent distillation (ECJRC, 2002). Figure_Apx B-1 (BASF, 2017).



Figure_Apx B-1: General Process Flow Diagram for 1,4-Dioxane Manufacturing

Source: EPA-HQ-OPPT-2016-0723-0012 (BASF, 2017).

Two other reactions can be used to make 1,4-dioxane, but they are primarily used to make substituted dioxanes and not known to be used for industrial 1,4-dioxane production (ECJRC, 2002).

B.1.2 Processing and Distribution

B.1.2.1 Processing as a Reactant/Intermediate

1,4-Dioxane can be used as a chemical reactant in the production of pharmaceuticals, polyethylene terephthalate (PET) plastics, rubber, insecticides and pesticides, cement, deodorant fumigant, magnetic tape and adhesives [EPA-HQ-OPPT-2017-0723-0003 (U.S. EPA, 2017b)]. Exact process operations involved in the use of 1,4-dioxane as a chemical reactant are dependent on the final product that is being synthesized. For the use of 1,4-dioxane as a chemical reactant, operations would typically involve unloading 1,4-dioxane from transport containers and feeding the 1,4-dioxane into a reaction vessel(s), where the 1,4-dioxane would react either fully or to a lesser extent. Following completion of the reaction, the produced substance may or may not be purified further, thus removing unreacted 1,4-dioxane (if any exists). Reacted 1,4-dioxane is assumed to be destroyed and is thus not expected to be released or cause potential worker exposures.

B.1.2.2 Processing – Non-Incorporative

1,4-Dioxane is used as a process solvent during the manufacturing of cellulose acetate, resins, waxes and fats [EPA-HQ-OPPT-2017-0723-0003 (U.S. EPA, 2017b)].

B.1.2.3 Repackaging

Typical repackaging operations involve transferring of chemicals into appropriately sized containers to meet customer demands/needs.

B.1.2.4 Recycling

1,4-Dioxane is used as a solvent in several applications. In this capacity, 1,4-dioxane can be regenerated and recycled for reuse.

B.1.3 Uses

B.1.3.1 Processing Aids, Not Otherwise Listed

Processing aids are chemical substances used to improve the processing characteristics or the operation of process equipment or to alter or buffer the pH of the substance or mixture, when added to a process or to a substance or mixture to be processed. Processing agents do not become a part of the reaction product and are not intended to affect the function of a substance or article created (U.S. EPA, 2016c). 1,4-Dioxane is used in a number of industrial processes as a processing aid. These processes include wood pulping, extraction of animal and vegetable oils, textile processing, polymerization, pharmaceutical purification and etching of fluoropolymers [EPA-HQ-OPPT-2017-0723-0003; (U.S. EPA, 2017b); EPA-HQ-OPPT-2016-0723-0012 (BASF, 2017)]. Exact process operations involved in the use of 1,4-dioxane as a processing aid are dependent on the final product that is being synthesized.

B.1.3.1 Functional Fluids (Open and Closed Systems)

Functional fluids are liquid or gaseous chemical substances used for one or more operational properties (U.S. EPA, 2016c). 1,4-Dioxane is used in polyalkylene glycol lubricants, synthetic metalworking fluids, cutting and tapping fluids and hydraulic fluids [EPA-HQ-OPPT-2017-0723-0003 (U.S. EPA, 2017b)]. Exact operations involved in the use of 1,4-dioxane as a functional fluid are dependent on the final product.

B.1.3.2 Laboratory Chemicals

1,4-Dioxane is used in laboratories as a chemical reagent, reference material, stable reaction medium, liquid scintillation counting medium, spectroscopic and photometric measurement, cryoscopic solvent and histological preparation [EPA-HQ-OPPT-2017-0723-0003 (U.S. EPA, 2017b)]. Laboratory procedures are generally done within a fume hood, on a bench with local exhaust ventilation or under general ventilation.

B.1.3.3 Adhesives and Sealants

1,4-Dioxane is found in film cement and as a residual contaminant in two-component glues and adhesives [EPA-HQ-OPPT-2017-0723-0003 (U.S. EPA, 2017b)]. The application procedure depends on the type of adhesive and the type of substrate. After the adhesive is received by the user, it may be diluted or mixed prior to application. The formulation is then loaded into the application reservoir or apparatus and applied to the substrate via spray, roll, curtain or syringe or bead application. Application may be manual or automated. After application, the adhesive or sealant is allowed to dry, usually at ambient temperature, such that the solvent completely evaporates and a bond is formed between the substrates (OECD, 2015).

B.1.3.4 Other Uses

Other conditions of use where 1,4-dioxane may be formulated into a product or used as part of another process may include use in fuels and fuel additives [EPA-HQ-OPPT-2016-0723-0012 (BASF, 2017)], spray polyurethane foam and in printing and printing compositions [EPA-HQ-OPPT-2017-0723-0003 (U.S. EPA, 2017b)].

B.1.4 Disposal

1,4-Dioxane is disposed of to a variety of environmental media: land, water and air. Land disposals include Class I underground injection, RCRA Subtitle C landfills and to other uncategorized land points. 1,4-Dioxane is sometimes discharged to water. Wastewater treatment may or may not precede these water releases. Additionally, 1,4-dioxane is also commonly incinerated (U.S. EPA, 2015c).

B.2 Occupational Exposure Data

EPA presents below an example of occupational exposure-related information from the preliminary data gathering. EPA will consider this information and data in combination with other data and methods for use in the risk evaluation.

Table_Apx B 1 summarizes OSHA CEHD data by North American Industry Classification System (NAICS) code (OSHA, 2017a).

Table_Apx B-1. Summary of Industry Sectors with 1,4-Dioxane Personal Monitoring Air Samples Obtained from OSHA Inspections Conducted Between 2002 and 2016

NAICS	NAICS Description
315225	Men's and Boys' Cut and Sew Work Clothing Manufacturing
325199	All Other Basic Organic Chemical Manufacturing
334418	Printed Circuit Assembly (Electronic Assembly) Manufacturing
336399	All Other Motor Vehicle Parts Manufacturing
926150	Regulation, Licensing, and Inspection of Miscellaneous Commercial Sectors

Appendix C ANALYSIS: ENVIRONMENTAL CONCENTRATION OF CONCERN (COC)

The concentrations of concern (COC) for aquatic species were calculated based on the environmental hazard data for 1,4-dioxane summarized in Section 2.4.1. The methods for calculating the COCs are are based on published EPA/OPPT methods (U.S. EPA, 2013a, 2012d). The acute and chronic COC for 1,4-dioxane for each endpoint are determined based on the lowest toxicity value in the dataset. For a particular environment (e.g., aquatic environment), the COC is based and on the most sensitive species in that environment.

After selecting the lowest toxicity value, an assessment factor (AF) is applied according to EPA/OPPT methods (U.S. EPA, 2013a, 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. AFs are also account for differences in inter- and intra-species variability, as well as laboratory-to-field variability. These assessment factors are dependent upon the availability of datasets that can be used to characterize relative sensitivities across multiple species within a given taxa or species group, but are often standardized in risk assessments conducted under TSCA, since the data available for most industrial chemicals is limited. The acute COC for the aquatic plant endpoint is determined based on the lowest value in the dataset divided by an assessment factor (AF) of 4. 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.

Acute COC calculations

The lowest acute toxicity value for aquatic organisms (i.e., most sensitive species) for 1,4-dioxane is from a 96-hour fish toxicity study where the LC_{50} is >100 mg/L (Geiger et al., 1990). The lowest value was then divided by the assessment factor (AF) of 5 for aquatic invertebrates.

Lowest value for the 96-hour fish toxicity LC_{50} (>100 mg/L) / AF of 5 = 20,000 µg/L or ppb.

Chronic COC Calculations

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.

Lowest value for 32-day fish MATC = 145 mg/L / 10 = 14.5 x 1000 = 14,500 µg/L or ppb.

Summary

The acute concentration of concern for 1,4-dioxane is based on the 96-hour toxicity value for fish of >100 mg/L (Geiger et al., 1990) and the chronic COC is based on a 32-day MATC fish toxicity value of 145 mg/L (Brooke, 1987). The acute and chronic COCs for 1,4-dioxane are 20,000 ppb and 14,500 ppb, respectively.

Appendix D SUPPORTING TABLE FOR INDUSTRIAL AND COMMERCIAL ACTIVITIES AND USES CONCEPTUAL MODEL

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. All possible exposure scenarios for each condition of use were identified according to the COU in Table 2-3 and the conceptual model in Figure 2-2 and are presented in Table_Apx D-1. EPA used readily available fate, engineering, exposure and/or toxicity information to determine whether to conduct further analysis on each exposure scenario.

EPA has identified release/occupational exposure scenarios and mapped them to relevant conditions of use in the table 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 may further refine 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_Apx D-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	Pharmaceutical Intermediate Polymerization catalyst	Pharmaceutical product manufacture 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-	Pharmaceutical and medicine	Pharmaceutical product	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

	incorporative	manufacturing (process solvent)	manufacture					magnitude lower than via inhalation and will not be further analyzed.
Processing		Basic organic chemical manufacturing (process solvent)	Basic organic chemical manufacture	Vapor	Inhalation	Workers	Yes	Due to high volatility at room temperature, inhalation exposure from vapor should be further evaluated.
Processing	Repackaging		Repackaging to large and small containers	Liquid Contact	Dermal	ONU	No	Dermal exposure is expected to be primarily to workers directly involved in handling the chemical.
Processing		Bulk to packages, then distribute		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	Workers	Yes	Workers are expected to routinely handle liquids containing 1,4-dioxane.
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 Processing aids, not otherwise listed	Agricultural chemical intermediate Plasticizer intermediate Catalysts and reagents for anhydrous acid reactions, brominations and sulfonations Polymerization catalyst	Agricultural product manufacture Plasticizer manufacture Anhydrous acid, bromination and sulfonation reaction chemical manufacture Polymer 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				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				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				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 Extraction of animal and vegetable oils Wetting and dispersing agent in textile processing	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.
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	Purification of pharmaceuticals	Pharmaceutical product manufacture	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			Vapor	Inhalation	Workers	Yes	Due to high volatility at room temperature, inhalation exposure from vapor should be further evaluated.

	otherwise listed							
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	No	Mist generation is not expected.
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 Cutting and Tapping Fluid Synthetic metalworking fluid Hydraulic fluid	Use of lubricants Use of metalworking fluids Servicing hydraulic equipment and charging hydraulic fluids in original equipment manufacture	Liquid Contact	Dermal	Workers	Yes	Workers are expected to routinely handle liquids containing 1,4-dioxane.
Industrial use	Functional fluids (closed/open system)			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	Functional fluids (closed/open system)			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	Dermal 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	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	measurement Liquid scintillation and counting medium Stable reaction medium Cryoscopic solvent for molecular mass determinations Preparation of histological sections for microscopic examination		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	Dermal 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			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			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 Printing and printing compounds	Application of spray polyurethane foam through a nozzle Use of Printing Inks	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	Yes	Mist generation may occur during these processes.
Manufacture, processing, use, Disposal	Emissions to air Wastewater	Air Industrial pre-treatment Industrial	Worker Handling of wastes	Liquid Contact	Dermal	Workers	Yes	Workers are expected to routinely handle liquids containing 1,4-dioxane.
Manufacture, processing, use, Disposal				Vapor	Dermal	Workers	No	The absorption of 1,4-dioxane vapor via skin is expected to be orders of

	Solid wastes and liquid wastes	wastewater treatment Publicly owned treatment works (POTW) Underground Injection Municipal landfill Hazardous landfill						magnitude lower than via inhalation and will not be further analyzed.
Manufacture, processing, use, Disposal				Vapor	Inhalation	Workers	Yes	Due to high volatility at room temperature, inhalation exposure from vapor should be further evaluated.
Manufacture, processing, use, Disposal				Liquid Contact	Dermal	ONU	No	Dermal exposure is expected to be primarily to workers directly involved in handling the chemical.
Manufacture, processing, use, Disposal				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, processing, use, Disposal				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.

Appendix E SUPPORTING TABLE FOR ENVIRONMENTAL RELEASES AND WASTES CONCEPTUAL MODEL

All possible exposure scenarios for each condition of use were identified according to the COU in Table 2-3 and the environmental releases conceptual model in Figure 2-3 and are presented in Table_Apx E-1. 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. EPA may further refine the mapping/grouping of exposure scenarios based on factors corresponding to conditions of use as additional information is identified during risk evaluation.

Table_Apx E-1: 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	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).

		Owned Treatment Works (POTW)					
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 F INCLUSION AND EXCLUSION CRITERIA FOR FULL TEXT SCREENING

Appendix F contains the eligibility criteria for various data streams informing the TSCA risk evaluation: environmental fate; engineering and occupational exposure; exposure to the general population and consumers; and human health hazard. The criteria are applied to the *on-topic* references that were identified following title and abstract screening of the comprehensive search results published on June 22, 2017.

Systematic reviews typically describe the study eligibility criteria in the form of PECO statements or a modified framework. PECO stands for **P**opulation, **E**xposure, **C**omparator and **O**utcome and the approach is used to formulate explicit and detailed criteria about those characteristics in the publication that should be present in order to be eligible for inclusion in the review. EPA/OPPT adopted the PECO approach to guide the inclusion/exclusion decisions during full text screening.

Inclusion and exclusion criteria were also used during the title and abstract screening, and documentation about the criteria can be found in the *Strategy for Conducting Literature Searches* document published in June 2017 along with each of the TSCA Scope documents. The list of *on-topic* references resulting from the title and abstract screening is undergoing full text screening using the criteria in the PECO statements. The overall objective of the screening process is to select the most relevant evidence for the TSCA risk evaluation. As a general rule, EPA is excluding non-English data/information sources and will translate on a case by case basis.

The inclusion and exclusion criteria for ecotoxicological data have been documented in the ECOTOX SOPs. The criteria can be found at https://cfpub.epa.gov/ecotox/help.cfm?helptabs=tab4) and in the *Strategy for Conducting Literature Searches* document published along with each of the TSCA Scope documents.

Since full text screening commenced right after the publication of the TSCA Scope document, the criteria were set to be broad to capture relevant information that would support the initial scope. Thus, the inclusion and exclusion criteria for full text screening do not reflect the refinements to the conceptual model and analysis plan resulting from problem formulation. As part of the iterative process, EPA is in the process of refining the results of the full text screening to incorporate the changes in information/data needs to support the revised scope.

These refinements will include changes to the inclusion and exclusion criteria discussed in this appendix to better reflect the revised scope of the risk evaluation and will likely reduce the number of data/information sources that will undergo evaluation.

F.1 Inclusion Criteria for the Data Sources Reporting Environmental Fate Data

EPA/OPPT developed a generic PESO statement to guide the full text screening of environmental fate data sources. PESO stands for Pathways and Processes, Exposure, Setting or Scenario, and Outcomes. Subsequent versions of the PESO statement may be produced throughout the process of screening and evaluating data for the chemicals undergoing TSCA risk evaluation. Studies that comply with the inclusion criteria in the PESO statement are eligible for inclusion, considered for evaluation, and possibly included in the environmental fate assessment. On the other hand, data sources are excluded if they do not meet the criteria in the PESO statement.

During the development of conceptual models and consideration of the nexus between TSCA and other EPA regulations for 1,4-dioxane it was determined that no pathways for consumer or environmental exposure requiring environmental fate information would be further analyzed. As described in Section 2.5.2, EPA does not plan to evaluate exposure pathways to human receptors from consumer uses of 1,4-dioxane. As described in Section 2.5.3, there are no exposure pathways for general population or ecological receptors from environmental releases and waste streams associated with industrial and commercial activities for 1,4-dioxane that EPA plans to include and further analyze in the risk assessment.

For 1,4-dioxane no exposure pathways to human and ecological receptors from consumer products, environmental releases, or waste streams associated with industrial and commercial activities will be further analyzed in risk evaluation. In the absence of exposure pathways for further analysis, environmental fate data will not be evaluated further. Therefore, no PESO statement or fate data needs and associated processes, media and exposure pathways considered in the development of the environmental fate assessment for 1,4-dioxane will be presented.

F.2 Inclusion Criteria for Data Sources Reporting Engineering and Occupational Exposure Data

EPA/OPPT developed a generic RESO statement to guide the full text screening of engineering and occupational exposure literature (Table_Apx F-1). RESO stands for Receptors, Exposure, Setting or Scenario, and Outcomes. Subsequent versions of the RESO statement may be produced throughout the process of screening and evaluating data for the chemicals undergoing TSCA risk evaluation. Studies that comply with the inclusion criteria specified in the RESO statement will be eligible for inclusion, considered for evaluation, and possibly included in the environmental release and occupational exposure assessments, while those that do not meet these criteria will be excluded.

The RESO statement should be used along with the engineering and occupational exposure data needs table (Table_Apx F-2) when screening the literature.

Since full text screening commenced right after the publication of the TSCA Scope document, the criteria for engineering and occupational exposure data were set to be broad to capture relevant information that would support the risk evaluation. Thus, the inclusion and exclusion criteria for full text screening do not reflect the refinements to the conceptual model and analysis plan resulting from problem formulation. As part of the iterative process, EPA is in the process of refining the results of the full text screening to incorporate the changes in information/data needs to support the risk evaluation.

Table_Apx F-1: Inclusion Criteria for Data Sources Reporting Engineering and Occupational Exposure Data

RESO Element	Evidence
Receptors	• **Humans:** Workers, including occupational non-users Please refer to the conceptual models for more information about the human receptors included in the TSCA risk evaluation.

Exposure	• Worker exposure and relevant environmental releases of the chemical substance of interest
	  ○ Dermal and inhalation exposure routes (as indicated in the conceptual model)
	  ○ Surface water (as indicated in the conceptual model)
	
	Please refer to the conceptual models for more information about the routes and media/pathways included in the TSCA risk evaluation.

Setting or Scenario	• Any occupational setting or scenario resulting in worker exposure and relevant environmental releases (includes all manufacturing, processing, use, disposal indicated in Table_Apx F-2 below.
Outcomes	• Quantitative estimates* of worker exposures and of relevant environmental releases from occupational settings • General information and data related and relevant to the occupational estimates*

* Metrics (e.g., mg/kg/day or mg/m^3 for worker exposures, kg/site/day for releases) are determined by toxicologists for worker exposures and by exposure assessors for releases; also, the Engineering Data Needs (Table_Apx F-2) provides a list of related and relevant general information.
TSCA=Toxic Substances Control Act

Table_Apx F-2: Engineering, Environmental Release and Occupational Data Necessary to Develop the Environmental Release and Occupational Exposure Assessments

Objective Determined during Scoping	Type of Data
General Engineering Assessment (may apply for either or both Occupational Exposures and / or Environmental Releases)	1. Description of the life cycle of the chemical(s) of interest, from manufacture to end-of-life (e.g., each manufacturing, processing, or use step), and material flow between the industrial and commercial life cycle stages. {Tags: Life cycle description, Life cycle diagram}[a] 2. The total annual U.S. volume (lb/yr or kg/yr) of the chemical(s) of interest manufactured, imported, processed, and used; and the share of total annual manufacturing and import volume that is processed or used in each life cycle step. {Tags: Production volume, Import volume, Use volume, Percent PV} [a] 3. Description of processes, equipment, unit operations, and material flows and frequencies (lb/site-day or kg/site-day and days/yr; lb/site-batch and batches/yr) of the chemical(s) of interest during each industrial/ commercial life cycle step. Note: if available, include weight fractions of the chemicals (s) of interest and material flows of all associated primary chemicals (especially water). {Tags: Process description, Process material flow rate, Annual operating days, Annual batches, Weight fractions (for each of above, manufacture, import, processing, use)} [a] 4. Basic chemical properties relevant for assessing exposures and releases, e.g., molecular weight, normal boiling point, melting point, physical forms, and room temperature vapor pressure. {Tags: Molecular weight, Boiling point, Melting point, Physical form, Vapor pressure, Water solubility} [a] 5. Number of sites that manufacture, process, or use the chemical(s) of interest for each industrial/ commercial life cycle step and site locations. {Tags: Numbers of sites (manufacture, import, processing, use), Site locations} [a]
Occupational Exposures	6. Description of worker activities with exposure potential during the manufacture, processing, or use of the chemical(s) of interest in each industrial/commercial life cycle stage. {Tags: Worker activities (manufacture, import, processing, use)} [a] 7. Potential routes of exposure (e.g., inhalation, dermal). {Tags: Routes of exposure (manufacture, import, processing, use)} [a] 8. Physical form of the chemical(s) of interest for each exposure route (e.g., liquid, vapor, mist) and activity. {Tags: Physical form during worker activities (manufacture, import, processing, use)} [a] 9. Breathing zone (personal sample) measurements of occupational exposures to the chemical(s) of interest, measured as time-weighted averages (TWAs), short-term exposures, or peak exposures in each occupational life cycle stage (or in a workplace scenario similar to an occupational life cycle stage). {Tags: PBZ measurements (manufacture, import, processing, use)} [a] 10. Area or stationary measurements of airborne concentrations of the chemical(s) of interest in each occupational setting and life cycle stage (or in a workplace scenario similar to the life cycle stage of interest). {Tags: Area measurements (manufacture, import, processing, use)} [a] 11. For solids, bulk and dust particle size characterization data. {Tags: PSD measurements (manufacture, import, processing, use)} [a] 12. Dermal exposure data. {Tags: Dermal measurements (manufacture, import, processing, use)} 13. Data needs associated with mathematical modeling (will be determined on a case-by-case basis). {Tags: Worker exposure modeling data needs (manufacture, import, processing, use)} [a] 14. Exposure duration (hr/day). {Tags: Worker exposure durations (manufacture, import, processing, use)} [a] 15. Exposure frequency (days/yr). {Tags: Worker exposure frequencies (manufacture, import, processing, use)} [a] 16. Number of workers who potentially handle or have exposure to the chemical(s) of interest in each occupational life cycle stage. {Tags: Numbers of workers exposed (manufacture, import, processing, use)} [a] 17. Personal protective equipment (PPE) types employed by the industries within scope. {Tags: Worker PPE (manufacture, import, processing, use)} [a] 18. Engineering controls employed to reduce occupational exposures in each occupational life cycle stage (or in a workplace scenario similar to the life cycle stage of interest), and associated data or estimates of exposure reductions. {Tags: Engineering controls (manufacture, import, processing, use), Engineering control effectiveness data} [a]

Objective Determined during Scoping	Type of Data
Environmental Releases	19. Description of relevant sources of potential environmental releases, including cleaning of residues from process equipment and transport containers, involved during the manufacture, processing, or use of the chemical(s) of interest in each life cycle stage. {Tags: Release sources (manufacture, import, processing, use)} [a] 20. Estimated mass (lb or kg) of the chemical(s) of interest released from industrial and commercial sites to relevant environmental media (water) and treatment and disposal methods (POTW), including releases per site and aggregated over all sites (annual release rates, daily release rates) {Tags: Release rates (manufacture, import, processing, use)} [a] 21. Relevant release or emission factors. {Tags: Emission factors (manufacture, import, processing, use)} [a] 22. Number of release days per year. {Tags: Release frequencies (manufacture, import, processing, use)} [a] 23. Data needs associated with mathematical modeling (will be determined on a case-by-case basis). {Tags: Release modeling data needs (manufacture, import, processing, use)} [a] 24. Waste treatment methods and pollution control devices employed by the industries within scope and associated data on release/emission reductions. {Tags: Treatment/ emission controls (manufacture, import, processing, use), Treatment/ emission controls removal/ effectiveness data} [a]

Notes:

[a] These are the tags included in the full text screening form. The screener makes a selection from these specific tags, which describe more specific types of data or information.

Abbreviations:
hr=Hour
kg=Kilogram(s)
lb=Pound(s)
yr=Year
PV=Particle volume
PBZ=
POTW=Publicly owned treatment works
PPE=Personal projection equipment
PSD=Particle size distribution
TWA=Time-weighted average

F.3 Inclusion Criteria for Data Sources Reporting Environmental and General Population Exposure

EPA/OPPT developed a generic PECO statement to guide the full text screening of environmental and general population exposure data sources. PECO stands for Population, Exposure, Comparator and Outcome and the approach is used to formulate explicit and detailed criteria about those characteristics in the publication that should be present to be eligible for inclusion in the review. Subsequent versions of the PECO statement may be produced throughout the process of screening and evaluating data for the chemicals undergoing TSCA risk evaluation. Exposure pathways to human and ecological receptors from environmental releases associated with industrial and commercial activities will not be further analyzed in risk evaluation (see Section 2.5.3.2 and Section 2.5.3.3). In the absence of exposure pathways for further analysis, data related to environmental and general population exposure will not be further analyzed.

F.4 Inclusion Criteria for Data Sources Reporting Human Health Hazards

Table_Apx F-3: Inclusion and Exclusion Criteria for Data Sources Reporting Human Health Hazards Related to 1,4-Dioxane Exposure[a]

PECO Element	Evidence Stream	Papers/Features Included	Papers/Features Excluded
Population	*Human*	• Any population • All lifestages • Study designs: ○ Controlled exposure, cohort, case-control, cross-sectional, case-crossover, case studies, and case series for all endpoints	
	Animal	• All non-human whole-organism mammalian species • All lifestages	• Non-mammalian species
	Mechanistic	• Human or animal cells, tissues, or biochemical reactions (e.g., ligand binding assays) with *in vitro* exposure regimens; bioinformatics pathways of disease analysis; or high throughput screening data.	
Exposure	*Human*	• Exposure based on administered dose or concentration of 1,4-dioxane, biomonitoring data (e.g., urine, blood or other specimens), environmental or occupational-setting monitoring data (e.g., air, water levels), job title or residence • Primary metabolites of interest (e.g., HTTA) as identified in biomonitoring studies • All routes of exposure • Any number of exposure groups • Quantitative, semi-quantitative or qualitative estimates of exposure • Exposures to multiple chemicals/mixtures only if 1,4-dioxane or related metabolites were independently measured and analyzed	• Multiple chemical/mixture exposures with no independent measurement of or exposure to 1,4-dioxane (or related metabolite)
	Animal	• A minimum of 2 quantitative dose or concentration levels of 1,4-dioxane plus a negative control group [a] • Acute, subchronic, chronic exposure from oral, dermal, inhalation routes • Exposure to 1,4-dioxane only (no chemical mixtures)	• Only 1 quantitative dose or concentration level in addition to the control [a] • Route of exposure ***not*** by inhalation, oral or dermal type (e.g., intraperitoneal, injection) • No duration of exposure stated • Exposure to 1,4-dioxane in a chemical mixture
	Mechanistic	• Exposure based on concentrations of the neat material of 1,4-dioxane • A minimum of 2 dose or concentration levels tested plus a control group [a]	• Only 1 quantitative dose or concentration level in addition to the control [a] • Exposure to 1,4-dioxane in a chemical mixture
Comparator	*Human*	• A comparison population [not exposed, exposed to lower levels, exposed below detection] for all endpoints	• No comparison population for all endpoints
	Animal	• Negative controls that are vehicle-only treatment and/or no treatment	• Negative controls ***other than*** vehicle-only treatment or no treatment
	Mechanistic	• Exposed to vehicle-only treatment and/or no treatment • ***For genotoxicity studies only***, studies using positive controls	• Negative controls ***other than*** vehicle-only treatment or no treatment • ***For genotoxicity studies only***, a lack of positive controls

Outcome	*Human and Animal*	• Endpoints described in the 1,4-dioxane scope document [b]:
		  ○ Cancer
		  ○ Liver toxicity	

PECO Element	Evidence Stream	Papers/Features Included	Papers/Features Excluded
		○ Kidney toxicity ○ Neurotoxicity ○ Irritation ○ Acute Toxicity/Poisoning • Other endpoints [c]	
	Mechanistic	• All mechanistic data that may inform the following health outcomes: ○ Cancer ○ Genotoxicity ○ Neurological/Behavior ○ Renal ○ Hepatic ○ Irritation ○ Acute Toxicity/Poisoning ○ ADME/PBPK	• Data related to other mechanisms of toxicity [a]
General Considerations		**Papers/Features Included**	**Papers/Features Excluded**
		• Written in English [d] • Reports a primary source or meta-analysis [a] • Full-text available • Reports both 1,4-dioxane exposure ***and*** a health outcome (or mechanism of action)	• Not written in English [d] • Reports a secondary source (e.g., review papers) [a] • No full-text available (e.g., only a study description/abstract, out-of-print text) • Reports a 1,4-dioxane-related exposure ***or*** a health outcome, but not both (e.g. incidence, prevalence report)

[a] Some of the studies that are excluded based on the PECO statement may be considered later during the systematic review process. For 1,4-dioxane, EPA will evaluate studies related to susceptibility after other data are reviewed. Finally, EPA may also review other data as needed (e.g., animal studies using one concentration, review papers).

[b] EPA will review key and supporting studies in the IRIS assessment that were considered in the dose-response assessment for non-cancer and cancer endpoints as well as studies published after the IRIS assessment.

[c] EPA may screen for hazards other than those listed in the scope document if they were identified in the updated literature search that accompanied the scope document.

[d] EPA may translate studies as needed.

F.5 List Of Retracted Papers

The following reference was retracted by the journal:

HERO ID: 3538089 (1,4-dioxane; HBCD)
Kreipke, CW; Rafols, JA; Reynolds, CA; Schafer, S; Marinica, A; Bedford, C; Fronczak, M; Kuhn, D; Armstead, WM. (2011). Clazosentan, a novel endothelin A antagonist, improves cerebral blood flow and behavior after traumatic brain injury. Neurol Res 33: 208-213. http://dx.doi.org/10.1179/016164111X12881719352570