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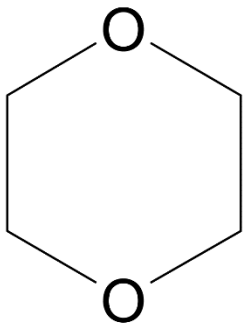
Office of Chemical Safety and
Pollution Prevention

TSCA Work Plan Chemical
Problem Formulation and Initial Assessment

1,4-Dioxane
CASRN: 123-91-1



April 2015

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Docket

Please visit the public docket (www.regulations.gov; Docket: EPA-HQ-OPPT-2015-0078) to view supporting information.

ABBREVIATIONS

ACC	American Chemistry Council
ACGIH	American Conference of Government Industrial Hygienists
AEGL	Acute Exposure Guideline Level
AES	Alkyl ethoxy sulphates
ATSDR	Agency for Toxic Substances and Disease Registries
BCF	Bioconcentration factor
CAA	Clean Air Act
CASRN	Chemical Abstract Service Registry Number
CBI	Confidential Business Information
CCL	Candidate Contaminant List
CDR	Chemical Data Reporting
CPSC	Consumer Product Safety Commission
CSF	Cancer Slope Factor
EC	European Commission
ECHA	European Chemicals Agency
EPA	Environmental Protection Agency
EU	European Union
EUSES	European System for the Evaluation of Substances
FDA	Food and Drug Administration
HEAA	β-hydroxyethoxy acetic acid
Hg	Mercury
HHS	Department of Health and Human Services
HPV	High Production Volume
IARC	International Agency for Research on Cancer
IRIS	Integrated Risk Information System
IUR	Inventory Update Reporting Rule; Inhalation Unit Risk
kg	Kilogram(s)
K_{ow}	Octanol:Water partition coefficient
lb	Pound
LOEC	Lowest Observed Effect Concentration
LOEL	Lowest Observed Effect Level
Log K_{ow}	Logarithmic Octanol:Water partition coefficient
MATC	Maximum Acceptable Toxicant Concentration
mg	Milligram(s)
MOE	Margin of Exposure
MRL	Minimal Risk Level
NIOSH	National Institute of Occupational Safety and Health
NOEC	No Observed Effect Concentration
NOAEL	No Observed Adverse Effect Level
NPL	National Priorities List
NTP	National Toxicology Program

OAR	Office of Air and Radiation
OCSPP	Office of Chemical Safety and Pollution Prevention
OECD	Organisation for Economic Co-operation and Development
OPPT	Office of Pollution Prevention and Toxics
OSHA	Occupational Safety and Health Administration
OSWER	Office of Solid Waste and Emergency Response
OW	Office of Water
PBPK	Physiologically Based Pharmacokinetic
PBT	Persistent, Bioaccumulative, Toxic
PDE	Permitted Daily Exposure
PEC	Predicted Environmental Concentration
PEL	Permissible Exposure Level
ppb	Parts per billion
ppm	Parts per million
PV	Production Volume
PWS	Public Water System
RA	Risk Assessment
RAR	Risk Assessment Report
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
REL	Recommended Exposure Level
RfC	Reference Concentration
RfD	Reference Dose
TCA	1,1,1-trichloroethane
TLV	Threshold Limit Value
TRI	Toxic Release Inventory
TSCA	Toxic Substances Control Act
UCMR	Unregulated Contaminant Monitoring Rule
US	United States
WHO	World Health Organisation
WWTP	Wastewater Treatment Plant
Yr	Year

EXECUTIVE SUMMARY

As part of EPA's comprehensive approach to enhance the Agency's management of existing chemicals, in March 2012 EPA/OPPT identified a work plan of chemicals for further assessment under the Toxic Substances Control Act (TSCA)[1]. Chemical risk assessments will be conducted if, as a result of scoping and problem formulation, there are exposures of concern, identified hazards and sufficient data for quantitative analysis. If an assessment identifies unreasonable risks to humans or the environment, EPA will pursue risk management. This document presents the problem formulation and initial assessment for 1,4-dioxane as part of the TSCA Work Plan program.

The conclusions from this problem formulation and initial assessment are that:

- EPA/OPPT will further assess potential risks to workers exposed during product formulation and use as a cleaning agent.
- EPA/OPPT will further assess potential risks to workers and consumers exposed during the use of TSCA-use products that contain 1,4-dioxane as a contaminant, such as paints, varnishes, adhesives, cleaners and detergents.
- Risk to the general population through inhalation exposure to ambient air emissions is estimated to be low.
- An assessment of risk from exposure through drinking water is not needed at this time because 1,4-dioxane is currently being monitored and EPA will determine whether or not regulatory action is needed as part of EPA's Regulatory Determination process.
- Based on the low hazard profile for 1,4-dioxane to aquatic organisms, risks to these organisms are expected to be low. Lack of hazard data for sediment and soil organisms precludes determination of risk to these environmental compartments. Therefore, further analysis of environmental risk is not planned.

1,4-Dioxane is an industrial solvent used in the production of a wide variety of products, as a laboratory reagent, a chemical intermediate, an extraction medium for fats and oils, and as part of a polymerization catalyst. Other uses of 1,4-dioxane are in commercial and consumer products such as lacquers, varnishes, paint strippers, dyes, greases, cleaners and detergents, adhesives, cosmetics and deodorants. 1,4-Dioxane is also present as an unintended byproduct in cosmetics, detergents, and shampoos. Historically, 90% of all 1,4-dioxane was used as a stabilizer in chlorinated solvents such as 1,1,1-trichloroethane (TCA). Use of 1,4-dioxane has decreased since 1,1,1-trichloroethane was phased out by the Montreal Protocol in 1996 for all uses except a few select applications. In the 1980's and early 1990's, 10 to 50 million pounds were manufactured yearly and from 1994 to 2006, the yearly U.S. production volume of 1,4-

[1] http://www.epa.gov/oppt/existingchemicals/

dioxane has been 1 to 10 million pounds. Recent data show that 1.1 million pounds is released to the environment.

During scoping and problem formulation, EPA/OPPT reviewed previous risk assessments and additional published studies on the fate, exposure and hazard of 1,4-dioxane. EPA/OPPT examined likely exposure and hazard scenarios based on current production, use, and fate information to identify scenarios amenable to risk analysis. The scenarios considered were:

- Workers potentially exposed during manufacturing and formulation of 1,4-dioxane or in industrial or laboratory facilities where 1,4-dioxane is used.
- Workers and consumers potentially exposed during the use of products that contain 1,4-dioxane as a contaminant.
- The general population potentially exposed via inhalation of ambient air receiving emissions from manufacturing/formulating facilities, as well as incineration of waste streams/products.
- The general population potentially exposed to 1,4-dioxane through contaminated drinking water.

The routes of potential human exposure to 1,4-dioxane are inhalation, ingestion and dermal contact. Dermal exposures are not addressed due to high volatilization, low absorption and lack of dermal toxicity studies. Potential human health effects from inhalation and ingestion include cancer and noncancer outcomes (liver, kidney and nasal effects) in workers, consumers and the general population.

EPA/OPPT reviewed the ecological hazards of 1,4-dioxane and determined that acute and chronic hazard is low for aquatic species. There are no sediment or soil toxicity data to assess the hazard to organisms in these environmental compartments. A conceptual model was not developed for environmental health and further analysis of environmental risk is not planned.

The results of problem formulation as illustrated in the conceptual model for human health and described under the assessment questions indicate that:

- A 2002 European assessment found potential risk to workers for occupational exposures via the dermal and inhalation routes during product formulation and the use of 1,4-dioxane as a cleaning agent. Availability of EPA's recently updated benchmarks for human health suggest that human health risks should be reassessed. While US data on occupational exposures are limited, EPA/OPPT will further assess the risk to workers from inhalation of 1,4-dioxane during manufacture, formulation and use of products using available data or modeled exposures in the absence of data.
- Workers and consumers may be exposed to 1,4-dioxane present as a contaminant in products such as personal care products, paints, adhesives, varnishes, cleaners and detergents. Risk assessments in Canada and Europe concluded that levels of contamination do not pose concerns for human health. While personal care products are regulated by the

FDA, uses in paints, adhesives, varnishes, cleaners and detergents fall under TSCA authority. Availability of EPA's recently updated benchmarks for human health suggest that human health risks should be reassessed. Therefore, EPA/OPPT plans to further assess potential risks posed to consumers by 1,4-dioxane in products covered under TSCA.

- The general population may be exposed from inhalation to ambient levels of 1,4-dioxane in air. Regulations for air pollution are in place through the Clean Air Act (CAA). 1,4-Dioxane is short lived in the environment and historical ambient air levels of 1,4-dioxane are considered low. Risk assessments in Canada and Europe concluded that there are no risks of concern from exposure to 1,4-dioxane in ambient air. Given that 1,4-dioxane is regulated under the CAA as a hazardous air pollutant (US EPA, 2000) and EPA/OPPT's comparison of historical air concentrations of 1,4-dioxine against the recent EPA IRIS benchmarks (RfC and IUR) indicate these concentrations are below levels of concern, assessment of general population exposure to 1,4-dioxane in ambient air will not be further analyzed by EPA/OPPT under TSCA.
- The general population may be exposed to 1,4-dioxane in contaminated drinking water. EPA's Office of Water is currently monitoring public drinking water systems in order to evaluate the risk to defined populations. Potential source contributions to drinking water are uncertain. Since 1,4-dioxane is being monitored through December 2015, decisions as to whether or not to regulate the contaminant in drinking water will be considered as part of the EPA's Regulatory Determination process.

In summary, as a result of problem formulation, EPA/OPPT plans to conduct additional risk analysis on potential worker and consumer exposures under the TSCA Existing Chemicals Program using existing data and methods. EPA/OPPT plans to carefully review and evaluate the results of previous exposure assessments and health benchmarks. EPA will develop margins of exposure and cancer risk estimates to evaluate the potential risks from worker and consumer exposure to 1,4-dioxane. EPA does not have risk concerns for the general population through inhalation exposure to ambient air emissions.

1 INTRODUCTION

As a part of EPA's comprehensive approach to enhance the Agency's management of existing chemicals, in March 2012 EPA/OPPT identified a work plan of chemicals for further assessment under the Toxic Substances Control Act (TSCA)[2]. After gathering input from stakeholders, EPA/OPPT developed criteria used for identifying chemicals for further assessment[3]. The criteria focused on chemicals that meet one or more of the following factors: (1) potentially of concern to children's health (for example, because of reproductive or developmental effects); (2) neurotoxic effects; (3) persistent, bioaccumulative and toxic (PBT); (3) probable or known carcinogens; (4) used in children's products; or (5) detected in biomonitoring programs. Using this methodology, EPA/OPPT identified a TSCA Work Plan of chemicals as candidates for risk assessment in the next several years. In the prioritization process, 1,4-dioxane was identified for assessment based on classification as a probable human carcinogen, wide use in consumer products, high reported releases to the environment, and presence in groundwater, ambient air and indoor environments.

EPA/OPPT is performing risk assessments on chemicals in the work plan. If an assessment identifies unacceptable risks to humans or the environment, EPA will pursue risk management. The target audience for the final risk assessment is primarily EPA risk managers; however, it may also be of interest to the broader risk assessment community as well as US stakeholders interested in 1,4-dioxane. The information presented in the risk assessment may be of assistance to other federal, state and local agencies as well as to members of the general public who are interested in understanding whether there are risks from exposure to 1,4-dioxane.

The initial step in the EPA/OPPT risk assessment development process, which is distinct from the initial prioritization exercise, includes planning, scoping and problem formulation. During these steps EPA/OPPT may review currently available data and information, including but not limited to, assessments conducted by others (e.g., authorities in other countries), published or readily available reports and published scientific literature. The problem formulation data review could result in refinement of pathways of interest previously identified in the initial prioritization.

This document includes the results of scoping, problem formulation, and initial assessment for 1,4-dioxane. In the scoping stage, EPA/OPPT determined which chemical(s) to include and what uses to consider in the assessment. During problem formulation, EPA/OPPT identified available fate, exposure and hazard data, and characterized potential exposures, receptors and effects. EPA/OPPT developed a conceptual model and an analysis plan as a result of problem formulation.

[2] http://www.epa.gov/oppt/existingchemicals/pubs/workplans.html
[3] http://www.epa.gov/oppt/existingchemicals/pubs/wpmethods.pdf

1.1 Scope of the Assessment

The TCSA Work Plan chemical 1,4-dioxane is a high production volume chemical (up to 10 million lbs/yr, based on publicly available information), has a variety of industrial uses and may be present in both consumer and commercial products. 1,4-Dioxane is used as an industrial solvent in the production of a wide variety of products, as a laboratory reagent, a chemical intermediate, an extraction medium for fats and oils and as part of a polymerization catalyst (ATSDR, 2012). 1,4-dioxane is also used in commercial and consumer products such as lacquers, varnishes, paint strippers, dyes, greases, cleaners and detergents, adhesives, cosmetics and deodorants (European Chemicals Bureau, 2002; US EPA, 2014d). In addition, 1,4-dioxane is present as a contaminant in consumer cosmetics/toiletries, household detergents, pharmaceuticals, foods, agricultural and veterinary products and ethylene glycol-based antifreeze coolants, because it is a byproduct of certain ethoxylated substances (ATSDR, 2012).

Workers, consumers and the general population may be exposed to 1,4-dioxane by inhalation, ingestion and dermal routes. Because 1,4-dioxane is not intentionally added to consumer products, only workers are exposed to products which intentionally contain 1,4-dioxane. Inhalation is expected to be the predominant route of exposure due to the high vapor pressure and volatility of 1,4-dioxane. Workers and consumers may be exposed to products that contain 1,4-dioxane as an unwanted byproduct or an intermediate that is not fully reacted and the concentrations of 1,4-dioxane in these cases are lower, usually measured in parts per million or less. The general population may be exposed environmentally from air or water containing 1,4-dioxane.

Absorption of 1,4-dioxane occurs readily through the lungs and gastrointestinal system and poorly through the skin. After absorption, 1,4-dioxane is rapidly eliminated from the body and does not accumulate. EPA classifies 1,4-dioxane as “likely to be carcinogenic to humans” by all routes of exposure based on liver tumors in rats and mice following chronic drinking water exposure (US EPA, 2013b). Nasal tumors were observed in rats following chronic inhalation or drinking water exposure. Short-term exposure may result in irritation of the eyes and throat (ATSDR, 2012) and chronic exposure may result in dermatitis, eczema, drying and cracking of skin, and liver and kidney damage (ATSDR, 2012).

In the environment, 1,4-dioxane partitions to water and is highly mobile in soil. 1,4-Dioxane is highly volatile, has a short residence time in air and does not readily biodegrade in water. Toxicity to aquatic organisms is not expected based on low hazard values.

Given the common use, widespread exposure and potential human health hazards of 1,4-dioxane, EPA/OPPT conducted a problem formulation and evaluation of readily available data and information to determine the exposures and hazards of interest for risk assessment. Available data were used including chemical structure, physical chemistry, production volume,

reported uses and toxicological information from existing assessments to develop a conceptual model and an analysis plan.

1.2 Regulatory and Assessment History

EPA/OPPT reviewed and considered the regulatory and assessment history of 1,4-dioxane (Appendix A: Regulatory and Assessment History).

National (U.S.)

1,4-Dioxane is a known animal carcinogen according to the National Toxicology Program (NTP) (NTP, 2014). The US Department of Health and Human Services (DHHS) considers 1,4-dioxane as reasonably anticipated to be a human carcinogen (US DHHS, 1993). EPA has determined that 1,4-dioxane is likely to be carcinogenic to humans (US EPA, 1999).

Occupational exposure limits have been set by federal agencies and organizations in the US (OSHA, NIOSH, ACGIH) and are summarized in Appendix A. A recent Toxicological Profile for 1,4-dioxane (ATSDR, 2012) provided a detailed analyses of available hazard data. The data were used to derive minimal risk levels (MRLs), exposure levels posing minimal risk to humans, for inhalation and oral exposures. The EPA Integrated Risk Information System (IRIS) Program recently updated the assessment of 1,4-dioxane, including the results of a two-year inhalation bioassay (US EPA, 2013b). IRIS developed cancer and non-cancer reference values for inhalation and drinking water exposure. Acute Exposure Guideline Levels (AEGLs) for 1,4-dioxane have been established (NAS/COT Subcommittee for AEGLs, 2005). The MRLs, IRIS benchmarks and AEGLs are provided in Appendix A.

The Food and Drug Administration (FDA) does not require 1,4-dioxane to be listed on labels of personal care products and considers it a contaminant. FDA has indicated that the levels of 1,4-dioxane found in their monitoring of cosmetics do not present a hazard to consumers and recommended a level of 3.8 mg/day (380 ppm) as the “permitted daily exposure (PDE)” for 1,4-dioxane that is an acceptable intake of residual solvents in drugs and dietary supplements (US FDA, 2011). FDA limits 1,4-dioxane levels in glycerides and polyglycerides of hydrogenated vegetable oils used as a food additive to 10 mg/kg.

Industries manufacturing, processing or using 1,4-dioxane are legally required to report releases to EPA’s Toxic Release Inventory (TRI) if they manufacture or process more than 25,000 pounds of a TRI-listed chemical or otherwise use more than 10,000 pounds of a listed chemical in a given year.

The EPA Office of Water (OW) has included 1,4-dioxane on the third Candidate Contaminant List (CCL3). No federal drinking water standards have been established for 1,4-dioxane and it is being monitored in public water systems as part of the Unregulated Contaminant Monitoring Rule 3 (UCMR3) list. OW is conducting a three-year (2013-2015) monitoring program of public water systems to collect data for contaminants suspected to be present in finished drinking

water including 1,4-dioxane (USEPA, 2013). Information about UCMR3 and 1,4-dioxane monitoring in Public Water Systems (PWS) can be found at: http://water.epa.gov/lawsregs/rulesregs/sdwa/ucmr/data.cfm.

EPA's Office of Air and Radiation (OAR) regulates 1,4-dioxane as a Hazardous Air Pollutant (http://www.epa.gov/ttn/uatw/hlthef/dioxane.html). EPA's Office of Solid Waste and Emergency Response (OSWER) regulates the Superfund sites that are historically a source of 1,4-dioxane in ground water around those sites. 1,4-Dioxane has been reported at 32 National Priorities List (NPL) sites (http://www.atsdr.cdc.gov/SPL/index.html). Examples include sites in New Hampshire (http://www.epa.gov/region1/removal-sites/NH14DioxaneSite.html) and Massachusetts (http://www.epa.gov/region1/superfund/sites/graceacton/507061.pdf).

States

1,4-Dioxane is listed on California's Proposition 65 list because it is known to cause cancer (CA EPA OEHHA, 2007, 2014). The action level under California Proposition 65 for 1,4-dioxane in personal care products is above 10 ppm. California also lists 1,4-dioxane on the Informational "Initial" Candidate Chemicals List and the Informational Candidate Chemicals List under California's Safer Consumer Products regulations (State of California, 2010). Further, Minnesota and Washington classify 1,4 dioxane as a chemical of high concern (Minnesota Department of Health (MDH), 2013; Washington State, 2013).

International

The International Agency for Research on Cancer (IARC) has determined that 1,4-dioxane is possibly carcinogenic to humans (IARC, 1976) based on inadequate evidence in humans and sufficient evidence in experimental animals.

A Canadian screening assessment (Environment Canada and Health Canada, 2010) evaluated the risk of 1,4-dioxane to human health. Ecological risks were not assessed since 1,4-dioxane did not meet the criteria for bioaccumulation and inherent toxicity to aquatic organisms. Exposures to the general population from intake from air, water, soil, diet, use of personal care products and household products were estimated. The report concluded that 1,4-dioxane is not entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

The European Union Risk Assessment Report (EU RAR, 2002) concluded that there is no concern for human safety with regard to repeated-dose toxicity, carcinogenicity and reproductive toxicity. The assessed risk concern was low for the general population (inhalation and drinking water), direct and indirect consumer exposures in cosmetic/toiletries and household detergents, pharmaceuticals, foods, agricultural and veterinary products, and ethylene glycol-based antifreeze coolants and ecological exposures. A potential risk concern for workers was found for occupational exposures via the dermal and inhalation routes during product formulation and the use of cleaning agents containing 1,4-dioxane.

2 PROBLEM FORMULATION

Problem formulation aims to determine the major factors to be considered in an assessment, including exposure pathways, receptors and health endpoints (US EPA, 1998, 2014b). Accordingly, this problem formulation summarizes the exposure pathways, receptors and health endpoints that EPA/OPPT considered to determine whether to conduct further risk analysis and what exposure/hazard scenarios to include in a potential risk assessment. To make this determination, EPA/OPPT conducted a preliminary data review to identify available fate, exposure and hazard data and determine its likely suitability for quantitative analysis and to identify exposure pathways, receptors and health endpoints for quantitative analysis.

The outcome of this evaluation is summarized in a conceptual model (Figure 2-2) that illustrates the exposure pathways, receptors and effects that were considered for potential risk assessment. An analysis plan is developed if the results of problem formulation indicate the need for further analysis.

2.1 Physical and Chemical Properties

1,4-Dioxane is a clear liquid at room temperature. The cyclic structure (Figure 2-1) has oxygen molecules attached at the first and fourth bonds, each with free electrons (US EPA, 2006b). 1,4-Dioxane is expected to volatilize from dry soil surfaces based on its high vapor pressure (40 mm Hg at 25 °C) (US EPA, 2009). 1,4-Dioxane has a Log K_{ow} value of -0.27, which indicates that this chemical is hydrophilic, readily miscible in water (US EPA, 2009). A summary of the physical and chemical properties of 1,4-dioxane are listed in Figure 2-1.

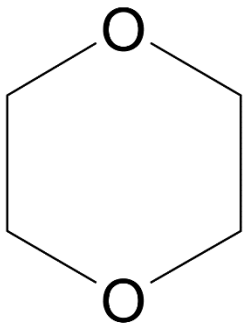

Figure 2-1: Chemical structure of 1,4-dioxane.

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

Property	Value	References
Molecular Weight	88.1 g/mol	(Howard, 1990)
Melting Point	11.85 °C (measured)	(Lide, 2008-2009)
Boiling Point	101.1 °C (measured)	(O'Neil et al., 2006)
Vapor Pressure	40 mm Hg at 25 °C	(Lewis, 2000)
Water Solubility	> 8.00×10^2 g/L	(Yalkowsky and He, 2003)
Log K_{OW}	-0.27	(Hansch et al., 1995)
Henry's Law Constant	4.8×10^{-6} atm-m^3/mol at 25 °C	(Howard, 1990)

2.2 Production and Uses

The EPA's Inventory Update Reporting (IUR) and 2012 Chemical Data Reporting (CDR) databases were searched to identify the uses and associated production volumes of 1,4-dioxane. Some information was claimed as Confidential Business Information (CBI) and is not included in this report. Additional information on uses and specific end products that may contain 1,4-dioxane can be found in Appendix B: Summary of Uses and End Products.

Production

In 2006, the U.S. production volume of 1,4-dioxane was between 1 million and 10 million pounds, including both imports and domestic manufacture (US EPA, 2010). Data from the 2012 CDR for reporting years 2010 and 2011 were claimed as CBI and indicate only domestic manufacture of 1,4-dioxane (US EPA, 2014c). The non-confidential U.S. production volumes of 1,4-dioxane, as submitted by companies under the IUR or CDR for 1986 to 2012, are given in Table 2-2.

Table 2-2: 1986-2012 National Production Volume Data for 1,4-Dioxane (Millions of Pounds).

1986 IUR	1990 IUR	1994 IUR	1998 IUR	2002 IUR	2006 IUR	2012 CDR
10-50	10-50	1-10	1-10	1-10	1-10	Withheld
Source: (US EPA, 2006a, 2010, 2012b)						

Uses

1,4-Dioxane is currently used as both an industrial and a commercial solvent. As a result of chemical ethoxylation of surfactants, 1,4-dioxane can be formed as a byproduct and may be present as a contaminant in commercial and consumer products. Historically, the main use of

1,4-dioxane (90 percent) was as a stabilizer in chlorinated solvents such as 1,1,1-trichloroethane (TCA). Use of TCA was phased out under the 1995 Montreal Protocol and the use of 1,4-dioxane as a stabilizer is no longer significant (European Chemicals Bureau, 2002; NTP, 2014).

Industrial Uses. At present, 1,4-dioxane is used as an industrial solvent in the manufacture of chemicals because it is capable of solubilizing most organic and many inorganic compounds (ATSDR, 2012; Ullman's, 2012). As an industrial solvent, 1,4-dioxane is used as:

- a processing solvent
- a reaction medium solvent
- an industrial solvent with an unspecified function in the production of various end products (ATSDR, 2012; US EPA, 2006a)

Other industrial uses include:

- as an extraction medium
- an inert (chemically inactive) ingredient in pesticides and fumigants
- a chemical intermediate
- a polymerization catalyst
- a dehydrating agent
- a wetting and dispersing agent
- a degreasing agent (ATSDR, 2012; US EPA, 2006a)

Appendix B lists examples of end products for each of these industrial uses. Table 2-3 provides the industrial use data as reported in the 2012 CDR database[4].

Commercial and Consumer Uses. As an industrial processing solvent or chemical intermediate, 1,4-dioxane has previously been reported to be used in the production of products that may have commercial or consumer applications such as paints, adhesives, detergents, and pesticides (ATSDR, 2012; US EPA, 2006a, 2014c). In the most recent CDR database, no consumer uses were reported for 1,4-dioxane in the US (Table 2-3). Additional US sources do not differentiate between consumer and commercial products (ATSDR, 2012; US EPA, 2006a). EPA was unable to identify any US sources that definitively stated the chemical is used in the production of consumer products. A European risk assessment stated that the chemical is used as a solvent in the production of several products that may be used by consumers (European Chemicals Bureau, 2002).

Contaminant in Consumer Products. 1,4-dioxane may be present as a contaminant in consumer cosmetics/toiletries, household detergents, pharmaceuticals, foods, agricultural and veterinary products and ethylene glycol-based antifreeze coolants. It is formed as a byproduct

[4] The manufacturer submitted a correction to EPA to revise the 2012 CDR to reflect that 1,4-dioxane is not used for the categories 'Paints and Coatings' and 'Laundry and Dishwashing Products'. The correction was received and is not yet indicated in the CDR public database.

during the manufacture of ethoxylated surfactants. Manufacturers can remove most of the 1,4-dioxane in consumer products through a vacuum stripping process (ATSDR, 2012), although the extent that this occurs is unknown.

Table 2-3: CDR Industrial and Consumer Use Data.

Manufacturing Site	Parent Company	Industrial Use Data				Consumer and Commercial Use Data		
		Sector	Function Category	Industrial Use	Percent of Production Volume	Product Category*	Commercial or Consumer Use	Percent of Production Volume
Novolyte Performance Materials 111 West Irene Road Zachary, LA 70791	BASF	All Other Basic Organic Chemical Manufacturing	Processing aids, not otherwise listed	Use-non-incorporative activities*	CBI	Paints and Coatings	Commercial	CBI
						Laundry and Dishwashing Products	Commercial	CBI

Note: Use in non-incorporative activities would include uses such as chemical processing aids or chemical manufacturing aids, where the chemical is not intended to remain in or become part of the final product, or ancillary activities where a chemical is used at a facility for purposes other than aiding chemical processing or manufacturing (e.g. degreasers or cleaners).
Source: The public 2012 CDR Database; updated June 11, 2014 (US EPA, 2012b).
*A correction was received that is not yet indicated in the CDR public database.

2.3 Fate and Transport

Environmental fate properties are summarized in Table 2-4.

Based on available environmental fate data, 1,4-dioxane is expected to volatilize readily from dry surfaces, reside in water and soil compartments if released to the environment, and have high persistence and low bioaccumulation potential in the environment. 1,4-Dioxane is not readily biodegradable under normal environmental conditions.

1,4-Dioxane is expected to volatilize from dry surfaces and dry soil due to its high vapor pressure. It reacts with hydroxyl radicals (OH•) in the atmosphere where the estimated atmospheric photooxidation half-life of 1,4-dioxane is 4.6 hours (US EPA, 2013a). 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-UV light wavelengths (Lyman et al., 1982; NIH, 2006). 1,4-dioxane will not hydrolyze in water because it does not have functional hydrolyzable groups (ATSDR, 2012).

Due to a high water solubility of > 8.00×10^2 g/L (Yalkowsky and He, 2003) and a low Henry's Law constant of 4.8×10^{-6} atm-m^3/mol at 25 °C (Howard, 1990; US EPA, 2009), 1,4-dioxane is expected to be only slightly volatile from water surfaces and moist soil. Once it enters the environment, 1,4-dioxane is expected to have high mobility in soil based on its negligible K_{oc} value of 0.4 (US EPA, 2013a). 1,4-dioxane is not expected to significantly sorb to suspended solids and sediment and, therefore, may migrate rapidly to surface waters and groundwater.

In a ready biodegradation test, following OECD Guideline 301 F (Manometric Respirometry Test), reported by the European Chemicals Agency (ECHA), 1,4-dioxane was degraded less than 10 percent in 29 days (ECHA, 2014a). In another ready biodegradation test following OECD Guideline 310 (Headspace Test) 1,4-dioxane was degraded less than 5 percent in 60 days (ECHA, 2014b). 1,4-dioxane is considered to be not readily biodegradable.

In a soil microcosm study which analyzed the potential for bacteria to degrade 1,4-dioxane, 1,4-dioxane was not biodegraded during a 120 day period by indigenous bacteria. During the next 6 months, the bacteria removed about 60% of the added 1,4-dioxane. The reason for the delayed biodegradation was not clear (Kelley et al., 2001).

In a bioaccumulation test using the common carp (*Cyprinus carpio*) following OECD Test Guideline 305, measured bioconcentration factor (BCF) values of 0.3-0.7 at a concentration of 10 mg/L, and 0.2-0.6 at a concentration of 1 mg/L were reported (ECHA, 2014c). These values indicate that bioaccumulation 1,4-dioxane is low.

Using the environmental fate estimation model EPISuite™ (Estimation Program Interface Suite for Microsoft Windows) v 4.11, a level III fugacity model with equal releases of 1,4-dioxane to

air, water, soil, and sediment, estimates that 1,4-dioxane will tend to partition mostly to soil (52.6%), and water (44.7%) (US EPA, 2013a) (Table 2-4).

Table 2-4: Environmental Fate Endpoints for 1,4-Dioxane.

Endpoint	Environmental Fate Data	References
Photodegradation Half-life	4.579 hours (estimated rate constant of 2.8×10^{-11} cm^3/molec-sec 1.5×10^6 hydroxyl radicals per cm^3 12-hour day)	(US EPA, 2013a)
Hydrolysis Half-life	Does not undergo hydrolysis	(ATSDR, 2012)
Biodegradation	<10% in 29 days (OECD 301F) <5% in 60 days (OECD 310) 0% after 120 days in soil microcosms; 60% after 300 days	(ECHA, 2014a) (ECHA, 2014b) (Kelley et al., 2001)
Bioconcentration	BCF = 0.2 – 0.6 (measured in carp at 1 mg/L) BCF = 0.3 – 0.7 (measured in carp at 10 mg/L)	(ECHA, 2014c)
Log K_{oc}	0.4 (estimated)	(US EPA, 2013a)
Fugacity (Level III Model) Air (%) Water (%) Soil (%) Sediment (%)	 2.65 44.7 52.6 0.0868 (The input values for this estimation are the melting point, boiling point, vapor pressure, water solubility, Log K_{OW} and Henry's Law constant values provided in Table 2.1 above, and the following SMILES notation: O(CCOC1)C1)	(US EPA, 2013a)

2.4 Exposures

The exposure data identified and considered during problem formulation and used to construct the conceptual model and pose assessment questions is summarized. Use and exposure scenarios were selected for inclusion in the conceptual model by the identification of high volume uses that are known or likely to be associated with significant exposures.

Releases to the environment were assessed to determine potential pathways of exposure for both human and ecological receptors. Exposures to workers, consumers and the general population were evaluated to determine the potential exposure to 1,4-dioxane during manufacturing, formulation and use of products. Environmental exposure of the general population to 1,4-dioxane in air or water was also considered.

2.4.1 Releases to the Environment

Environmental releases of 1,4-dioxane to air and water may contribute to ecological and general population exposures. The potential for release of 1,4-dioxane to air is high due to the high vapor pressure of 1,4-dioxane and disposal through incineration. Industrial and commercial use of 1,4-dioxane and presence in consumer products suggest releases to water are possible. Readily available sources of information for environmental releases that may lead to exposures were reviewed including the EPA Toxic Release Inventory (TRI) database (US EPA, 2012c).

An analysis of TRI data from 1988 to 2007 indicates that total on-site releases of 1,4-dioxane are generally decreasing. During this period, the high was 1,234,968 pounds in 1993 and the low was 182,338 pounds in 2007; 69% of the 2007 total releases from 45 facilities were to air (ATSDR, 2012). Data from the most recent TRI indicate that 82% of the total on- and off-site releases of 106,300 pounds from 39 sites (including the manufacturing site) were to air (on-site fugitive and point sources) and 18% were to surface water. An additional 1,035,300 pounds were reported released from two additional sites that primarily inject 1,4-dioxane in underground wells (on-site and off-site) or send to waste brokers (US EPA, 2012c). Releases to these wells and to waste brokers are not usually a concern for human exposures. Facilities that release less than 25,000 pounds are not required to report data to the TRI.

The EPISuite™ model (Table 2-4) indicates that following release, 1,4-dioxane will partition predominantly to water and moist soil. Likely exposure pathways are by atmospheric deposition and runoff into surface water and leaching into groundwater.

2.4.2 Presence in the Environment

EPA/OPPT reviewed available information on the presence of 1,4-dioxane in the environment from the 2002 EU Risk Assessment Report (RAR), a leachate study from two landfills, a groundwater plume study and two WWTP studies.

The EU RAR included predicted environmental concentrations (PECs) for wastewater effluent and surface water and a limited number of measured data of 1,4-dioxane in surface water, drinking water, wastewater effluent and leachate from the vicinity of landfills (European Chemicals Bureau, 2002). Site-specific and generic location emission data were used to generate estimated regional release values to surface water and WWTPs and develop the PECs. The PECs in surface water were based on estimated regional releases to water of 434 kg/d and the estimated regional release via WWTP was 304 kg/d (European Chemicals Bureau, 2002). PECs of 1,4-dioxane in wastewater effluent ranged from 0.002 – 183 mg/L based on life cycle stages or scenarios. PECs in surface water during an emission episode ranged from 0.001 mg/L (contaminated alkyl ethoxy sulphates) to 18.3 mg/L (processing pharmaceuticals and pesticides) (European Chemicals Bureau, 2002).

In the EU RAR, surface water data in a Dutch study were compared to the predicted regional environmental concentration of 1.3 μg/L and was within the study values of 1-10 μg/L. The measured data for the WWTP effluent from unintentional release from a PET plant was much higher (100 mg/L) than the PEC of 0.01 – 6.9 mg/L for site-specific emission data for various unintentional 1,4-dioxane releases. However, the EU RAR noted that the source of the measured 100 mg/L value used may be unreliable (European Chemicals Bureau, 2002).

The primary method of disposal of 1,4-dioxane is by incineration (ATSDR, 2012). In a study, that investigated 1,4-dioxane in landfill leachate, extremely high levels of 1,4-dioxane (89 and 340 mg/L) were detected in the leachate from two landfill sites. Analysis of leachate and measurement of 1,4-dioxane in incineration residues suggest that the most likely source of 1,4-dioxane in the leachate is the fly ash produced by municipal solid waste incinerators (Fujiwara et al., 2008).

Groundwater beneath the city of Ann Arbor, Michigan is currently contaminated with 1,4-dioxane after it was used as an industrial solvent and the contaminated waste water was stored in unlined wastewater lagoons between 1976 and 1986 (City of Ann Arbor, 2015). Since then, the chemical has seeped through the soil and entered the groundwater in the Ann Arbor area. Concentrations up to 7,000 ppb have been detected in the plume at the source. The maximum concentration of 1,4-dioxane detected at an off-site monitoring well near the center of the plume was 3,788 ppb (Pall Corporation, 2004). In 2004, concentrations of 1,4-dioxane in influent and effluent were measured in a WWTP in Ann Arbor, MI. In February, April and June, raw wastewater influent concentrations were 3, 2 and 3 μg/L, respectively. Treated effluent concentrations were 3, 1 and 3 for those same months (Skadsen, 2004). The similar influent and effluent values suggest that 1,4-dioxane is not readily removed and passes through a municipal WWTP.

Samples of waste water effluent were collected from 40 municipal WWTPs that receive predominantly domestic wastewater from households. Sampling took place in 2010 and included WWTPs at select sites in 15 states. Of the WWTPs effluents samples, two had 1,4-dioxane concentrations below the LOQ (<0.30 μg/L) and 38 samples had concentrations between 0.30 and 3.30 μg/L (Simonich et al., 2013).

2.4.3 Occupational Exposure

Occupational exposure data from three sources were reviewed: the 2002 EU RAR, the OSHA Chemical Exposure Health Data database, and a data set provided by an American Chemistry Council (ACC) member company.

Manufacturing sites produce 1,4-dioxane in liquid form at 90 percent concentration or higher. Workers may be exposed by inhalation and skin contact when they work with 1,4-dioxane. The high vapor pressure of 1,4-dioxane causes a high potential for air releases and associated worker inhalation exposure. Dermal exposure may occur, but due to a low rate of absorption through the skin and rapid volatilization, inhalation is considered the predominant route of exposure.

Occupational exposure limits can affect the handling and processing of chemicals, thereby reducing the potential for exposures. The US has several regulatory and non-regulatory exposure limits for 1,4-dioxane (ACGIH, 2009): 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).

Public CDR information (US EPA, 2012c) indicates there is one domestic manufacturing site, 25 to 99 industrial processing sites and two commercial/ consumer product categories (Paints and Coatings and Laundry and Dishwashing Products) for this chemical[5]. Information on current domestic processing and use of 1,4-dioxane that may result in exposures is limited. 1,4-dioxane has been potentially formulated into specialized products for industries in Europe with no expected consumer uses. Also, some processes to make other chemicals produce 1,4-dioxane as a reaction byproduct (e.g., ethoxylation reactions), and these chemicals have a variety of uses that may result in worker and consumer exposures.

[5] The manufacturer submitted a correction to EPA to revise the 2012 CDR to reflect that 1,4-dioxane is not used for the categories 'Paints and Coatings' and 'Laundry and Dishwashing Products'. The correction was received and is not yet indicated in public database.

In the US, limited worker inhalation monitoring data for this chemical were found in the OSHA Chemical Exposure Health Data database (OSHA, 2014). During the most recent 15 year period (1997 - 2011), 21 samples were taken from 6 sites, with 2 detects of 0.21 and 0.22 ppm and 19 non-detects. Worker monitoring data specific to an American Chemistry Council (ACC) member company facility where 1,4-dioxane is produced as a byproduct in its manufacturing process were collected from 2001 to 2003 (Franz, 2014). All of the 21 samples taken at this facility were below analytical detection limits, which ranged from 0.044 to 0.9 ppm (0.16 to 3.24 mg/m^3). The two sets of data are too limited to consider representative of potential exposures that may occur throughout the US (Appendix C: Occupational Exposure Data).

Estimates of worker exposure in Europe are provided in the EU RAR (European Chemicals Bureau, 2002) for 1,4-dioxane. Inhalation concentrations and dermal doses for worker exposures in five "Worker Use Activity" scenarios (Table 2-5) were estimated: production, formulation and three end uses (cleaning agents in industries such as metal fabrication; paints and varnishes in the production of precision and optical instruments, watches and clocks; and lab solvents). All of these scenarios were relevant primarily to industrial and laboratory facilities.

Table 2-5: Exposure Concentrations for Occupational Scenarios in European Industrial and Laboratory Facilities.

Worker Use Activity	Reasonable Worst-case inhalation concentration (mg/m^3, TWA)	Typical inhalation concentration (mg/m^3, TWA)
Manufacturing	10 (measured)	0.2 (measured)
Processing/ formulating	180 (modeled)	40 (modeled)
Use of cleaning agent	50 (measured)	15 (measured)
Use of paint	11 (modeled)	2 (modeled)
Use of solvent in lab	25 (calc. from measured values)	5 (measured)

Table Note: "It is not clear whether the chemical is still used in cleaning agents." Source: Table 4-4 in (European Chemicals Bureau, 2002).

Comparing the concentrations of 1,4-dioxane estimated for worker inhalation in Europe (Table 2-5) to US limits and recommended action levels, exposures did not exceed the OSHA Permissible Exposure Limit (PEL), but typically exceeded the NIOSH Recommended Exposure Limit (REL). EPA/OPPT could not determine whether the worker exposures estimated in the EU assessment are similar to those in the US.

The European report did not estimate worker exposures for processes that produce 1,4-dioxane as a reaction byproduct (e.g., ethoxylation reactions). Concentrations of 1,4-dioxane as a contaminant in detergents and paints are expected to be lower than the estimated concentrations of 1,4-dioxane in processed formulations. Formulations typically contain 10 weight percent or higher handled by workers in the assessed European scenarios. Worker exposures to commercial products (such as detergents and paints) containing 1,4-dioxane as a

contaminant could therefore be orders of magnitude below the EU RAR estimated exposure concentrations.

No information was found regarding the current total number of workers exposed to 1,4-dioxane. Historical estimates from the 1970s and 1980s indicate that the number of workers potentially exposed to 1,4-dioxane could have been up to 466,000 individuals (ATSDR, 2012). Of those workers, significant numbers were estimated to have been exposed as a result of the use of 1,4-dioxane as a stabilizer in TCA. While there is no data on current worker populations, the numbers are expected to be much lower assuming production of 1,4-dioxane has been reduced, particularly for use as a stabilizer in 1,1,1-trichloroethane (TCA).

In conclusion, workers in the US may be exposed to 1,4-dioxane. Several very limited worker monitoring data sets for US workers showed exposures to be below both the OSHA PEL and the NIOSH REL, but these data are very limited and may not be representative of exposures in the US. Worker exposure estimates in the EU could be a reasonable starting point for assessing exposures in the US. In order to better characterize worker exposures to 1,4-dioxane in the US, information on current uses and volumes, processes used during production/formulation, worker activities and measurements of exposure levels are needed.

2.4.4 General Population Exposure

General population exposures were identified and considered during problem formulation. A review of available data and assessments for 1,4-dioxane revealed that potential general population exposure can occur from ingesting contaminated drinking water and inhaling 1,4-dioxane in the air. Exposures to 1,4-dioxane in food and cosmetics are outside the scope of TSCA, have been addressed by other organizations such as FDA and are not addressed in this assessment.

Exposure in Air

Air releases of 1,4-dioxane have decreased notably due to the ban of TCA according to historical data. The TRI data indicate that air is the media with the greatest releases (ATSDR, 2012; US EPA, 2012c). TRI data is summarized in Section 2.4.1 Releases to the Environment.

Exposure in Drinking Water

Recent actions from the State of California (CSWRCB, 2014) have labeled 1,4-dioxane as an emerging contaminant because of its increased presence in drinking water. The California Department of Public Health's Drinking Water Program measured 1,4-dioxane levels in drinking water systems from 2000 to 2013. The program reported a mean concentration of 0.0042 mg/L; a median of 0.003 mg/L; and maximum concentration of 0.053 mg/L in the 2,592 samples taken.

High concentrations of 1,4-dioxane have been found in runoff ditches around Superfund sites and nearby drinking water wells have been contaminated at levels above concern for health effects (ATSDR, 2012).

EPA/OW's three year monitoring program (i.e. UCMR) of public water systems (PWS) tests for 1,4-dioxane and other chemicals in finished drinking water (US EPA, 2014e). Samples are collected at entry points to the distribution system (i.e., the point at which water is discharged into the distribution system from a well, storage tank, pressure tank or water treatment plant). Source water (i.e., ambient surface or ground water) is not measured as part of the UCMR.

Monitoring data from PWSs during the first two years of the UCMR program as of January 2015 are summarized in Table 2-6. The results include 243 PWSs representing 708 samples with results greater than the 10^{-6} cancer reference concentration (0.35 μg/l) and no PWSs with detections above the 10^{-4} cancer reference concentration level (35 ppb). It is unknown whether additional monitoring data will result in higher occurrence or detection levels of 1,4-dioxane in PWSs. Since 1,4-dioxane is being monitored through December 2015, decisions as to whether or not to regulate the contaminant in drinking water will be considered as part of the EPA's Regulatory Determination process (US EPA, 2014e). The reference concentrations used for 1, 4-dioxane are based on publically-available health information found in the 2012 Drinking Water Standards and Health Advisory (US EPA, 2012a) and range from 0.35 to 35 μg/l, based on cancer risk of 10^{-6} to 10^{-4}, respectively. The draft reference concentration does not represent an "action level"; EPA requires no particular action based simply on the fact that UCMR monitoring results exceed draft reference concentrations, nor should the draft reference concentration be interpreted as any indication of EPA's intent to establish a future drinking water regulation for the contaminant at this or any other level (US EPA, 2014e).

Table 2-6: Preliminary Data from the EPA UCMR 3 (January 2015).

Contaminant	MRL[1]	Reference Conc. [1,2]	Total # of results	# of results ≥MRL	# of results > Ref. Conc.[2]	% of total results > Ref. Conc.[2]	Total number of PWSs with results	# of PWSs with results ≥MRL	# of PWSs with results >Ref. Conc. [2]	% of PWSs with results >Ref. Conc. [2]
1,4-dioxane	0.07	0.35 / 35	22,611	6132	708 / 0	3.1% / 0%	5873	727	243 / 0	6.8% / 0%

(http://water.epa.gov/lawsregs/rulesregs/sdwa/ucmr/upload/epa815s15001.pdf

[1]Measured in μg/L (ppb)

[2]Where two reference concentrations are listed, the first number is associated with a 10^{-6} cancer risk; the second number a 10^{-4} cancer risk. Where two results are presented the first number is associated with the first reference concentration; the second number is associated with the second reference concentration.

2.4.5 Consumer Exposure

The primary route of consumer exposure to 1,4-dioxane is by inhalation and dermal contact with contaminated consumer products containing ethoxylated surfactants such as personal care products, soaps and detergents. Limited data on concentrations in consumer products exist. Currently, manufacturers may voluntarily 1) minimize the formation of the 1,4-dioxane as by-product during manufacture of alkyl ethoxy sulfates (AES), or 2) remove 1,4-dioxane by stripping the AES paste before formulation of ethoxylated surfactants into consumer cosmetics and household products. The extent to which manufacturers use these practices is uncertain.

Cosmetics and personal care products are regulated by FDA. FDA has estimated consumer exposure to 1,4-dioxane to be low (US FDA, 2007). FDA reported that levels of 1,4-dioxane present in products such as shampoo and body wash do not pose a significant risk to consumers since products do not remain in contact with the skin for a long period of time (US FDA, 2007). FDA does not consider concentrations of 1,4-dioxane measured in cosmetics and toiletries to be a risk of concern (ATSDR, 2012). These uses are outside the jurisdiction of TSCA regulatory authority.

EPA/OPPT reviewed limited data on measured concentrations of 1,4-dioxane in products. Levels of 1,4-dioxane in cosmetics are reported from two sources as 6-34 ppm (Black, 2001) and non-detectable to 487 ppm (European Chemicals Bureau, 2002). When used as a chemical intermediate, 1,4-dioxane concentrations are 100-380 ppm in pharmaceuticals and 1.0 to 2.8% w/w% in household adhesives (ATSDR, 2012). Unintentional contamination levels of 1,4-dioxane in products are < 10 ppm in food (European Chemicals Bureau, 2002), 6-160 ppm in household detergents (ATSDR, 2012) and 0.1 – 22 ppm in antifreeze and deicing products (European Chemicals Bureau, 2002). An analysis of consumer products by the Campaign for Safe Cosmetics found 1,4-dioxane in 32 out of 48 personal care products and cosmetics tested (67%) at levels ranging from 0.27 to 35 ppm. The Organic Consumers Association tested 100 organic and natural consumer products and found detectable levels of 1,4-dioxane in 47 products. In a study of household products (soaps, shampoos, cleaners and detergents) in Japan, 1,4-dioxane was detected in 40 out of 51 products at concentrations from 0.05 to 33 mg/kg with a mean of 2.7 mg/kg (Tanabe and Kawata, 2008).

The European risk assessment evaluated risk of exposure to several consumer products: shampoos, baby lotion and hand dishwashing liquid via dermal and inhalation routes using ConsExpo, a well-documented exposure model for substances from consumer products (European Chemicals Bureau, 2002). The worst case scenario yielded a combined total internal dose of 3.3 µg/kg-bw/day and the “very worst case” combined total internal dose was 10 µg/kg-bw/day (European Chemicals Bureau, 2002). The margins of safety for consumer inhalation and dermal exposure scenarios for the three product categories ranged from greater than 1000 to greater than 10,000 using health benchmarks available at the time.

The Canadian risk assessment presented aggregate exposure estimates for various age groups including infants, children and adults (Environment Canada and Health Canada, 2010). Adult

women were considered the highest exposed demographic group due to the use of cosmetics and well as other consumer products. The estimated aggregate intake of 1,4-dioxane for daily use of hair conditioner, hair shampoo, skin moisturizer (body cream) and body wash was 1.2 µg/kg-bw per day. The margins of safety for daily intake (dermal and inhalation) for aggregate exposure of the general population and consumers ranged from 7620 to 50,000 using the same point of departure (Kociba et al., 1974) as used to derive the oral IRIS RfD.

EPA/OPPT concludes that exposure to consumers can result from the use of soaps and detergents and other products that contain 1,4-dioxane as a contaminant. Adult women who use multiple cosmetics and cleaning products are likely the most exposed population as determined in the Canada assessment. The EU RAR and Canada separately assessed aggregate risks from exposure to several consumer products and found no risk of concern. However, the assumptions used in those assessments may differ from EPA risk assessment guidelines, and EPA IRIS recently published an updated review of health benchmarks for non-cancer and cancer endpoints that includes new studies not considered in the previous assessments.

2.5 Hazard Endpoints

2.5.1 Environmental Hazard

The available ecotoxicity studies for 1,4-dioxane on fish, aquatic invertebrates and aquatic plants are summarized in Appendix D. There are no studies for 1,4-dioxane on sediment, soil or terrestrial organisms.

The hazard of 1,4-dioxane to aquatic organisms is low. The hazard of 1,4-dioxane is expected to be low for soil organisms due to its high potential to volatilize from soil surfaces and low for sediment-dwelling organisms due to its low adsorption potential to sediment.

2.5.2 Human Health Hazard

A detailed summary of human health studies is in Appendix E-1 and additional information can be found in the EPA IRIS Toxicological Review of 1,4-Dioxane (with Inhalation Update) available at: http://www.epa.gov/IRIS/toxreviews/0326tr.pdf.

Several national and international organizations have evaluated the human health hazard of 1,4-dioxane. Previous assessments were reviewed to identify potential hazard concerns of 1,4-dioxane including a 2013 IRIS review (US EPA, 2013b), a 2012 ATSDR Toxicological Profile (ATSDR, 2012), a Canadian screening assessment (Environment Canada and Health Canada, 2010) and the EU RAR (European Chemicals Bureau, 2002).

Moderate to high hazard concerns for repeated exposures are based on subchronic and chronic oral and inhalation studies. In subchronic studies, the primary target organs are the liver,

kidney and nasal/respiratory epithelium. Chronic studies have reported an apparent progression to tumor formation at these sites that appears to be independent of genotoxicity.

Physiologically based pharmacokinetic models (PBPK) models have been developed for 1,4-dioxane in rats, mice, humans and lactating women (US EPA, 2013b). Animal studies indicate 1,4-dioxane is readily absorbed via oral and inhalation exposures, with less absorption through the skin (ATSDR, 2012). No data are available on the distribution of 1,4 dioxane in humans, and no data on distribution are available in animals via oral or inhalation routes. Metabolism of 1,4-dioxane in humans and experimental animals is extensive. Rats were shown to metabolize inhaled 1,4-dioxane to β-hydroxyethoxy acetic acid (HEAA). Elimination of 1,4-dioxane in humans and rats is via the urine in the form of HEAA.

Mortality was observed in multiple acute high-dose studies in rats, mice and rabbits. The acute oral, dermal and inhalation toxicity of 1,4-dioxane is low in rats, mice and rabbits. Repeated-dose toxicity studies in rats via oral administration with 1,4-dioxane at mid- and high-dose, showed variable degrees of kidney and liver changes and mortality. Liver and nasal carcinomas were observed in rats via the inhalation route.

Delayed ossification of the sternebrae and reduced fetal body weights were observed in a prenatal developmental toxicity study with 1,4-dioxane. No reproductive toxicity studies have been performed with 1,4-dioxane; however, no histopathological changes were reported in the reproductive organs of male and female rats/mice exposed in subchronic and chronic studies. The high dose at which developmental effects occurred suggests a low hazard for developmental and reproductive toxicity.

The genotoxic potential of 1,4-dioxane has been evaluated using *in vitro* and *in vivo* assay systems. The majority of *in vitro* assays with 1,4-dioxane were nongenotoxic. Fifty-percent of *in vivo* studies with 1,4-dioxane were positive. EPA (US EPA, 2013b) concluded that 1,4-dioxane is nongenotoxic or weakly genotoxic based on the IRIS review.

No treatment-related effects were observed in a single dose dermal irritation assay in rats. In a 90-day inhalation study, no gross or microscopic alterations were reported in the skin of rats. However, this study was conducted via inhalation and does not provide an adequate representation of dermal toxicity.

Evidence of carcinogenicity in animals (liver and nasal tumors, mesotheliomas of the peritoneum in male rats and an increase in mammary gland adenomas in female rats) indicates that 1,4-dioxane is “likely to be carcinogenic to humans” (US EPA, 2013b). A cancer slope factor (CSF) of 0.1 $(mg/kg/day)^{-1}$ was derived from the tumor incidence data for nasal squamous cell carcinomas in mice and gall bladder carcinomas in guinea pigs. A new two-year inhalation bioassay in rats was used to calculate an inhalation unit risk (IUR) of 5×10^{-6} $(\mu g/m^3)^{-1}$ (US EPA, 2013b).

2.6 Results of Problem Formulation

The results of problem formulation are a conceptual model, key assessment questions and an analysis plan for human health (US EPA, 2014b). A conceptual model was not developed for environmental health due to the low ecotoxicity hazard values reported from standard acute and chronic ecological toxicity tests.

2.6.1 Conceptual Model

The following conceptual model (Figure 2-2) illustrates the sources and potential pathways (arrows) of 1,4-dioxane from chemical manufacture and formulation, releases to the environment and potential exposure pathways for human (workers, consumer and general population) receptors. The blue solid and dotted blue lines in the conceptual model represent pathways from potential sources, and the red solid and dotted lines represent potential exposure pathways via inhalation or ingestion for human receptors. Dermal exposures are not addressed due to a low rate of absorption, high volatilization and lack of dermal toxicity studies. Potential human health effects include cancer (progression of tumor formation) and noncancer outcomes (liver, kidney and nasal effects) in workers, consumers and the general population.

The source-exposure-receptor pathways, labeled numerically in the conceptual model, are described as follows:

1. Workers may be potentially exposed from inhalation exposures during manufacturing and formulation of 1,4-dioxane or in industrial or laboratory facilities where 1,4-dioxane is used.

2. Workers and consumers may be potentially exposed by inhalation during the use of products that contain 1,4-dioxane as a contaminant.

3. Inhalation exposures may occur to the general population as a result of emissions from manufacturing/formulating/use facilities, as well as incineration of waste streams/products.

4. Oral exposures to the general population may occur from drinking contaminated water. 1,4-Dioxane in surface water or ground water may travel through public drinking water treatment plants (DWTPs) and private wells to the “tap”. The source contributions to drinking water are uncertain and may originate from wastewater effluent, leaching from landfills and disposal sites to groundwater and surface water.

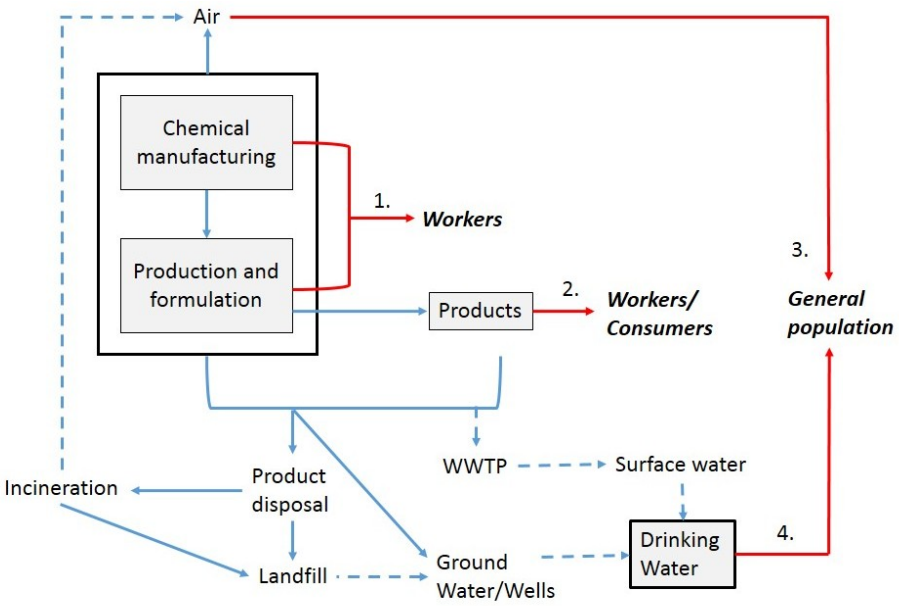

Figure 2-2: Conceptual Model of Potential Exposure Pathways for 1,4-Dioxane.

Solid blue lines represent potential source pathways; solid red lines represent exposure pathways to receptors; dotted blue lines indicate pathways with limited data to assess.

Four key assessment questions were developed from the Conceptual Model:

1. Are there risks to workers exposed during manufacturing and formulation of 1,4-dioxane or in industrial or laboratory facilities where 1,4-dioxane is used?

A 2002 European assessment found potential risk to workers for occupational exposures via the dermal and inhalation routes during product formulation and the use of 1,4-dioxane as a cleaning agent. Comparing the estimates of worker inhalation in Europe to US limits and recommended action levels, exposures did not exceed the OSHA Permissible Exposure Limit (PEL), but typically exceeded the NIOSH Recommended Exposure Limit (REL). Exceeding the NIOSH REL may indicate potential exposure concerns. The few US data on worker exposure were below the NIOSH REL. However, EPA's recently updated IRIS cancer and non-cancer benchmarks for human health suggest that human health risks should be reassessed.

2. Are there risks to workers and consumers potentially exposed by inhalation during the use of products that contain 1,4-dioxane as a contaminant?

Workers and consumers may be exposed to 1,4-dioxane present as a contaminant in products such as personal care products, paints, adhesives, varnishes, cleaners and detergents. Previous risk assessments in Canada and Europe concluded that levels of contamination do not pose concerns for human health. However, the assumptions used in those assessments may differ from EPA risk assessment guidelines. EPA's recently updated IRIS benchmarks for non-cancer

and cancer human health endpoints, including new studies, were not considered in the previous assessments. EPA/OPPT should reassess risks to workers and consumers from products. While personal care products are regulated by the FDA, uses in paints, adhesives, varnishes, cleaners and detergents fall under TSCA authority.

3. Are air emissions of 1,4-dioxane a potential risk to the general population from inhalation exposure?

EPA/OPPT considered the exposure of the general population to ambient air levels of 1,4-dioxane. Minimal data on 1,4-dioxane uses and releases to the environment exist for estimating the ambient levels of 1,4-dioxane in air and recent monitoring data is unavailable. TRI data (US EPA, 2012c) indicate that there are 39 sites reporting the release of 106,300 pounds of 1,4-dioxane to on- and off-site releases with 82% of these air releases to onsite fugitive and point sources and 18% to surface water. There was an additional 1,035,300 pounds from two sites with almost all going to underground injection wells (on-site and off-site) and waste brokers.

Since phasing out of the use of 1,4-dioxane as a stabilizer in chlorinated solvents except for select uses, air releases of 1,4-dioxane have decreased as can be seen in the TRI data (Section 2.4.1). Air monitoring data from urban areas in the 1980s and 1990s showed significant decreases in 1,4-dioxane over the period covering the phase out. Since the 1990's, the reduction seems to have leveled off. The latest TRI data indicate that air releases continue to occur.

During problem formulation, EPA/OPPT considered that 1,4-dioxane is: 1) regulated under the CAA as a hazardous air pollutant (US EPA, 2000); 2) photooxidized in the environment with a $t_{1/2}$ of 1-3 days; and, 3) historical levels of 1,4-dioxane range from 0.0001 to 0.0004 mg/m^3 (i.e., 0.1 µg/m^3 to 0.4 µg/m^3) (ATSDR, 2012). Canada assessed the exposure of the general population to 1,4-dioxane in air and concluded that there is no risk of concern (Environment Canada and Health Canada, 2010). Compared to the IRIS Reference Concentration (RfC) (US EPA, 2013b) for noncancer effects (0.03 mg/m^3), the historical levels are 75 to 300 times lower than the RfC. Calculation of lifetime cancer risk using the IRIS IUR (5×10^{-6} (µg/m^3)$^{-1}$) (US EPA, 2013b) indicates that risks associated with historical 1,4-dioxane levels range from 5×10^{-7} to 2×10^{-6}, which are below EPA's target risk range of 1×10^{-6} to 1×10^{-4}.

4. Are there risks to the general population from drinking water contaminated with 1,4-dioxane?

Data being generated by EPA's OW show that the general population may be exposed to 1,4-dioxane from contamination of finished drinking water. Groundwater may also be a source of general population exposures especially around Superfund sites. However, based on the limited data, it may be premature for EPA/OPPT to conduct a TSCA risk assessment of the drinking water pathway because there is too much uncertainty to adequately characterize source contributions of 1,4-dioxane in drinking water from TSCA uses. EPA's OW is currently monitoring for 1,4-dioxane as part of the UCMR 3 monitoring program until December 2015.

EPA will determine whether or not regulatory action is needed as part of the EPA's Regulatory Determination process.

2.6.2 Analysis Plan

Based on Problem Formulation, EPA/OPPT plans to use available data to evaluate:

1. Potential occupational risks of exposure to 1,4-dioxane during manufacturing and formulation of 1,4-dioxane or in industrial or laboratory facilities where 1,4-dioxane is used.

2. Potential risks to workers and consumers exposed by inhalation during the use of products that contain 1,4-dioxane as a contaminant.

For the exposure assessment, EPA/OPPT plans to use the following data and information to estimate worker exposures:

- Physico-chemical data on 1,4-dioxane
- Production volume and use information (non-confidential)
- Data on concentrations of 1,4-dioxane in commercial products from published literature or provided by industry or consumer groups
- Data and information on production, formulation and use processes
- Data from the OSHA Chemical Exposure Health Data database or provided by industry
- Measured and modeled data and information from exposure scenarios considered in the Canadian and European assessments.

For the hazard assessment, EPA/OPPT plans to carefully review the existing human health benchmarks established by OSHA, NIOSH, ATSDR and EPA IRIS (Appendix B). EPA/OPPT will select the relevant benchmarks according to the relevant route of exposure. The exposure estimates will be corrected for expected duration and frequency in agreement with the hazard assessment.

For the risk characterization, EPA/OPPT will compare measured or estimated exposures to the selected hazard benchmarks and calculate cancer risk estimates and non-cancer margins of exposure for workers and consumers exposed to 1,4-dioxane through inhalation.

Given the limited amount of exposure data identified during problem formulation, EPA/OPPT will search for additional data and information on current uses and production volumes, processes used during production/formulation, worker activities, concentrations in products and measurements of exposure levels.

Following review of comments and consideration of any additional data or information EPA/OPPT may receive, EPA/OPPT plans to publish a final assessment for 1,4-dioxane.

2.6.3 Uncertainties and Data Gaps

The industrial and commercial use data as reported in the 2012 CDR database indicate no current consumer uses (US EPA, 2012b). The 2012 CDR does not give a complete picture of all uses because only manufacturers of more than 25,000 pounds of a chemical at a single site are required to report. Downstream industrial, consumer and commercial use data are reported only if they manufactured more than 100,000 pounds of a chemical during a particular year. Processing and use is often not under the control of the manufacturers and they may have incomplete knowledge of these activities (US EPA, 2014a). As a result of these factors, the processing and use information in the CDR public database presents only a limited picture of the actual processing and use situation in the United States (US EPA, 2014a). Recent production volume and use data are claimed confidential by the manufacturer. EPA was unable to identify any US sources that definitively stated the chemical is used in the production of consumer products, and therefore assumes there are no current consumer uses. As a contaminant, data on the concentrations of 1,4-dioxane in consumer products are limited.

Data to understand the sources and pathways by which 1,4-dioxane enters the environment are limited. The total actual releases from facilities that formulate or use 1,4-dioxane have some uncertainties. For example, these releases may be higher than the total reported since facilities that release less than 25,000 pounds are not required to report data to the TRI. Legacy contamination, wastewater effluent and non-point sources may also contribute to releases of 1,4-dioxane into the environment. Recent ambient air data are needed to better understand current worker exposures.

EPA/OPPT is uncertain whether worker exposures to 1,4-dioxane in the US may be similar to those estimated in the EU RAR (European Chemicals Bureau, 2002). EPA/ OPPT is also uncertain whether the limited 1,4-dioxane inhalation monitoring data for US workers are representative of occupational exposures in the US. Also, the historical total numbers of workers exposed to 1,4-dioxane is expected to be much higher than the current total, which is unknown. Information on current uses and volumes, processes used during production/formulation, worker activities and measurements of exposure levels are not available. The extent to which manufacturers use processes to reduce the contamination of 1,4-dioxane in products is unknown.

In the human health hazard assessment, EPA IRIS noted uncertainties in the development of the cancer risk values including the use of low-dose extrapolation, dose metric, cross-species scaling, alternative bioassays, species/gender combination, human relevance to mouse tumor data and human population variability in metabolism and response/sensitive subpopulations. There is a data gap in human health hazard since no multigeneration reproductive toxicity studies are available for 1,4-dioxane.

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APPENDICES

Appendix A Regulatory and Assessment History

Table A-1: History of Regulatory and Assessment Actions in the U.S. and Internationally.

COUNTRY	REGULATORY/ASSESSMENT ACTION
UNITED STATES Occupational Exposure Limits	Occupational exposure limits are established: • **1989 OSHA PEL:** 25 ppm (90 mg/m^3) TWA • **1994 NIOSH REL:** 1 ppm (3.6 mg/m^3) 30-minute ceiling, [skin] • **1993-1994 ACGIH TLV:** 25 ppm (90 mg/m^3) TWA
UNITED STATES ATSDR Minimal Risk Levels (MRLs) 2013	<u>Inhalation MRLs:</u> • Acute-duration inhalation exposure (14 days or less) = 7.2 mg/m^3 (2 ppm) was derived from a NOAEL of 72 mg/m^3 (20 ppm) for eye and respiratory irritation and pulmonary function effects in humans. • Intermediate-duration inhalation exposure (15 to 364 days) = 0.72 mg/m^3 (0.2 ppm) was derived from a $BMCL_{10}$ of 101 mg/m^3 (27.99 ppm) (subsequently adjusted for duration) for increased incidence of nasal lesions in rats. • Chronic-duration inhalation exposure (365 days or more) = 0.11 mg/m^3 (0.03 ppm) was derived from a LOAEL of 180 mg/m^3 (50 ppm) (subsequently adjusted for duration) for increased incidence of nasal lesions in rats (Kasai et al, 2009). <u>Oral MRLs:</u> • Acute-duration oral exposure (14 days or less) = 5 mg/kg-bw/day was derived from a NOAEL of 516 mg/kg-bw/day for developmental and maternal effects in rats. • Intermediate-duration oral exposure (15 to 364 days) = 0.5 mg/kg-bw/day was derived from a NOAEL of 52 mg/kg-day for liver effects in rats. • Chronic-duration oral exposure (365 days or more) = 0.1 mg/kg-bw/day was derived from a NOAEL of 9.6 mg/kg-day for liver effects in rats (Kociba et al, 1974).
UNITED STATES IRIS Cancer and Non-cancer Benchmarks 2013	• Cancer Slope Factor: 0.1 (mg/kg/day)$^{-1}$ (based on Kano et al, 2009) • Drinking Water Unit Risk: 2.9 × 10^{-6} µg/L • Inhalation Unit Risk: 5 × 10^{-6} (µg/m^3)$^{-1}$ • RfD = 0.03 mg/kg-day based on degenerative liver effects as the most sensitive endpoint observed in a chronic bioassay; point of departure = 9.6 mg/kg-day (Kociba et al, 1974) • RfC = 3.0 × 10^{-2} mg/m^3 (0.0083 ppm) based on co-critical effects of olfactory

COUNTRY	REGULATORY/ASSESSMENT ACTION
	epithelium atrophy and respiratory metaplasia in rats exposed for 2 years via inhalation; point of departure = 32.2 mg/m^3 (Kasai et al, 2009). • http://www.epa.gov/iris/subst/0326.htm
UNITED STATES Drinking Water Limits 2012	• Health advisory levels for 1,4-dioxane in drinking water: 4 mg/L (one-day, 10-kg child), 0.4 mg/L (ten-day, 10-kg child), 1 mg/L (DWEL), 0.2 mg/L (Life-time), and 0.035 mg/L at 10^{-4} cancer risk. (USEPA, 2012) • On the EPA Unregulated Contaminant Monitoring Rule 3 (UCMR3) list.
UNITED STATES Cancer Classification	• EPA - classified as B2- Probable human carcinogen (EPA 2003) - "1,4-dioxane is 'likely to be carcinogenic to humans' based on evidence of carcinogenicity in several 2-year bioassays conducted in four strains of rats, two strains of mice, and guinea pigs. • The National Toxicology Program concluded that 1,4-dioxane is 'reasonably anticipated to be a human carcinogen' (NTP 2005). • IARC classifies 1,4-dioxane as 'possibly carcinogenic to humans' (IARC 1999
UNITED STATES Hazardous Air Pollutant	• Listed as a hazardous air pollutant under the Clean Air Act (CAA)
UNITED STATES Wastes, Releases, and Remediation	• May be regulated as hazardous waste when used as a solvent stabilizer • Reportable quantity of 100 pounds has been established under CERCLA • Facilities manufacturing, processing, or otherwise using 1,4-dioxane are required to report releases to EPA's Toxic Release Inventory (TRI).
UNITED STATES Food and Drugs	• FDA set limits of 10 ppm in approving glycerides and polyglycerides for use in dietary supplements, and for spermicides.
EUROPEAN UNION 2002	The European Union Risk Assessment Report (EU RAR) concluded that: • Environmental risk, risk to consumers, and risk to general populations are not expected. • Risks are expected to workers due to: (i) skin effects during production, formulation and use of the substance or the product containing the substance, and (ii) systemic toxicity and carcinogenicity due to dermal exposure from the use of the substance as cleaning agent, and due to inhalation during formulation of the substance.
CANADA 2010	• Environment Canada (2010) assessed risks to human health based on potential exposure and carcinogenicity and concluded that 1,4-dioxane is not entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.
Australia 1998	• Priority existing chemical, report published in 1998. • The occupational risk assessment concluded that, for known Australian work situations, 1,4-dioxane is unlikely to cause acute or chronic adverse effects, including inhalation and dermal exposure. However, estimated exposure based on modeled data to workers involved in optical lens manufacture indicate a potential risk. • The public health risk assessment concluded there are no significant health risks to the general public from the only source of potential exposure

COUNTRY	REGULATORY/ASSESSMENT ACTION
	(consumer products containing 1,4-dioxane as impurity). • The environmental risk assessment indicated that the majority of 1,4-dioxane will be released to wastewater, and that the chemical does not present a significant risk of adverse effects to the Australian aquatic environment.
Japan	• Priority Assessment Chemical Substance (PACS). PACS are substances whose long-term toxicity to humans or to flora and fauna in the human living environment is unclear, that have been found, or are expected to be found, inconsiderable amounts over a substantially extensive area of the environment. These substances are designated as chemicals that require a priority assessment to assess the risk they may pose.)

Appendix B Summary of Uses and End Products

Table B-1: Summary of All Uses of 1,4-Dioxane and End Products.

Use	End Product(s)
Processing solvent	• Waxes • Fats • Lacquers and varnishes • Cleaning and detergent preparations • Adhesives • Cosmetics* • Deodorant fumigants • Emulsions and polishing compositions • Wood pulp
Reaction medium solvent	• Organic chemicals
Industrial solvent with an unspecified function	• Fluid for scintillation counter (radiation detector) samples • Specific applications in biological procedures (histology) • Cellulose acetate membranes used as filters • Dye baths • Lacquers and paints • Waxes • Varnishes and stains • Printing compositions • Paint and varnish removers • Laboratory reagent (e.g., mobile phase in chromatography)
Extraction medium	• Animal and vegetable oils
Inert ingredient	• Pesticides and fumigants
Chemical intermediate	• Pharmaceuticals • PET plastic • Rubber • Insecticides and herbicides • Cements • Deodorant fumigants • Magnetic tape • Adhesives
Polymerization catalyst	• Plastics (unspecified plastic type)
Dehydrating agent	• Unknown
Wetting and dispersing agent	• Textiles
Degreasing agent	• Unknown
Unintentional Impurity	• Food (as a result of food additives or pesticides) • Cosmetics • Agricultural/veterinary products • Industrial detergents • Household detergents • Pharmaceuticals • Antifreeze and deicing products
*As listed in ECHA, 2002 and not confirmed by US sources. **Sources:** EPA, 2006; ASTDR, 2012; ECHA, 2002; FDA, 2007; Environment Canada, 2010	

Appendix C Occupational Exposure Data

Appendix C contains US occupational exposure inhalation data from two sources.

Table C-1: Summary of 1,4 Dioxane Occupational Monitoring Data for Process Operators in the Synthesis Area from an ACC Member Company where 1,4-Dioxane is Produced as a Byproduct in its Manufacturing Process.

Sample Date	Activity	Results (ppm, 8-hour TWA)
10/29/01	Emptying & Boiling out Vessel	LT 0.044
10/29/01	Emptying & Boiling out Vessel	LT 0.054
10/29/01	Emptying & Boiling out Vessel	LT 0.045
10/29/01	Emptying & Boiling out Vessel	LT 0.045
10/29/01	Emptying & Boiling out Vessel	LT 0.046
10/29/01	Emptying & Boiling out Vessel	LT 0.043
10/29/01	Emptying & Boiling out Vessel	LT 0.046
07/11/02	Running PO and EO into [Product] batch	LT 0.1
05/29/03	Drumming [Product]	LT 0.9
06/03/03	Drumming [Product]	LT 0.3
06/09/03	Sampling and Drumming [Product]	LT 0.3
06/09/03	Adding [Raw Material] to [Product]	LT 0.3
06/11/03	Drumming [Product]	LT 0.3
06/13/03	Drumming [Product]	LT 0.3
06/16/03	Sampling and Drumming [Product]	LT 0.3
06/19/03	Drumming [Product]	LT 0.4
06/23/03	Sampling [Product]	LT 0.3
07/02/03	Sampling and Drumming [Product]	LT 0.3
07/06/03	Dumping P2O5 into [Product]	LT 0.3
07/09/03	Drumming [Product]	LT 0.3
07/14/03	Drumming [Product]	LT 0.3

Source: Franz, 2014.
Key: LT = Less than (the value provided is the limit of detection (LOD)).
TWA = time weighted average over an 8-hour period

Table C-2: 1,4-Dioxane - OSHA Chemical Exposure Health Data, 1997 – 2011.

Establishment	City	State	Zip	Date	SIC	NAICS	Type	Time (minutes)	Result (ppm)
Peter Cremer North America, Lp	Cincinnati	OH	45204	15-May-08	2869	325199 D46774	P	15	ND
Peter Cremer North America, Lp	Cincinnati	OH	45204	15-May-08	2869	325199 D46775	P	19	ND
Peter Cremer North America, Lp	Cincinnati	OH	45204	15-May-08	2869	325199 D46773	P	15	ND
Crystal, Inc. - Pmc	Lansdale	PA	19446	16-Jun-00	2841	0 E77374	P	32	ND
Crystal, Inc. - Pmc	Lansdale	PA	19446	16-Jun-00	2841	0 E77370	P	65	ND
Crystal, Inc. - Pmc	Lansdale	PA	19446	16-Jun-00	2841	0 E77372	P	30	ND
Crystal, Inc. - Pmc	Lansdale	PA	19446	16-Jun-00	2841	0 E77368	P	60	ND
Crystal, Inc. - Pmc	Lansdale	PA	19446	16-Jun-00	2841	0 E77369	P	84	0.2117
Crystal, Inc. - Pmc	Lansdale	PA	19446	16-Jun-00	2841	0 E77371	P	50	0.2242
Crystal, Inc. - Pmc	Lansdale	PA	19446	16-Jun-00	2841	0 E77373	P	60	ND
Tex-Tube, Inc.	Houston	TX	77024	13-Jul-98	3498	0 E65998	P	18	ND
Raytheon Aircraft Company	Wichita	KS	67206	2-Apr-98	3721	0 E63443	A	75	ND
Raytheon Aircraft Company	Wichita	KS	67206	2-Apr-98	3721	0 E63444	A	40	ND
Raytheon Aircraft Company	Wichita	KS	67206	2-Apr-98	3721	0 E63441	A	75	ND
Raytheon Aircraft Company	Wichita	KS	67206	2-Apr-98	3721	0 E63440	A	75	ND
Raytheon Aircraft Company	Wichita	KS	67206	2-Apr-98	3721	0 E63442	A	75	ND
Raytheon Aircraft Company	Wichita	KS	67206	2-Apr-98	3721	0 E63439	A	75	ND
Yellow Freight Systems, Inc.	Columbus	OH	43228	9-Mar-98	4231	0 J61640	P	17	ND
Yellow Freight Systems, Inc.	Columbus	OH	43228	9-Mar-98	4231	0 J61642	B	0	ND
Yellow Freight Systems, Inc.	Columbus	OH	43228	9-Mar-98	4231	0 J61639	P	25	ND
Baker Petrolite	Sand Springs	OK	74063	17-Feb-98	2869	0	P	225	ND

Source: https://www.osha.gov/opengov/healthsamples.html accessed 3/7/14
Key: SIC = Standard Industrial Classification; NAICS = North American industrial Classification System; ND = Not Detected; Types: P = Personal, A = Area, B = Bulk
The detection limits for samples labeled as ND are not given.

Appendix D Ecological Hazard Studies

The ecological hazard summary of 1,4-dioxane is based on available hazard data. In addition, an updated literature survey was conducted to identify articles on ecological toxicity published between 2003 and 2014. The search terms included freshwater and saltwater fish, aquatic invertebrates, and aquatic plants; pelagic and benthic organisms; acute and chronic sediment toxicity in freshwater and saltwater and terrestrial toxicity to soil organisms, birds, and mammals. The test species, test conditions, toxicity endpoints, statistical significance, and strengths/limitations of the study were evaluated for data quality.

1,4-dioxane has been tested for acute and chronic aquatic toxicity. In order to characterize the effects of 1,4-dioxane to the environment, a hazard rating was assigned based on EPA methodology for existing chemical classification (US EPA, 2009). Included in this assessment are eight acute aquatic toxicity studies and three chronic aquatic toxicity studies. There is one study that characterizes the toxicity of 1,4-dioxane for aquatic plants. Acute and chronic toxicity data for 1,4-dioxane exist for freshwater and saltwater fish, daphnia, and green algae. There are no available sediment, soil, or avian toxicity studies found in literature for 1,4-dioxane. Also, EPA/OPPT agrees with the classification of studies previously reviewed in the EU RAR (European Chemicals Bureau, 2002). The European Chemicals Agency (ECHA) database on 1,4-dioxane contains updated hazard studies that were used to supplement the EU RAR.

A summary of the available ecotoxicity data for 1,4-dioxane is provided below. The data show that there is a low acute and chronic ecotoxicity for fish, aquatic invertebrates and aquatic plants Hazard to soil and sediment organisms are expected to be low based on the lack of partitioning to and persistence in these environmental compartments. The EU RAR (European Chemicals Bureau, 2002) also concluded low hazard for soil and sediment organisms.

D-1 Acute Toxicity to Aquatic Organisms

Acute aquatic toxicity studies considered for this assessment are summarized in Table D-1. Based on the available studies, fish, invertebrates and algae, 1,4-dioxane exhibits low acute toxicity for aquatic species.

Table D-1: Aquatic Toxicity Data for 1,4-Dioxane - Acute Toxicity.

Test Species	Fresh/ Salt Water	Duration	End-point	Conc. (mg/L)	Test Analysis	Effect	References
Fish							
Bluegill sunfish (*Lepomis macrochirus*)	Fresh	96-hour	LC_{50}	>1,000	Nominal	Mortality	Dawson et al. (1977) as cited in Verschueren, (2010)
Fathead minnow (*Pimphales promelas*)	Fresh	96-hour	LC_{50}	1,080 to 9,850	Measured	Mortality	Geiger, et al. (1990)
Fathead minnow (*Pimphales promelas*)	Fresh	96-hour	LC_{50}	9,872	Measured	Mortality	Brooke (1987)
Fathead minnow (*Pimphales promelas*)	Fresh	96-hour	LC_{50}	12,326	Nominal	Mortality	Brooke (1987)
Fathead minnow (*Pimphales promelas*)	Fresh	96-hour	LC_{50}	>100	Nominal	Mortality	Dow (1991) as cited in the EU RAR (2002)
Inland Silversides (*Menidia beryllina*)	Salt	96-hour	LC_{50}	67,000	Nominal	Mortality	Dawson et al. (1977)
Aquatic Invertebrates							
Water flea (*Daphnia magna*)	Fresh	48-hour	EC_{50}	>1,000	Nominal	Immobilization	ECHA Assessment Report (2014)
Water flea (*Ceridodaphnia dubia*)	Fresh	48-hour	EC_{50}	>299	Nominal	Immobilization	Dow (1989) as cited in the 2002 EU RAR

Acute Toxicity to Aquatic Invertebrates

For this assessment, there are two studies on the acute ecotoxicity to aquatic invertebrates. The water flea (*Daphnia magna*) were exposed to unspecified concentrations of 1,4-dioxane for 48-hours under semi-static conditions. The highest concentration tested was 1,000 mg/L. No effects were seen at the highest concentration of 1,000 mg/L. A 48-hour EC_{50} of >1,000 mg/L was reported (European Chemicals Bureau, 2002). In the other study, *Ceridodaphnia dubia* was tested under the same conditions. A 48-hour EC_{50} of >299 mg/L was reported (Dow Chemical, 1989). These values show that the acute toxicity of 1,4-dioxane to aquatic invertebrates is low.

Acute Toxicity to Fish

The acute 96-hour LC_{50} values range~~s~~ from >100 mg/L for fathead minnows (*Pimephales promelas*) to 67,000 mg/L for the Inland Silversides (*Menidia beryllina*). Overall, the acute toxicity of 1,4-dioxane to fish is low (European Chemicals Bureau, 2002).

D-2 Chronic Toxicity to Aquatic Organisms

Table D-2: Aquatic Toxicity Data for 1,4-Dioxane - Chronic Toxicity.

Test Species	Fresh/ Salt Water	Duration	End-point	Conc. (mg/L)	Test Analysis	Effect	References
Aquatic Plants							
Green algae (*Pseudokirchnerella subcapitata*)	Fresh	72-hour	EC_{50}	580 1,000	unspecified	growth biomass	ECHA Assessment Report, 2014
Aquatic Invertebrates							
Water flea (*Daphnia magna*)	Fresh	21-day	NOEC	>1,000	Unspecified	Reproduction	ECHA Assessment Report, 2014
Fish							
Medaka (*Oryzias latipes*)	Fresh	28-day	NOEC	565	Measured	Not Reported	Johnson et al. (1993) as cited in EPA's Ecotox Database, 2014
Fathead minnow (*Pimphales promelas*)	Fresh	32-day	MATC	145	Measured	Development, Hatching, Survival	TSCATS, (1989) as cited in the EU RAR (2002)

Toxicity to Aquatic Plants

Only one adequate study is available to characterize the toxicity of 1,4-dioxane to aquatic plants. 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 (growth rate) was reported. A NOEC of 580 mg/L (biomass) and a NOEC of 1,000 mg/L were reported (ECHA Assessment Report, 2014). This study indicates the toxicity of 1,4-dioxane to aquatic plants is low.

Chronic Toxicity to Aquatic Invertebrates

One study is available that characterizes 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 Assessment Report, 2014). The reported NOEC indicates the chronic effects of 1,4-dioxane to aquatic invertebrates is low.

There are no available studies on the toxicity of 1,4-dioxane to sediment-dwelling organisms. EPA/OPPT agrees with the EU RAR (European Chemicals Bureau, 2002) that there is low potential of 1,4-dioxane to adsorb to sediment and elevated levels are not expected in sediments.

Chronic Toxicity to Fish

There are three available studies that characterize the chronic toxicity of 1,4-dioxane to freshwater fish. 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. The effects on growth and survival were reported (Johnson et al., 1993). No effects were seen. A no observed effect concentration (NOEC) of 565 mg/L was reported. In another study, fathead minnows (*P. promelas*) were exposed to mean measured concentrations of 27.6, 40.3, 65.3, 99.7, and 145 mg/L of 1,4-dioxane to observe the effects of the chemical on hatching, development and survival for 32 days under flow-through conditions. 1,4-dioxane had no significant effects on embryo development, hatching, larvae survival or larvae weight. A NOEC of >103 and a maximum acceptable toxicant concentration (MATC) of >145 mg/L were reported (European Chemicals Bureau, 2002).

D-3 Terrestrial Plants Toxicity

One study was found that characterizes the hazard of 1,4-dioxane to terrestrial plants. Lettuce (*Actuca sativa*) was exposed to 1,4-dioxane in a germination/root elongation toxicity test for 3-days. An EC_{50} of 1,450 mg/L was reported for germination (Reynolds, 1989). This is a non-guideline study. Currently, EPA has no available hazard criteria that applies to this endpoint.

D-4 Soil Invertebrate and Avian Toxicity

There are no available acute or chronic toxicity studies that characterize the hazard of 1,4-dioxane to soil or terrestrial organisms. However, the toxicity of 1,4-dioxane is expected to be low in these environments based on the chemical's high vapor pressure and it's propensity to volatilize from soil. 1,4-dioxane is slightly volatile from water surfaces and moist soil due to its high water solubility. No toxicity data are available for 1,4-dioxane to birds.

Appendix E Human Health Hazard Studies

The human health studies summarized here and in Table E- are referenced in the EPA IRIS Toxicological Review of 1,4-Dioxane (with Inhalation Update) available at: http://www.epa.gov/IRIS/toxreviews/0326tr.pdf.

E-1 Acute Toxicity Studies

Mortality was observed in multiple acute high-dose studies in rats, rabbits, and mice via the oral, dermal, or inhalation route. The oral LD_{50} values calculated for rats ranged from 5,170 – 7,339 mg/kg-bw; the dermal LD_{50} in rabbits is equal to 7,885 mg/kg-bw, and the inhalation LC_{50} in mice is equal to 36,700 mg/m^3 and ranged from 46,000 – 52,000 mg/m^3 in rats.

E-2 Repeated-Dose Toxicity Studies

Oral Toxicity

A 90-day oral repeated-dose toxicity study in male and female F344 rats and BDF1-mice with 1,4-dioxane in drinking water (Kano et al, 2008) showed a dose-depended increase in the relative weights of the kidney and lung in rats and mice with a relative liver weight increase only in rats. A no-observed-adverse-effect level (NOAEL) was determined at 170 mg/kg-bw/day in mice and 52 mg/kg-bw/day in rat.

Kociba et al (1974), conducted a study in which Sherman rats were administered 1,4-dioxane in drinking water for up to 716 days. No treatment-related effects were observed at the lowest dose tested for either sex. Both sexes that were treated at the mid-dose, showed variable degrees of renal and hepatic degenerative changes with no occurances of tumors. Hepatocellular and renal degenerative changes, and hepatocellular and nasal carcinomas observed at the highest dose were considered equivalent to previous reported study results. A LOAEL of 94 mg/kg-bw/day and a NOAEL of 9.6 mg/kg-bw/day were determined.

Dermal Toxicity

The 90-day study conducted by Kasai et al (2008) via inhalation does not provided appropriated details of the dermal toxicity of 1,4-dioxane.

Inhalation Toxicity

A 90-day repeated-dose toxicity study with F344 with vaporized 1,4-dioxane for 6 hours/day and 5/days/week as reported by Kasai (2008), showed mortality at the highest dose tested. Histopathological changes in the liver, kidney, nasal epithelium, and lung were observed at 360 mg/m^3. A LOAEC of 360 mg/m3 is based on histopathological changes in the liver, kidney, nasal epithelium, and lung.

E-3 Reproductive and Developmental Toxicity Studies

No reproductive toxicity studies have been performed; however, no histopathological changes were reported in the reproductive organs of male and female rats/mice exposed to 1,4-dioxane in subchronic and chronic studies, which suggests a low concern for reproductive toxicity.

Pregnant female Sprague Dawley rats given 1,4-dioxane by oral gavage in water on gestation days 6-15, showed decreases in maternal body weight gain at 1000 mg/kg-bw/day (Giavini et. al., 1985). A slight decrease in fetal weight and ossification of the sternebrae was also observed at 1000 mg/kg-bw/day.

E-4 Skin Irritation and Sensitization Studies

Clark et al (1994) conducted a dermal irritation assay where male (COBS/Wister rats (number not stated) were shaved on specific areas of the back and flank then exposed to a single dose of 1,4-dioxane at 8,300 mg/kg and observed for 14 days. No treatment-related effects were observed.

The 90-day study conducted by Kasai et al (2008) via inhalation does not provide appropriate details of the dermal toxicity of 1,4-dioxane.

E-5 Genotoxicity and Cancer Studies

The genotoxic potential of 1,4-dioxane has been evaluated using *in vitro* and *in vivo* assay systems. The majority of *in vitro* assays with 1,4-dioxane were nongenotoxic. Fifty-percent of *in vivo* studies with 1,4-dioxane were positive. EPA's IRIS program concluded that 1,4-dioxane is nongenotoxic or weakly genotoxic based on reviewed gene mutation and chromosome aberration studies.

In the Kociba et al (1974) repeated-dose oral drinking water study in rats previously mentioned, 1,4-dioxane increased tumor progression in the liver *via* the oral route.

Kasai et al (2009) conducted a two-year bioassay in male F344 rats exposed to 1,4-dioxane *via* vapor inhalation at various concentrations for 6 hours/day, 5/days/week. Mortality was observed at the mid- and high dose. A statistically significant dose-dependent increase in nasal squamous cell carcinomas, hepatocellular adenomas, and peritoneal mesotheliomas were observed predominantly at the high dose. Renal cell carcinomas, mammary gland fibroadenomas, and adenomas were observed in a dose-dependent manner. Nasal cavity and liver preneoplastic lesions were observed at all doses. At 50 ppm, nonneoplastic lesions, nuclear enlargement, atrophy, and respiratory metaplasia in the nasal cavity were significantly increased. 1,4-Dioxane increased the incidence of tumors in rats.

The IRIS cancer slope factor (CSF) was based on the development of liver tumors in female mice (Kano et al, 2009). In this study, male and female F344/DuCrj rats and Crj:BDF(1) mice were exposed up to 5000 ppm (rats) and 8000 ppm in mice of 1,4-dioxane in the drinking water for 2 years. A significant induction of nasal squamous cell carcinomas (females), hepatocellular adenomas and carcinomas (males and females), peritoneal mesotheliomas (males), and mammary gland adenomas (females) were observed. Mice showed a significant induction of hepatocellular tumors in males and females.

In a supporting study (NCI, 1978), Osborne-Mendel rats (0, 240, and 530 mg/kg-bw/day- males; 0, 350 and 640 mg/kg-bw/day-females) and B6C3F1 mice (0, 720, and 830 mg/kg-bw/day-males; 0, 380, and 860 mg/kg-bw/day-females) were exposed to 1,4-dioxane (v/v) via drinking water for 2-years. 1,4-Dioxane induced squamous-cell carcinomas of the nasal turbinates in treated rats and hepatocellular carcinomas in treated mice.

Table E-1: Human Health Endpoints for 1,4-Dioxane.

Endpoint	Hazard Determination	References (all are as cited in (US EPA, 2013b))
Acute Oral Toxicity LD_{50} (mg/kg-bw)	5,170 – 7,339 (rat)	Laug et al. (1939); Smyth et al. (1941); Nelson (1951); Pozzani et al. (1959); JBRC (1998)
Acute Dermal Toxicity LD_{50} (mg/kg-bw)	7,885 (rabbit)	Clark et al. (1984)
Acute Inhalation Toxicity LC_{50} (mg/L)	36,700 (mouse)	Fairley et al. (1934); Wirth and Klimmer (1936)
	46,00 – 52,000 (rat)	Failey et al. (1934); Nelson (1951); Pozzani et al. (1959)
Repeated-Dose Toxicity Oral (mg/kg-bw/day)	**NOAEL = 170 mg/kg-bw/day (mice); NOAEL = 52 mg/kg-bw/day (rat)** Moderate hazard via the oral route based on histopathological changes in the liver, kidney and bronchial epithelium	Kano et al. (2008 and 2009)
	LOAEL = 94 mg/kg-bw/day; NOAEL = 9.6 mg/kg-bw/day (rat) High hazard based on degeneration and necrosis of renal cells and hepatocytes (non-cancer)	Kociba et al (1974). *Endpoint used as the point of departure (POD) for the IRIS Reference Dose (RfD).*
Inhalation (mg/L/day)	**NOAEC = 360 mg/m^3 (rat)** Moderate hazard via the inhalation route based on histopathological changes in the liver, kidney, nasal epithelium, and lung	Kasai et al. (2008)
Developmental Toxicity	**NOAEL = 500; LOAEL = 1,000 mg/kg-bw/day** Low hazard based on delayed ossification of the sternebrae and reduced body weights in rats	Giavini et al. (1985)
Reproductive Toxicity	**No specific reproductive studies have been performed** Low hazard based on no histopathological changes in reproductive organs of male and female mice in subchronic and chronic studies.	Giavini et al. (1985)
Genetic Toxicity, gene mutation In vitro	**Nongenotoxic** Low hazard based on available *in vitro* studies	Morita and Hayashi (1998); Stott et al. (1981); Hellmer and Bolcsfoldi (1992); Zimmerman et al. (1985)

Endpoint	Hazard Determination	References (all are as cited in (US EPA, 2013b))
In vivo	**Nongenotoxic or weakly genotoxic** Low hazard based on available *in vitro* and *in vivo* studies	Roy et al. (2005); Morita and Hayashi (1998); Stott et al. (1981)
Genetic Toxicity, chromosomal aberrations **In vitro**	**Nongenotoxic** Low hazard based on available *in vitro* studies	Galloway et al. (1987); Morita and Hayashi (1998)
In vivo	**Nongenotoxic or weakly genotoxic** Low hazard based on available *in vitro* and *in vivo* studies	Miyagawa et al. (1999); Goldsworthy et al. (1991); Stott et al. (1981)
Chronic (Non-Cancer) **Oral**	**NOAEL = 9.6; LOAEL = 94 mg/kg-bw/day** **NOAEL = 170; LOAEL = 387 mg/kg-bw/day**	Kociba et al. (1974); Giavini et al. (1985); Kano et al. (2008)
Inhalation	**NOAEC = 360 mg/m^3**	Kasai et al. (2008) *Endpoint used as the POD for IRIS Reference Concentration (RfC)*
Carcinogenicity **Oral**	**"Likely to be carcinogenic to humans based on evidence of carcinogenicity in several 2-year bioassays"** High hazard base on tumor progression in the liver via the oral route	Kociba et al (1974); Kano et al (2009); NCI (1978)
Inhalation	**"Likely to be carcinogenic to humans based on evidence of carcinogenicity in several 2-year bioassays"** High hazard base on tumor progression tumor progression at multiple sites via inhalation	Kasai et al. (2009)
Dermal Irritation	**Not irritating**	Clark et al (1994)
Skin Sensitization	**No Data**	Kasai et al. (2008)
Respiratory Sensitization	**Positive for Sensitization**	Kasai et al. (2009)