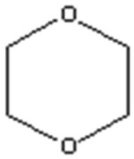
Fact Sheet Date: April 8, 2021

NEW YORK STATE
HUMAN HEALTH FACT SHEET

Ambient Water Quality Value for
Protection of Human Health and Sources of Potable Water[1]

SUBSTANCE: 1,4-Dioxane



CAS REGISTRY NUMBER: 123-91-1

AMBIENT WATER QUALITY VALUE: 0.35 micrograms/liter (0.35 mcg/L)

BASIS: Oncogenic Effects (6 NYCRR 702.4)

INTRODUCTION

1,4-Dioxane is a manufactured chemical that does not occur naturally. It is used as a solvent for a wide variety of chemical products and is a contaminant of some ingredients used in the manufacture of personal care products and cosmetics (ATSDR, 2012; US EPA, 2013). The toxicological properties of 1,4-dioxane have been summarized by ATSDR (2012), CA EPA (2009), Health Canada (2018) and US EPA (2013, 2014). Each agency identified important studies on the health effects of exposure to 1,4-dioxane, including studies (when available) on the chronic (oncogenic and nononcogenic), developmental, and reproductive effects observed in humans and animals. We derived the ambient water quality value of 0.35 mcg/L for 1,4-dioxane using available toxicological data and risk assessments, the definitions in 6 NYCRR 700.1, and the procedures outlined in 6 NYCRR 702.2 through 702.7.

702.3. PROCEDURES FOR DERIVING STANDARDS AND GUIDANCE VALUES BASED ON SPECIFIC MCLS AND PRINCIPAL ORGANIC CONTAMINANT CLASSES

1,4-Dioxane has a Specific MCL of 1.0 mcg/L as defined in 6 NYCRR 700.1. Thus, the potential ambient water quality value for 1,4-dioxane under 6 NYCRR 702.3 is 1.0 mcg/L.

[1] A list of commonly used abbreviations and acronyms is attached as Exhibit 3.

702.4. PROCEDURES FOR DERIVING STANDARDS AND GUIDANCE VALUES BASED ON ONCOGENIC EFFECTS

The NTP (2016) has summarized the evidence on the oncogenicity of 1,4-dioxane.

Carcinogenicity

1,4-Dioxane is reasonably anticipated to be a human carcinogen based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to 1,4-dioxane caused tumors in several species of experimental animals and at several different tissue sites. Administration of 1,4-dioxane in drinking water caused benign or malignant liver tumors (hepatocellular adenomas or carcinoma) in mice of both sexes, female rats, and male guinea pigs. It also caused cancer of the nasal cavity (squamous-cell carcinoma) in rats of both sexes and gallbladder cancer (carcinoma) in male guinea pigs (IARC 1976, NCI 1978). In an initiation-promotion study, dermal exposure to 1,4-dioxane promoted the induction of skin tumors (squamous-cell carcinoma, sarcoma and papilloma) by 7,12-dimethylbenzanthracene in mice of both sexes (IARC 1976).

Since 1,4-dioxane was listed in the *Second Annual Report on Carcinogens*, additional studies in rodents have been identified. 1,4-Dioxane administered in the drinking water increased the combined incidence of benign and malignant liver tumors (hepatocellular adenoma and carcinoma) in rats and mice of both sexes. In rats, it also caused nasal cancer (primarily squamous-cell carcinoma) and benign mammary-gland tumors (adenoma) in females and abdominal-cavity tumors (mesothelioma of the peritoneum) in males. Nasal tumors observed in male rats (squamous-cell carcinoma, esthesioneuropithelioma, rhabdomyosarcoma, and unspecified sarcoma) were considered to be exposure-related because of the rarity of these tumors (IARC 1999, Kano *et al*. 2009). As in the drinking-water studies, inhalation exposure of male rats to 1,4-dioxane caused benign liver tumors (hepatocellular adenoma), nasal cancer (squamous-cell carcinoma), and mesothelioma of the peritoneum. In addition, significant exposure-related trends were observed for tumors of the mammary gland (fibroadenoma), kidney (renal-cell carcinoma), and Zymbal gland (adenoma) (Kasai *et al.* 2009), although the incidences at the highest dose were not significantly higher than in the control group. In male strain A/J mice (a strain with a high spontaneous incidence of lung tumors), intraperitoneal injection of 1,4-dioxane increased the number of benign lung tumors (adenoma) per animal (Maronpot et al. 1986).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to 1,4-dioxane. A small prospective study of 165 U.S. workers exposed intermittently to low levels of 1,4-dioxane found no excess of death from cancer; however, the study was limited by the small number of cancer deaths (3) among the exposed workers (Buffler et al. 1978).

The results of a large variety and number of short-term tests (i.e., genotoxicity tests) indicative of the oncogenic potential of 1,4-dioxane are mostly negative, with a few positive results at concentrations that induced other toxic effects (ATSDR, 2012; IARC, 1999; US EPA, 2013). These results indicate that 1,4-

dioxane is either a non-genotoxic compound or a weakly genotoxic compound (ATSDR, 2012; US EPA, 2013).

1,4-Dioxane has induced tumors at multiple sites in three mammalian species (ATSDR, 2012; IARC, 1999; NTP, 2016; US EPA, 2013), and thus has oncogenic effects as defined in 6 NYCRR 700.1(a)(39)(ii). The mode-of-action for 1,4-dioxane oncogenicity, however, is unknown (US EPA, 2013).[2,3] Consequently, under 6 NYCRR 702.4, "...the standard or guidance value shall be based on the 95 percent lower confidence limit on the human dose corresponding to an excess lifetime oncogenic risk of one-in-one-million."

Two public health agencies (CA EPA, 2009; US EPA, 2013, 2014) have evaluated the available scientific literature on the oncogenic effects of 1,4-dioxane and have derived a recommended agency CPF based on good quality experimental studies in animals exposed via drinking water (Table 1). Each agency identified a different chronic study, and thus, different dose-response data, as the basis of its CPF derivation. The CA EPA (2009) and US EPA (2013, 2014) based their CPF derivations on the incidence of liver tumors in female mice observed in NCI (1978) and Kano et al. (2009), respectively. The US EPA (2013, 2014) selected Kano et al. (2009) rather than NCI (1978) because the study used a greater number of experimental groups (three compared to two) and lower doses (0, 66, 278, and 964 mg/kg-day compared to 0, 380, 869 mg/kg-day). Kano et al. (2009) was not available when CA EPA (2009)[4] completed its risk assessment of 1,4-dioxane. Thus, we selected the US EPA derivation (see Exhibit 1) as the basis for a potential ambient water quality value (oncogenic effects) for 1,4-dioxane.

The US EPA (2013, 2014) used a $BMDL_{50}$ estimated with the log-logistic model to derive its CPF (0.10 per mg/kg-day). The US EPA determined that the multistage cancer model did not adequately describe the dose-response data within the range of observation (see US EPA, 2013). Therefore, the US EPA (2013) used other BMD models to describe the data, and selected the results from the log-logistic model for use in the CPF derivation because it provided the best description of the experimental data (see Table 1 for additional details). This approach is permitted under 6 NYCRR 702.4, and is consistent with recent US EPA cancer risk-assessment guidance and practice (Gehlhaus et al., 2011; US EPA, 2005b, 2012). Consequently, we did not

[2] Health Canada (2018) proposed a health-based value based in part on the conclusion that 1,4-dioxane causes liver tumors by a non-genotoxic mode of action involving cytotoxicity followed by regenerative hyperplasia and stimulation of endogenously formed mutations. There is no clear consensus among health agencies on the mode of action for liver tumors and the evidence for a nonlinear (threshold) mode of action for other types of tumors caused by 1,4-dioxane (e.g., nasal cavity and mammary gland) is insufficient. Consequently, there is not unequivocal evidence of a non-linear mode of action (as required under 6 NYCRR 702.4(d)(2)), and we considered 1,4-dioxane a linear-at-low-dose oncogen as defined under 6 NYCRR 700.1.

[3] US EPA (2005a) guidance recommends the use of age dependent adjustment factors (ADAFs) when assessing the cancer risks of chemicals that act through a mutagenic mode of action (MOA) for carcinogenicity. Given that the oncogenic MOA for 1,4-dioxane is unknown, ADAFs were not used in the derivation of potential ambient water quality values for 1,4-dioxane (oncogenic effects).

[4] The CA EPA (2009) derivation was based on a CPF derived in 1989.

consider alternate results from other BMD models.

The US EPA (2013, 2014) used a BMR_{50} and $BMDL_{50}$ (rather than a BMR_{10} and $BMDL_{10}$) as the point of departure[5] "… because it is proximate to the response at the lowest dose tested." This choice is permitted with 6 NYCRR 702.4, and with recommendations in US EPA (2012). The US EPA (2013, 2014) calculated its HED_{BMDL50} from the $BMDL_{50}$ of 32.93 mg/kg-day using a $BW^{3/4}$ scaling factor assuming mouse and human body weights of 0.0358 kg and 70 kg, respectively, which is also consistent with 6 NYCRR 702.4.

$$HED_{BMDL50} = BMDL_{50} \text{ x (animal BW/human BW)}^{1/4}$$

$$HED_{BMDL50} = 32.93 \text{ mg/kg-day x } (0.0358 \text{ kg}/70 \text{ kg})^{1/4}$$

$$HED_{BMDL50} = 4.95 \text{ mg/kg-day}$$

We divided the HED_{BMDL50} by 500,000 to obtain the 95% LCL on the human dose (9.9×10^{-6} mg/kg-day or 0.0099 mcg/kg-day) corresponding to an increased lifetime oncogenic risk of one-in-one-million.[6] Using procedures that are consistent with 6 NYCRR 702.2 and 702.4, we calculated (shown below) a risk-specific (1×10^{-6}) water concentration (0.35 mcg/L) using the 1×10^{-6} human dose (0.0099 mcg/kg-day) and assuming a 70-kg adult consumes 2 liters of water per day. We selected 0.35 mcg/L as the potential ambient water quality value (oncogenic effects) for 1,4-dioxane.

$$\text{Risk-Specific } (1 \times 10^{-6}) \text{ Water Concentration} = \frac{\text{Risk Specific } (1 \times 10^{-6}) \text{Dose x Body Weight}}{\text{Drinking Water Consumption Rate}}$$

$$1 \times 10^{-6} \text{ Water Concentration} = \frac{0.0099 \text{ mcg/kg-day x } 70 \text{ kg}}{2\text{L/day}}$$

$$1 \times 10^{-6} \text{ Water Concentration} = 0.35 \text{ mcg/L}$$

702.5. PROCEDURES FOR DERIVING STANDARDS AND GUIDANCE VALUES BASED ON

[5] A BMDL is also known as an LED, which is the 95 percent lower confidence limit on the effective dose as described in 6 NYCRR 702.4.

[6] A dose at any lifetime excess cancer risk can be obtained from the straight line that extrapolates 50% excess lifetime cancer risk at the HED_{BMDL50} to zero excess risk at zero dose. For example, a one-in-one-million excess lifetime risk (equal to 0.000001) is 500,000-fold lower than an excess lifetime risk of 50% (equal to 0.5). Therefore, the dose at a one-in-one-million excess lifetime risk is obtained by dividing the dose at a 50% excess risk by 500,000 (equal to 0.5/0.000001).

NONONCOGENIC EFFECTS

Information on the health effects of 1,4-dioxane in humans is limited to occupation studies of accidental inhalation exposure to high concentrations or longer-term inhalation exposure to lower levels. Human studies on the health effects of 1,4-dioxane from oral exposure are not available (ATSDR, 2012; Health Canada, 2018; US EPA, 2013). Four public health agencies (ATSDR, 2012; Health Canada, 2018; US EPA, 2013, 2014; WHO, 2005) have evaluated the available scientific literature on the nononcogenic effects of 1,4-dioxane and derived a recommended agency RfD based on the same two-year drinking-water study in rats (Kociba et al., 1974).

Health Canada (2018) modeled a $BMDL_{05}$ of 5.4 mg/kg-day, which they used as a POD, based on liver necrosis[7] incidence data in male and female rats. A total UF of 1,000 was applied to the POD (10X for interspecies differences, 10X for intraspecies differences, and 10X for database deficiencies) to yield an RfD of 0.0054 mg/kg-day.

The other three agencies all identified the study NOAEL[8] as 9.6 mg/kg-day, based on liver (ATSDR, US EPA) or kidney effects (WHO) in male rats. Using procedures that are consistent with 6 NYCRR 702.5, we selected this NOEL as the POD for the derivation of a 1,4-dioxane RfD.[9] The ATSDR, US EPA, and WHO's RfD derivations included the application of a 10X UF to the NOAEL to compensate for animal-to-human differences in pharmacokinetics and pharmacodynamics. We reduced the UF for interspecies differences from 10 to 3 by using a dosimetric adjustment to account for pharmacokinetic differences between animals and humans.[10] Animal to human pharmacokinetic extrapolation of the animal POD is permitted under 6 NYCRR 702.5. This approach, which involves the use of body weight scaling ($BW^{3/4}$) to compensate for interspecies differences in pharmacokinetics, is also consistent with recent US EPA recommendations on deriving RfDs (US EPA, 2011a, b). We calculated an HED_{NOEL} from the rat NOEL.

$$HED_{NOEL} = NOEL_{rat} \times (\text{rat BW/adult human BW})^{1/4}$$

[7] Health Canada chose liver toxicity as the key endpoint for the basis of their health-based water value and considered cancer and noncancer effects together using a threshold approach. They deemed their health-based water value to be protective of both cancer and noncancer health effects.

[8] Also a NOEL as defined in 6 NYCRR 700.1.

[9] 6 NYCRR 702.5(b)(1) states that "The point-of-departure shall be the no-observed-effect level (NOEL), expressed as a dose in milligrams of substance per kilogram of body weight per day," and 6 NYCRR 702.5(b)(2) states that an alternative POD (such as a BMDL) may only be used "If neither a NOEL or LOEL are available." A NOEL is available in this case. Therefore, the NOEL, rather than the $BMDL_{05}$, is used as the POD.

[10] ATSDR and WHO derived RfDs using a total UF of 100X. The total UF used by US EPA was 300X. All three agencies applied UF of 10X for animal-to-human extrapolation and 10X for inter-human variability; the US EPA applied an additional UF of 3X to compensate for the deficiencies in the toxicity database for 1,4-dioxane, namely, the lack of a multi-generation reproductive toxicity study (US EPA 2013, 2014).

where,

$$NOEL_{rat} = 9.6 \text{ mg/kg-day}$$

$$\text{rat BW} = 0.43 \text{ kg (Kociba et al., 1974)}^{11}$$

$$\text{adult human BW} = 70 \text{ kg}$$

$$HED_{NOEL} = 9.6 \text{ mg/kg-day} \times (0.43 \text{ kg}/70 \text{ kg})^{1/4}$$

$$HED_{NOEL} = 2.7 \text{ mg/kg-day}$$

We then used the HED_{NOEL} to calculate an RfD (0.027 mg/kg-day) for 1,4-dioxane.

$$RfD = HED_{NOEL}/UF$$

Where,

UF = 100 (3X for animal-to-human differences in pharmacodynamics, 10X for inter-human variability, and 3X for database gaps)

$$RfD = 2.7 \text{ mg/kg-day}/100$$

$$RfD = 0.027 \text{ mg/kg-day or } 27 \text{ mcg/kg-day}$$

The choice of a total UF of 100 is consistent with 6 NYCRR 702.5 given the areas of uncertainty and variation. We concluded that the US EPA (2013) provided a plausible scientific rationale for the use of an UF of 3 for data gaps.[12] Thus, we selected this RfD (27 mcg/kg-day) for use in the derivation of a potential ambient water quality value (nononcogenic effects for) 1,4-dioxane.

We applied the procedure outlined in 6 NYCRR 702.2 and 702.5 to derive a potential ambient water quality value of 190 mcg/L (two significant figures) using the RfD (27 mcg/kg-day), allocating 20% (0.2) of the RfD to drinking water, and assuming a 70-kg adult consumes 2 liters of water per day.

$$\text{Potential Ambient Water Quality Value} = \frac{27 \text{ mcg/kg-day} \times 70 \text{ kg} \times 0.2}{2 \text{ L/day}} = 190 \text{ mcg/L}$$

[11] Estimated lifetime average BW of Sherman male rats based on Figure 3 in Kociba et al. (1974).

[12] US EPA (2013) noted, "An UF of 3 for database deficiencies was applied due to the lack of a multigeneration reproductive toxicity study."

The use of age-specific drinking-water consumption rates in the derivation to address the potential for children to be more sensitive than adults to the nononcogenic effects of 1,4-dioxane was considered, but was not used because the weight of scientific evidence is insufficient to suggest that exposure to 1,4-dioxane during childhood poses a greater risk of nononcogenic effects than exposure during adulthood (ATSDR, 2012; US EPA, 2013, 2014).

702.7. PROCEDURE FOR DERIVING STANDARDS AND GUIDANCE VALUES BASED ON CHEMICAL CORRELATION

Chemical-specific toxicological data are sufficient to derive potential ambient water quality values for 1,4-dioxane based on both its oncogenic (6 NYCRR 702.4) and nononcogenic effects (6 NYCRR 702.5). Thus, values based on oncogenic or nononcogenic effects using chemical correlation are unnecessary.

SELECTION OF VALUE

According to 6 NYCRR 702.2(b), the ambient water quality value [Health (Water Source)] shall be the most stringent of the potential values derived using the procedures found in 6 NYCRR 702.3 through 702.7. Using procedures from 6 NYCRR 702.4 and 702.5, respectively, we derived potential ambient water quality values of 0.35 mcg/L (oncogenic effects) and 190 mcg/L (nononcogenic effects) for 1,4-dioxane. The most stringent of the potential values is 0.35 mcg/L (6 NYCRR 702.4, Oncogenic Effects) and thus, this value is selected as the ambient water quality value [Health (Water Source)] for 1,4-dioxane.

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SEARCH STRATEGY

We reviewed publications by various state, federal, or international public health agencies (listed in fact sheet references) and identified important papers from the list of references within each document. We also searched the biomedical literature using PubMed (U.S. National Library of Medicine) and the search terms "1,4-dioxane" and "toxicity".

Bureau of Toxic Substance Assessment
New York State Department of Health
August 2019

EXHIBITS

Exhibit 1. US EPA Cancer Potency Factor Derivation for 1,4-Dioxane.
Exhibit 2. US EPA Reference Dose Derivation for 1,4-Dioxane.
Exhibit 3. List of Abbreviations and Acronyms Frequently Used in New York State Human Health Fact Sheets.

Table 1. Cancer Potency Factors for 1,4-Dioxane Derived by Authoritative Bodies.

Agency	Risk-Specific Dose[1] (mg/kg-day)	Cancer Potency Factor $(mg/kg\text{-}day)^{-1}$	Extrapolation Methods		Summary
			High to Low Dose	Animal to Human	
CA EPA (2009)	3.7×10^{-5}	0.027	linearized multistage model with linear extrapolation from the POD	$BW^{2/3}$ [(2)]	Based on the combined incidence of hepatocarcinomas and adenomas in female mice exposed via drinking water for 90 weeks (NCI, 1978)
US EPA (2013, 2014)	1×10^{-5}	0.10	log-logistic model[3] with linear extrapolation from the POD	$BW^{3/4}$ [(4)]	Based on incidence of hepatocellular adenomas and carcinomas in female mice exposed via drinking water for 2 years (Kano et al., 2009)

[1]The dose associated with an increased lifetime oncogenic risk of one-in-one million (i.e., 1×10^{-6} dose), where 1×10^{-6} dose = 1×10^{-6}/cancer potency factor.

[2]Body weight scaling factor for dose adjustment from animals to humans is animal dose x (animal body weight/human body weight)$^{1/3}$.

[3]Female mice were clearly the most sensitive group tested by Kano et al. (2009). The US EPA (2013) noted that the multistage cancer model did not adequately describe the data-response data for liver tumors in female mice) within the range of observation (i.e., the model did not provide an adequate fit to the data). Thus, the US EPA (2013) applied other BMD models to the data, and noted, "The log-logistic model was the only model that provided adequate fit for this data set due to the steep rise in the dose-response curve (70% incidence at the low dose) followed by a plateau at near maximal tumor incidence in the mid- and high-dose regions (82 and 92% incidence, respectively)." This approach is permitted under 6 NYCRR 702.4 and is consistent with recent US EPA cancer risk-assessment guidance (Gehlhaus et al., 2011; US EPA, 2005, 2012).

[4]Body weight scaling factor for dose adjustment from animals to humans is animal dose x (animal body weight/human body weight)$^{1/4}$.

Table 2. Reference Doses for 1,4-Dioxane Derived by Authoritative Bodies.

Agency	Reference Dose[1] (mg/kg-day)	Point of Departure		UF[2]	Critical Endpoint
		Dose (mg/kg-day)	Basis		
ATSDR (2012)	0.1	9.6	NOAEL[3]	100	Liver effects (hepatocellular degeneration and necrosis and evidence of hepatic regeneration as indicated by hepatocellular hyperplastic nodule formation) observed in male rats in Kociba et al. (1974)[4]
Health Canada (2018)	0.0054	5.4	$BMDL_{05}$	1000	Liver effects (hepatocellular necrosis using combined incidence data from male and female rats) from Kociba et al. (1974)
US EPA (2013, 2014)	0.03	9.6	NOAEL[3]	300	Liver effects (hepatocellular degeneration and necrosis, evidence of hepatic regeneration, as indicated by hepatocellular hyperplastic nodule formation) and kidney effects (renal tubular epithelial regenerative activity) observed in male rats in Kociba et al. (1974)[4]
WHO (2005)	0.096	9.6	NOAEL[3]	100	Kidney effects (renal tubular epithelial and hepatocellular degeneration and necrosis) observed in male rats exposed via drinking water for 2 years (Kociba et al. (1974)[4]

[1]Agencies use different terms for the reference dose, including acceptable daily intake, chronic minimal risk level, and tolerable daily intake.

[2]All three agencies applied UF of 10X for animal-to-human extrapolation and 10X for inter-human variability; the US EPA applied an additional UF of 3X to compensate for the deficiencies in the toxicity database for 1,4-dioxane, namely, the lack of a multi-generation reproductive toxicity study.

[3]This is also a NOEL as defined in 6 NYCRR 700.1.

[4]Study LOAEL = 94 mg/kg-day, which is also a LOEL as defined in 6 NYCRR 700.1.

EXHIBIT 1. 1,4-DIOXANE

US EPA CANCER POTENCY FACTOR DERIVATION FOR 1,4-DIOXANE[1]

Source: US EPA (U.S. Environmental Protection Agency). 2014. Integrated Risk Information System (IRIS). Summary Information. 1,4-Dioxane (CASRN 123-91-1). Last accessed on 04/28/2014 at http://cfpub.epa.gov/ncea/iris/index.cfm?fuseaction=iris.showSubstanceList&list_type=alpha&view=D.

II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name — 1,4-Dioxane
CASRN — 123-91-1
Last Revised — 08/11/2010

This section provides information on three aspects of the carcinogenic assessment for the substance in question: the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure. Users are referred to Section I of this file for information on long-term toxic effects other than carcinogenicity.

The rationale and methods used to develop the carcinogenicity information in IRIS are described in the Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005a) and the Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens (U.S. EPA, 2005b). The quantitative risk estimates are derived from the application of a low-dose extrapolation procedure, and are presented in two ways to better facilitate their use. First, route-specific risk values are presented. The "oral slope factor" is a plausible upper bound on the estimate of risk per mg/kg-day of oral exposure. Similarly, a "unit risk" is a plausible upper bound on the estimate of risk per unit of concentration, either per µg/L drinking water (see Section II.B.1.) or per µg/m3 air breathed (see Section II.C.1.). Second, the estimated concentration of the chemical substance in drinking water or air when associated with cancer risks of 1 in 10,000, 1 in 100,000, or 1 in 1,000,000 is also provided.

A previous cancer assessment for 1,4-dioxane was posted on the IRIS database in 1988. At that time, 1,4-dioxane was classified as a B2 carcinogen (probable human carcinogen), based on inadequate human data and sufficient evidence of carcinogenicity in animals (induction of nasal cavity and liver carcinomas in multiple strains of rats, liver carcinomas in mice, and gall bladder carcinomas in guinea pigs). An oral cancer slope factor (CSF) of 1.1×10^{-2} $(mg/kg\text{-}day)^{-1}$ was derived from the tumor incidence data for nasal squamous cell carcinoma in male rats exposed to 1,4-dioxane in drinking water for 2 years (NCI, 1978). The linearized multistage extra risk procedure was used for linear low dose extrapolation. An inhalation unit risk (IUR) was not previously derived.

II.A. EVIDENCE FOR HUMAN CARCINOGENICITY
II.A.1. WEIGHT-OF-EVIDENCE CHARACTERIZATION

In accordance with the Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005a), 1,4-dioxane is characterized as "likely to be carcinogenic to humans." This characterization is based on the following findings: (1) inadequate evidence of carcinogenicity in humans, and (2) sufficient evidence in animals (i.e., hepatic tumors in multiple species [three strains of rats, two strains of mouse, and in guinea pigs]; mesotheliomas of the peritoneum, mammary, and nasal tumors have also been observed in rats following 2 years of oral exposure to 1,4- dioxane).

[1] Contents of each section copied from US EPA online file; format altered to improve readability.

There is adequate evidence of liver carcinogenicity in several 2-year bioassays conducted in three strains of rats, two strains of mice, and in guinea pigs (Argus et al., 1965; Argus et al., 1973; Hoch-Ligeti and Argus, 1970; Hoch-Ligeti et al., 1970; JBRC, 1998a; Kano et al., 2009; Kociba et al., 1974; NCI, 1978; Yamazaki et al., 1994). Additionally, mesotheliomas of the peritoneum (JBRC, 1998a; Kano et al., 2009; Yamazaki et al., 1994), mammary (JBRC, 1998a; Kano et al., 2009; Yamazaki et al., 1994), and nasal tumors (Argus et al., 1973; Hoch-Ligeti et al., 1970; JBRC, 1998a; Kano et al., 2009; Kociba et al., 1974; NCI, 1978; Yamazaki et al., 1994) have been observed in rats due to exposure to 1,4-dioxane. Studies in humans are inconclusive regarding evidence for a causal link between occupational exposure to 1,4-dioxane and increased risk for cancer; however, only two studies were available and these were limited by small cohort size and a small number of reported cancer cases (Buffler et al., 1978; Thiess et al., 1976).

U.S. EPA's Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005a) indicate that for tumors occurring at a site other than the initial point of contact, the weight of evidence for carcinogenic potential may apply to all routes of exposure that have not been adequately tested at sufficient doses. An exception occurs when there is convincing information (e.g., toxicokinetic data) that absorption does not occur by other routes. Information available on the carcinogenic effects of 1,4-dioxane via the oral route demonstrates that tumors occur in tissues remote from the site of absorption. Information on the carcinogenic effects of 1,4-dioxane via the inhalation and dermal routes in humans and animals is absent. (Note: During the development of this assessment, new data regarding the toxicity of 1,4-dioxane through the inhalation route of exposure became available. These data have not been included in the current assessment and will be evaluated in a separate IRIS assessment.) Based on the observance of systemic tumors following oral exposure, and in the absence of information to indicate otherwise, it is assumed that an internal dose will be achieved regardless of the route of exposure. Therefore, 1,4-dioxane is "likely to be carcinogenic to humans" by all routes of exposure.

The available evidence does not establish a mode of action (MOA) by which 1,4-dioxane induces liver tumors in rats and mice. A MOA hypothesis involving sustained proliferation of spontaneously transformed liver cells has some support from data indicating that 1,4-dioxane acts as a tumor promoter in mouse skin and rat liver bioassays (King et al., 1973; Lundberg et al., 1987). Dose-response and temporal data support the occurrence of cell proliferation and hyperplasia prior to the development of liver tumors (JBRC, 1998a; Kociba et al., 1974) in the rat model. However, the dose-response relationship for induction of hepatic cell proliferation has not been characterized, and it is unknown if it would reflect the dose-response relationship for liver tumors in the 2-year rat and mouse studies. Conflicting data from rat and mouse bioassays (JBRC, 1998a; Kociba et al., 1974) suggest that cytotoxicity may not be a required precursor event for 1,4-dioxane-induced cell proliferation. Liver tumors were observed in female rats and female mice in the absence of lesions indicative of cytotoxicity (JBRC, 1998a; Kano et al., 2008; NCI, 1978). Thus, data regarding a plausible dose response and temporal progression from cytotoxicity and cell proliferation to eventual liver tumor formation are not available. The MOA by which 1,4-dioxane produces liver, nasal, peritoneal (mesotheliomas), and mammary gland tumors is unknown, and the available data do not support any hypothesized carcinogenic MOA for 1,4-dioxane.

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF).

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.8 (PDF)

II.A.2. HUMAN CARCINOGENICITY DATA

Human studies of occupational exposure to 1,4-dioxane were inconclusive to assess the evidence of carcinogenicity of 1,4-dioxane (see Section 4.1 in the Toxicological Review of 1,4-Dioxane, (U.S. EPA, 2010). In each case, the cohort size and number of reported cases were of limited size (Buffler et al., 1978; Thiess et al., 1976).

II.A.3. ANIMAL CARCINOGENICITY DATA

Three chronic drinking water bioassays provided incidence data for liver tumors in rats and mice, and nasal cavity, peritoneal, and mammary gland tumors in rats only (JBRC, 1998a; Kano et al., 2009; Kociba et al. 1974; NCI, 1978; Yamazaki et al., 1994). With the exception of the NCI, 1978 study, the incidence of nasal cavity tumors was generally lower than the incidence of liver tumors in exposed rats. The Kano et al., (2009) drinking water study was chosen as the principal study for derivation of an oral cancer slope factor (CSF) for 1,4-dioxane. This study used three dose groups in addition to controls and characterized the dose-response relationship at lower exposure levels, as compared to the high doses employed in the NCI, 1978 bioassay. The Kociba et al. (1974) study also used three low dose exposure groups; however, the study authors only reported the incidence of hepatocellular carcinoma, which may underestimate the combined incidence of rats with adenoma or carcinoma. In addition to increased incidence of liver tumors, chosen as the most sensitive target organ for tumor formation, the Kano et al., (2009) study also noted increased incidence of peritoneal and mammary gland tumors. Nasal cavity tumors were also seen in high-dose male and female rats; however, the incidence of nasal tumors was much lower than the incidence of liver tumors in both rats and mice.

As described in detail in Section 4.2.1.2.6 and Appendix E of the Toxicological Review of 1,4-Dioxane (U.S. EPA, 2010), the Japanese Bioassay Research Center conducted a 2-year drinking water study on the effects of 1,4-dioxane in both sexes of rats and mice. The results from that study were reported several times, once as conference proceedings (Yamazaki et al., 1994), once as a detailed laboratory report (JBRC, 1998a), and once as a published manuscript (Kano et al., 2009). As a result of the recent publication (Kano et al., 2009), the Toxicological Review of 1,4-Dioxane (U.S. EPA, 2010) was updated and the data in the new publication was considered. Although the data contained in the reports varied, the differences were minor and did not affect the conclusions of this assessment. The variations included: (1) the level of detail on dose information reported; (2) categories for incidence data reported (e.g., all animals or sacrificed animals); and (3) analysis of non- and neoplastic lesions.

II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

Several carcinogenicity bioassays have been conducted for 1,4-dioxane in mice, rats, and guinea pigs (Argus et al., 1965; Argus et al., 1973; Hoch-Ligeti and Argus, 1970; Hoch-Ligeti et al., 1970; JBRC, 1998a; Kano et al., 2009; Kociba et al. 1974; NCI, 1978; Torkelson et al., 1974; Yamazaki et al., 1994). Liver tumors have been observed following drinking water exposure in male Wistar rats (Argus et al., 1965), male guinea pigs (Hoch-Ligeti and Argus, 1970), male Sprague Dawley rats (Argus et al., 1973; Hoch-Ligeti et al., 1970), male and female Sherman rats (Kociba et al. 1974), female Osborne-Mendel rats (NCI, 1978), male and female F344/DuCrj rats (JBRC, 1998a; Kano et al., 2009; Yamazaki et al., 1994), male and female B6C3F1 mice (NCI, 1978), and male and female Crj:BDF1 mice (JBRC, 1998a; Kano et al., 2009; Yamazaki et al., 1994). In the earliest cancer bioassays, the liver tumors were described as hepatomas (Argus et al., 1965; Argus et al., 1973; Hoch-Ligeti and Argus, 1970; Hoch-Ligeti et al., 1970); however, later studies made a distinction between hepatocellular carcinoma and hepatocellular adenoma (JBRC, 1998a; Kano et al., 2009; Kociba et al. 1974; NCI, 1978; Yamazaki et al., 1994). Both tumor types have been seen in rats and mice exposed to 1,4-dioxane. Kociba et al. (1974) noted evidence of liver toxicity at or below the dose levels that produced liver tumors but did not report incidence data for these effects. Hepatocellular degeneration and necrosis were observed in the mid- and high-dose groups of male and female Sherman rats exposed to 1,4-dioxane, while tumors were only observed at the highest dose. Hepatic regeneration was indicated in the mid- and high-dose groups by the formation of hepatocellular hyperplastic nodules. Findings from JBRC, (1998a) also provided evidence of liver hyperplasia in male F344/DuCrj rats at a dose level below the dose that induced a statistically significant increase in tumor formation.

Nasal cavity tumors were also observed in Sprague Dawley rats (Argus et al., 1973; Hoch-Ligeti et al., 1970), Osborne-Mendel rats (NCI, 1978), Sherman rats (Kociba et al. 1974), and F344/DuCrj rats (JBRC, 1998a; Kano et al., 2009; Yamazaki et al., 1994) Most tumors were characterized as squamous cell carcinomas. Nasal tumors were not elevated in B6C3F1 or Crj:BDF1 mice. JBRC (1998a) was the only study that evaluated nonneoplastic changes in nasal cavity tissue following prolonged exposure to 1,4-dioxane in the drinking water. Histopathological lesions in female F344/DuCrj rats were suggestive of toxicity and regeneration in this tissue (i.e., atrophy, adhesion, inflammation, nuclear enlargement, and hyperplasia and metaplasia of respiratory and olfactory epithelium). Some of these effects occurred at a lower dose (83 mg/kg-day) than that shown to produce nasal cavity tumors (429 mg/kg-day) in female rats. Reexamination of tissue sections from the NCI, 1978 bioassay suggested that the majority of nasal tumors were located in the dorsal nasal septum or the nasoturbinate of the anterior portion of the dorsal meatus. Nasal tumors were not observed in an inhalation study in Wistar rats exposed to 111 ppm for 5 days/week for 2 years (Torkelson et al., 1974).

Tumor initiation and promotion studies in mouse skin and rat liver suggested that 1,4-dioxane does not initiate the carcinogenic process, but instead acts as a tumor promoter (Bull et al., 1986; King et al., 1973; Lundberg et al., 1987) (see Section 4.2.3 in the Toxicological Review of 1,4-Dioxane (U.S. EPA, 2010)).

In addition to the liver and nasal tumors observed in several studies, a statistically significant increase in mesotheliomas of the peritoneum was seen in male rats from the Kano et al., (2009) study (also (JBRC, 1998a; Yamazaki et al., 1994)). Female rats dosed with 429 mg/kg-day in drinking water for 2 years also showed a statistically significant increase in mammary gland adenomas (JBRC, 1998a; Kano et al., 2009; Yamazaki et al., 1994). A significant increase in the incidence of these tumors was not observed in other chronic oral bioassays of 1,4-dioxane (Kociba et al., 1974; NCI, 1978).

II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

II.B.1. SUMMARY OF RISK ESTIMATES

II.B.1.1. Oral Slope Factor: 1×10^{-1} per mg/kg-day

The derivation of the oral slope factor 1×10^{-1} per mg/kg-day is based on the incidence of hepatocellular adenomas and carcinomas in female mice exposed to 1,4-dioxane in drinking water for 2 years (Kano et al., 2009). The dose metric used in the current estimate of the human equivalent dose (HED) is the applied or external dose because a PBPK model was determined not to be suitable for species extrapolation (see Appendix B of the Toxicological Review of 1,4-Dioxane (U.S. EPA, 2010). The rat $BMDL_{50}$ of 32.93 mg/kg-day represents the POD used to calculate the $BMDL_{HED}$ of 4.95 mg/kg-day.

The oral slope factor is derived from the $BMDL_{HED}$, the 95% lower bound on the exposure associated with a 50% extra cancer risk, by dividing the risk (as a fraction) by the $BMDL_{HED}$, and represents an upper bound, continuous lifetime exposure risk estimate:

$BMDL_{50HED}$, lower 95% bound on exposure at 50% extra risk – 4.95 mg/kg-day
BMD_{50HED}, central estimate of exposure at 50% extra risk – 7.51 mg/kg-day

The slope of the linear extrapolation from the central estimate is $0.5/(7.51 \text{ mg/kg-day}) = 7 \times 10^{-2}$ per mg/kg-day

The slope factor for 1,4-dioxane should not be used with exposures exceeding the point of departure ($BMDL_{50HED}$ = 4.95 mg/kg-day), because above this level the fitted dose-response model better characterizes what is known about the carcinogenicity of 1,4-dioxane.

II.B.1.2. Drinking Water Unit Risk*: 2.9×10^{-6} per µg/L

Drinking Water Concentrations at Specified Risk Levels

Risk Level	Lower Bound on Concentration Estimate*
E-4 (1 in 10,000)	35 µg/L
E-5 (1 in 100,000)	3.5 µg/L
E-6 (1 in 1,000,000)	0.35 µg/L

*The unit risk and concentration estimates assume water consumption of 2 L/day by a 70 kg human.

II.B.1.3. Extrapolation Method

Log-logistic model with linear extrapolation from the POD ($BMDL_{50HED}$) associated with 50% extra cancer risk.

The log-logistic model provided the best-fit to the female mouse liver tumor data Kano et al. (2009) female data as indicated by the AIC and p-value as was chosen as the best-fitting model to carry forward in the analysis; however, this model resulted in a BMDL10 much lower than the response level at the lowest dose in the study (Kano et al. 2009). Thus, the log-logistic model was also run for BMR values of 30 and 50%. Using a higher BMR value resulted in BMDL values closer to the lowest observed response data, and a BMR of 50% was chosen to carry forward in the analysis.

II.B.2. DOSE-RESPONSE DATA

Tumor Type – hepatocellular adenoma and carcinoma
Test Species – female BDF1 mouse
Route – Oral, drinking water
References – Kano et al. (2009)

Incidence of liver tumors in female BDF1 female mice exposed to 1,4-dioxane in drinking water for 2 years

Tumor Dose	Dose (mg/kg-day)			
	0	66	278	964
Hepatocellular adenoma or carcinoma	5/50	35/50[a]	41/50[a]	46/50[a,b]

[a]Significantly different from control by Fisher's exact test ($p < 0.01$.)
[b]Statistically significant trend for increased tumor incidence by Peto's test ($p < 0.01$).

Source: Kano et al. (2009)

Oral Cancer Slope Factor (CSF) using linear low-dose extrapolation approach and interspecies extrapolation

Tumor	Dose groups modeled	BMD_{50} mg/kg-day	$BMDL_{50}$ mg/kg-day	BMD_{HED} mg/kg-day	$BMDL_{HED}$ mg/kg-day	Oral SF $(mg/kg\text{-}day)^{-1}$
Female mouse hepatocellular adenoma or carcinoma	0, 66, 278, 964 mg/kg-day	49.88	32.93	7.51	4.95	0.10

II.B.3. ADDITIONAL COMMENTS

Supplementary information not required.

II.B.4. DISCUSSION OF CONFIDENCE

Relevance to humans. The oral CSF was derived using the tumor incidence in the liver of female mice. A thorough review of the available toxicological data available for 1,4-dioxane provides no scientific justification to propose that the liver adenomas and carcinomas observed in animal models following exposure to 1,4-dioxane are not plausible in humans. Liver adenomas and carcinomas were considered plausible outcomes in humans due to exposure to 1,4-dioxane.

Choice of low-dose extrapolation approach. The range of possibilities for the low-dose extrapolation of tumor risk for exposure to 1,4-dioxane, or any chemical, ranges from linear to nonlinear, but is dependent upon a plausible MOA(s) for the observed tumors. The MOA is a key consideration in clarifying how risks should be estimated for low-dose exposure. Exposure to 1,4-dioxane has been observed in animal models to induce multiple tumor types, including liver adenomas and carcinomas, nasal carcinomas, mammary adenomas and fibroadenomas, and mesotheliomas of the peritoneal cavity (Kano et al. 2009). MOA information that is available for the carcinogenicity of 1,4-dioxane has largely focused on liver adenomas and carcinomas, with little or no MOA information available for the remaining tumor types. In Section 4.7.3 of the Toxicological Review of 1,4-Dioxane (U.S. EPA, 2010), hypothesized MOAs, other than a mutagenic MOA, were explored due to the lack of mutagenicity observed in genetic toxicology tests performed for 1,4-dioxane. Data were not available to support a carcinogenic MOA for 1,4-dioxane. In the absence of a MOA(s) for the observed tumor types associated with exposure to 1,4-dioxane, a linear low-dose extrapolation approach was used to estimate human carcinogenic risk associated with 1,4-dioxane exposure.

In the studies evaluated (Kano et al. 2009; Kociba et al. 1974; NCI, 1978), the multistage model provided good descriptions of the incidence of a few tumor types in male (nasal cavity) and female (hepatocellular and nasal cavity) rats and in male mice (hepatocellular) exposed to 1,4-dioxane (see Appendix D of the Toxicological Review of 1,4-Dioxane (U.S. EPA, 2010) for additional details). However, the multistage model did not provide an adequate fit for female mouse liver tumor dataset based upon the following (U.S. EPA, 2000):

- Goodness-of-fit p-value was not greater than 0.10;
- AIC was larger than other acceptable models;
- Data deviated from the fitted model, as measured by their $\chi 2$ residuals (values were greater than an absolute value of one).

BMDS software typically implements the guidance in the external review draft BMD technical guidance document (U.S. EPA, 2000) by imposing constraints on the values of certain parameters of the models. When these constraints were imposed, the multistage model and most other models did not fit the incidence data for female mouse liver adenomas or carcinomas.

The log-logistic model was selected because it provides an adequate fit for the female mouse data (Kano et al. 2009). A BMR of 50% was used because it is proximate to the response at the lowest dose tested and the BMDL50 was derived by applying appropriate parameter constraints, consistent with the recommended use of the BMDS in the BMD technical guidance document (U.S. EPA, 2000).

The human equivalent oral CSF estimated from liver tumor datasets with statistically significant increases ranged from 4.2×10^{-4} to 1.0×10^{-1} per mg/kg-day, a range of about three orders of magnitude, with the

extremes coming from the combined male and female data for hepatocellular carcinomas (Kociba et al. 1974) and the female mouse liver adenoma and carcinoma dataset (Kano et al. 2009).

Interspecies extrapolation. An adjustment for cross-species scaling ($BW^{0.75}$) was applied to address toxicological equivalence of internal doses between each rodent species and humans, consistent with the U.S. EPA's 2005 Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005a). It is assumed that equal risks result from equivalent constant lifetime exposures.

Statistical uncertainty at the POD. Parameter uncertainty can be assessed through confidence intervals. Each description of parameter uncertainty assumes that the underlying model and associated assumptions are valid. For the log-logistic model applied to the female mouse data, there is a reasonably small degree of uncertainty at the 50% excess incidence level (the POD for linear low-dose extrapolation).

Bioassay selection. The study by Kano et al. (2009) was used for development of an oral CSF. This was a well-designed study, conducted in both sexes in two species with a sufficient number of animals per dose group. The number of test animals allocated among three dose levels and an untreated control group was adequate, with examination of appropriate toxicological endpoints in both sexes of rats and mice. Alternative bioassays (NCI, 1978; Kociba et al., 1974) are available and were fully considered for the derivation of the oral CSF.

Choice of species/gender. The oral CSF for 1,4-dioxane was derived using the tumor incidence data for the female mouse, which was thought to be more sensitive than male mice or either sex of rats to the carcinogenicity of 1,4-dioxane. While all data, from both species and sexes reported from the Kano et al. (2009) study, were suitable for deriving an oral CSF, the female mouse data represented the most sensitive indicator of carcinogenicity in the rodent model. The lowest exposure level (66 mg/kg-day [animal dose] or 10 mg/kg-day [HED]) observed a considerable and significant increase in combined liver adenomas and carcinomas. Additional testing of doses within the range of control and the lowest dose (66 mg/kg-day [animal dose] or 10 mg/kg-day [HED]) could refine and reduce uncertainty for the oral CSF.

Human population variability. The extent of inter-individual variability in 1,4-dioxane metabolism has not been characterized. A separate issue is that the human variability in response to 1,4-dioxane is also unknown. Data exploring whether there is differential sensitivity to 1,4-dioxane carcinogenicity across life stages is unavailable. This lack of understanding about potential differences in metabolism and susceptibility across exposed human populations thus represents a source of uncertainty. Also, the lack of information linking a MOA for 1,4-dioxane to the observed carcinogenicity is a source of uncertainty.

II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)

II.D.1. EPA DOCUMENTATION

Source Document — (U.S. EPA, 2010)

This document has been provided for review to EPA scientists, interagency reviewers from other federal agencies and White House offices, and the public, and peer reviewed by independent scientists external to EPA. A summary and EPA's disposition of the comments received from the independent external peer reviewers and from the public is included in Appendix A of the Toxicological Review of 1,4-Dioxane (U.S. EPA, 2010). To review this appendix, exit to the Toxicological Review, Appendix A, Summary of External Peer Review and Public Comments and Disposition (PDF).

II.D.2. EPA REVIEW

Agency Completion Date — 08/11/2010

II.D.3. EPA CONTACTS

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202) 566-1676 (phone), (202) 566-1749 (fax), or hotline.iris@epa.gov (email address).

VI. Bibliography

Substance Name — 1,4-Dioxane
CASRN — 123-91-1
Section VI. Last Revised — 08/11/2010

VI.C. Carcinogenicity Assessment References

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EXHIBIT 2. 1,4-DIOXANE

US EPA REFERENCE DOSE DERIVATION FOR 1,4-DIOXANE[1]

Source: US EPA (U.S. Environmental Protection Agency). 2014. Integrated Risk Information System (IRIS). Summary Information. 1,4-Dioxane (CASRN 123-91-1). Last accessed on 04/28/2014 at http://cfpub.epa.gov/ncea/iris/index.cfm?fuseaction=iris.showSubstanceList&list_type=alpha&view=D.

I. HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS
I.A. REFERENCE DOSE (RfD) FOR CHRONIC ORAL EXPOSURE

Substance Name – 1,4-Dioxane
CASRN – 123-91-1
Section I.A. Last Revised – 08/11/2010

The RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfD is intended for use in risk assessments for health effects known or assumed to be produced through a nonlinear (presumed threshold) mode of action. It is expressed in units of mg/kg-day. Please refer to the guidance documents at http://www.epa.gov/iris/backgrd.html for an elaboration of these concepts. Because RfD values can be derived for the noncarcinogenic health effects of substances that are also carcinogens, it is essential to refer to other sources of information concerning the carcinogenicity of this chemical substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

There was no previous oral RfD for 1,4-dioxane on IRIS.

I.A.1. CHRONIC ORAL RfD SUMMARY

There was no previous oral RfD for 1,4-dioxane on IRIS.

Critical Effect	Point of Departure	UF	Chronic RfD
Liver and kidney toxicity; Chronic oral male rat study; Kociba et al. (1974)	NOAEL: 9.6 mg/kg-day	300	0.03 mg/kg-day

I.A.2. PRINCIPAL AND SUPPORTING STUDIES (ORAL RfD)

Liver and kidney toxicity were the primary noncancer health effects associated with exposure to 1,4-dioxane in humans and laboratory animals. Occupational exposure to 1,4-dioxane has resulted in hemorrhagic nephritis and centrilobular necrosis of the liver (Barber, 1934; Johnstone, 1959). In animals, liver and kidney degeneration and necrosis were observed frequently in acute oral and inhalation studies (David, 1964; de Navasquez, 1935; Drew et al., 1978; Fairley et al., 1934; JBRC, 1998b; Kesten et al., 1939; Laug et al., 1939; Schrenk and Yant, 1936). Liver and kidney effects were also observed following chronic oral exposure to 1,4-dioxane in animals (Argus et al., 1965; Argus et al., 1973; JBRC, 1998a; Kano et al., 2009; Kociba et al., 1974; NCI, 1978; Yamazaki et al., 1994) (see summary Table 4-17 in the Toxicological Review of 1,4-Dioxane (U.S. EPA, 2010)).

In the available chronic studies, Kociba et al. (1974) reported the most sensitive effects in the liver and kidney based on a NOAEL of 9.6 mg/kg-day and a LOAEL of 94 mg/kg-day in male Sherman rats. Kociba et al. (1974)

[1] Contents of each section copied from US EPA online file; format altered to improve readability.

reported toxic effects of hepatocellular degeneration and necrosis in the liver, while liver lesions reported in other studies (Argus et al., 1973; JBRC, 1998a) appeared to be related to the carcinogenic process. Kociba et al. (1974) also reported renal tubule epithelial cell degenerative changes and necrosis in the kidney which was supported by data in NCI (1978) and Argus et al. (1973); however, kidney toxicity was observed in these studies at higher doses. For degenerative liver effects resulting from 1,4-dioxane exposure, the Kociba et al. (1974) study represents the most sensitive effect and dataset observed in a chronic bioassay. As a result, Kociba et al. (1974) was chosen as the principal study for the derivation of the RfD.

Kociba et al. (1974) conducted a 2-year study in which four groups of 6–8-week-old Sherman rats (60/sex/dose level) were administered 1,4-dioxane in drinking water at levels of 0 (controls), 0.01, 0.1, or 1.0% for up to 716 days. Based on water consumption and BW data for specific exposure groups, Kociba et al. (1974) calculated mean daily doses of 9.6, 94, and 1,015 mg/kg-day for male rats and 19, 148, and 1,599 mg/kg-day for female rats during days 114–198 for the 0.01, 0.1, and 1.0% concentration levels, respectively. Rats were observed daily for clinical signs of toxicity, and BWs were measured twice weekly during the first month, weekly during months 2–7, and biweekly thereafter. Water consumption was recorded at three different time periods during the study: days 1–113, 114–198, and 446–460. Blood samples were collected from a minimum of five male and five female control and high-dose rats during the 4th, 6th, 12th, and 18th months of the study and at termination. Each blood sample was analyzed for packed cell volume, total erythrocyte count, hemoglobin, and total and differential WBC counts. Additional endpoints evaluated included organ weights (brain, liver, kidney, testes, spleen, and heart) and gross and microscopic examination of major tissues and organs (brain, bone and bone marrow, ovaries, pituitary, uterus, mesenteric lymph nodes, heart, liver, pancreas, spleen, stomach, prostate, colon, trachea, duodenum, kidneys, esophagus, jejunum, testes, lungs, spinal cord, adrenals, thyroid, parathyroid, nasal turbinates, and urinary bladder).

Histopathological lesions were restricted to the liver and kidney from the mid- and high-dose groups and consisted of variable degrees of renal tubular epithelial and hepatocellular degeneration and necrosis (no quantitative incidence data were provided). Rats from these groups also showed evidence of hepatic regeneration, as indicated by hepatocellular hyperplastic nodule formation and evidence of renal tubular epithelial regenerative activity (observed after 2 years of exposure). These changes were not seen in controls or in low-dose rats. The authors determined a NOAEL of 9.6 mg/kg-day and a LOAEL of 94 mg/kg-day for 1,4-dioxane based on the liver and kidney effects in male rats.

Methods of Analysis. Kociba et al. (1974) did not provide quantitative incidence or severity data for liver and kidney degeneration and necrosis. Benchmark dose (BMD) modeling could not be performed for this study, and the NOAEL for liver and kidney degeneration (9.6 mg/kg-day in male rats) was used as the point of departure (POD) in deriving the RfD for 1,4-dioxane.

Other datasets and alternative POD values were also considered as the basis for the 1,4-dioxane RfD, including incidence data reported for cortical tubule degeneration in male and female rats (NCI, 1978) and liver hyperplasia (JBRC, 1998a). The BMDL10 values of 22.3 mg/kg-day and 23.8 mg/kg-day from the (NCI, 1978) and (JBRC, 1998a) studies, respectively, are about double the NOAEL (9.6 mg/kg-day) observed by Kociba et al. (1974).

I.A.3. UNCERTAINTY FACTORS

$UF = 300 = 10\ (UF_A) \times 10\ (UF_H) \times 1\ (UF_S) \times 1\ (UF_L) \times 3\ (UF_D)$

An UF of 10 was applied for interspecies extrapolation (UF_A) to account for pharmacokinetic and pharmacodynamic differences between rats and humans. Physiologically based pharmacokinetic (PBPK) models available for 1,4-dioxane were found unsuitable and could not be used for interspecies oral

extrapolation. In the absence of data to quantify specific interspecies differences or a suitable PBPK model, an UF_A of 10 was applied.

An UF of 10 was applied to account for interindividual variability (UF_H) in toxicokinetics and toxicodynamics to protect potentially sensitive populations and lifestages. In the absence of information on the degree to which humans of varying gender, age, health status, or genetic makeup might vary in the disposition of, or response to, 1,4-dioxane, the default value of 10 was selected.

An UF for extrapolating from a subchronic exposure duration to a chronic exposure duration (UF_S) was not necessary, because the point of departure was derived from a study using a chronic exposure protocol (i.e., the $UF_S = 1$).

An UF to extrapolate from a LOAEL to a NOAEL (UF_L) was not necessary because the RfD was based on a NOAEL. Kociba et al. (1974) was a well-conducted, chronic drinking water study with an adequate number of animals. Histopathological examination was performed for many organs and tissues, but clinical chemistry analysis was not performed. NOAEL and LOAEL values were derived from the study based on liver and kidney toxicity.

An UF to account for deficiencies in the database (UF_D) of 3 ($10^{1/2} = 3.16$, rounded to 3) was selected. The oral database for this chemical is robust and includes a single oral prenatal developmental toxicity study in rats (Giavini et al., 1985). This developmental study indicated that the developing fetus may be a target of toxicity. An UF_D of 3 for database deficiencies was applied to account for the lack of a multigeneration reproductive toxicity study.

I.A.4. ADDITIONAL STUDIES/COMMENTS

The predominant noncancer effect of chronic oral exposure to 1,4-dioxane is degenerative effects in the liver and kidney. For degenerative liver effects resulting from 1,4-dioxane exposure, the Kociba et al. (1974) study represents the most sensitive effect and dataset observed in a chronic bioassay.

Kidney toxicity as evidenced by glomerulonephritis (Argus et al., 1965; Argus et al., 1973) and degeneration of the cortical tubule (Kociba et al., 1974; NCI, 1978) has also been observed in response to chronic exposure to 1,4-dioxane. Degenerative effects were observed in the kidney at the same dose level as effects in the liver (Kociba et al., 1974).

Rhinitis and inflammation of the nasal cavity were reported in both the NCI (1978) (mice only, dose ≥ 380 mg/kg-day) and JBRC (1998a) studies (≥ 274 mg/kg-day in rats, >278 mg/kg-day in mice). JBRC (1998a) reported nasal inflammation in rats (NOAEL 55 mg/kg-day, LOAEL 274 mg/kg-day) and mice (NOAEL 66 mg/kg-day, LOAEL 278 mg/kg-day).

Studies in experimental animals have also found that relatively high doses of 1,4-dioxane (1,000 mg/kg-day) during gestation can produce delayed ossification of the sternebrae and reduced fetal BWs (Giavini et al., 1985).

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.8 (PDF)

I.A.5. CONFIDENCE IN THE CHRONIC ORAL RfD

Study - Medium
Data Base - Medium
RfD - Medium

The overall confidence in the RfD is medium. Confidence in the principal study (Kociba et al., 1974) is medium. The 2-year drinking water study is a well-conducted, peer-reviewed study that used 3 dose groups plus a control. The study had adequate group sizes (60 rats/sex/dose group) and investigated multiple target organs.

Confidence in the oral database is medium due to the lack of a multigeneration reproductive toxicity study.

Reflecting medium confidence in the principal study and medium confidence in the database, confidence in the RfD is medium.

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF).

I.A.6. EPA DOCUMENTATION AND REVIEW OF THE CHRONIC ORAL RfD

Source Document – (U.S. EPA, 2010)

This document has been provided for review to EPA scientists, interagency reviewers from other federal agencies and White House offices, and the public, and peer reviewed by independent scientists external to EPA. A summary and EPA's disposition of the comments received from the independent external peer reviewers and from the public is included in Appendix A of the Toxicological Review of 1,4-Dioxane (U.S. EPA, 2010). To review this appendix, exit to the Toxicological Review, Appendix A, Summary of External Peer Review and Public Comments and Disposition (PDF).

I.A.7. EPA CONTACTS

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202) 566-1676 (phone), (202) 566-1749 (fax), or hotline.iris@epa.gov (email address).

VI. Bibliography

Substance Name — 1,4-Dioxane
CASRN — 123-91-1
Section VI. Last Revised — 08/11/2010

VI.A. Oral RfD References

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List of Abbreviations and Acronyms Frequently Used in New York State Human Health Fact Sheets.

1×10^{-6}	one-in-one million
ACPF	adjusted cancer potency factor
ADAF	age-dependent adjustment factor
ADI	acceptable daily intake
adj	adjusted
AIC	Akaike information criterion
ATSDR	Agency for Toxic Substance and Disease Registry
AUC	area under the curve
AWQGV	ambient water quality guidance value
BMC	benchmark concentration
BMCL	benchmark concentration, lower 95% confidence limit
BMD	benchmark dose
BMDL	benchmark dose, lower 95% confidence limit
$BMDL_{10}$	BMDL, 10% BMR
$BMDL_{50}$	BMDL, 50% BMR
$BMDL_{1SD}$	BMDL, BMR of one standard deviation
$BMDL_{ADJ}$	BMDL, adjusted to continuous exposure
BMR	benchmark response
BW	body weight
$BW^{2/3}$	body-weight raised to the 2/3 power scaling
$BW^{3/4}$	body-weight raised to the 3/4 power scaling
CA EPA	California Environmental Protection Agency
CASRN	Chemical Abstracts Service Registry Number
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CL	confidence limit
CNS	central nervous system
CPF	cancer potency factor
DAF	dosimetric adjustment factor
DNA	deoxyribonucleic acid
DWCR	drinking water consumption rate
EFSA	European Food Safety Authority
F_1	first filial generation (in experimental animals)
F_2	second filial generation (in experimental animals)
FAO	Food and Agriculture Organization of the United Nations
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
g	gram
GD	gestation day
HC	Health Canada
HEC	human equivalent concentration
HED	human equivalent dose
HED_{BMDL10}	human equivalent dose at the $BMDL_{10}$
HED_{LOEL}	human equivalent dose at the LOEL
HED_{NOEL}	human equivalent dose at the NOEL
HI	hazard index
hr	hour
HSDB	Hazardous Substance Data Bank

IARC	International Agency for Research on Cancer
IRIS	Integrated Risk Information System, US EPA
kg	kilogram
L	liter
L/day	liters per day
L/kg	liters per kilogram
L/kg-day	liters per kilogram day
LADC	lifetime average daily concentration
LADD	lifetime average daily dose
LCL	lower confidence limit
LED	lower bound on effective dose
LEL	lowest-effect level
LOAEL	lowest-observed-adverse-effect level
LOEL	lowest-observed-effect level
mcg	microgram
mcg/m^3	micrograms per cubic meter
mcg/kg-day	micrograms per kilogram body weight per day
mcg/L	micrograms per liter
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MDPH	Massachusetts Department of Public Health
mg	milligram
mg/kg	milligrams per kilogram
mg/L	milligrams per liter
mg/hr	milligrams per hour
mg-hr/L	milligrams-hour per liter
mg/kg-day	milligrams per kilogram body weight per day
mg/kg/day	milligrams per kilogram body weight per day
mg/m^3	milligrams per cubic meter
MLE	maximum likelihood estimate
MOA	mode-of-action
MRL	minimal risk level
MTD	maximum tolerated dose
NAS	National Academy of Sciences
NHANES	National Health and Nutrition Examination Survey
ng	nanogram
ng/L	nanograms per liter
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
NRC	National Research Council
NTP	National Toxicology Program
NYS	New York State
NYS DEC	New York State Department of Environmental Conservation
NYS DOH	New York State Department of Health
NYCRR	New York Code of Rules and Regulations
OPP	Office of Pesticide Programs, US EPA
P (value)	probability value
PBPK	physiologically-based pharmacokinetic
PDAF	pharmacodynamic adjustment factor
pg	picogram

pg/L	picograms per liter
PKAF	pharmacokinetic adjustment factor
POC	principal organic contaminant
POD	point-of-departure
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
RfC	reference concentration
RfD	reference dose
RPF	relative potency factor
RR	relative risk
RSC	relative source contribution
SAB	EPA Science Advisory Board
SD	standard deviation
TDI	tolerable daily intake
TEF	toxic equivalency factor
TEQ	toxicity equivalent
TW	time-weighted
TWA	time-weighted-average
UCL	upper confidence limit
UCMR	Unregulated Contaminant Monitoring Rule, US EPA
UF	uncertainty factor
UOC	unspecified organic contaminant
UR	unit risk
U.S.	United States
US EPA	United States Environmental Protection Agency
WBC	white blood cell
WCAF	water consumption adjustment factor
WHO	World Health Organization
wk	week