This document is a final draft. It has not been formally released by the U.S. Environmental Protection Agency and should not at this stage be construed to represent Agency position on this chemical. It is being circulated for review of its technical accuracy and science policy implications.

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

Note: A TOXICOLOGICAL REVIEW is available for this chemical in Adobe PDF Format (xxx pp, xxM). Similar documents can be found in the List of Available IRIS Toxicological Reviews.

Links to specific pages in the toxicological review are available throughout this summary. To utilize this feature, your Web browser and Adobe program must be configured properly so the PDF displays within the browser window. If your browser and Adobe program need configuration, please go to EPA's PDF page for instructions.

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1,4-Dioxane (CASRN: 123-91-1); 00/00/0000

Human health assessment information on a chemical substance is included in IRIS only after a comprehensive review of toxicity data by U.S. EPA health scientists from several program offices, regional offices, and the Office of Research and Development. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the positions that were reached during the review process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website at http://www.epa.gov/iris/backgrd.html .

STATUS OF DATA FOR 1,4-Dioxane

File First On-Line 08/22/1988

Category (section)	Status	Last Revised
Chronic Oral RfD Assessment (I.A.)	on-line	00/00/0000
Chronic Inhalation RfC Assessment (I.B.)	discussion	00/00/0000
Carcinogenicity Assessment (II.)	on-line	00/00/0000

Note: Hyperlinks to the reference citations throughout this document will take you to the NCEA HERO database (Health and Environmental Research Online) at http://epa.gov/hero. HERO is a database of scientific literature used by U.S. EPA in the process of developing science assessments such as the Integrated Science Assessments (ISA) and the Integrated Risk Information System (IRIS).

_I. Health Hazard Assessments for Noncarcinogenic Effects

__I.A. Reference Dose (RfD) for Chronic Oral Exposure

1,4-Dioxane
CASRN – 123-91-1
Section I.A. Last Revised -- 00/00/0000

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 RfDs 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

Critical Effect	Point of Departure	UF	Chronic RfD
Liver and kidney toxicity	NOAEL: 9.6 mg/kg-day	300	0.03 mg/kg-day
Chronic oral rat study			
Kociba et al. (1974, 062929)			

___I.A.2. PRINCIPAL AND SUPPORTING STUDIES

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 (Johnstone, 1959, 062927)(Barber, 1934, 062913). In animals, liver and kidney degeneration and necrosis were observed frequently in acute oral and inhalation studies (JBRC, 1998, 196242)(Drew et al., 1978, 067913)(David, 1964, 195954)(Kesten et al., 1939, 194972)(Laug et al., 1939, 195055)(Schrenk and Yant, 1936, 195076)(de Navasquez, 1935, 196174)(Fairley et al., 1934, 062919). Liver and kidney effects were also observed following chronic oral exposure to 1,4-dioxane in animals (Kano et al., 2009, 594539)(JBRC, 1998, 196240)(Yamazaki et al., 1994, 196120)(NCI, 1978, 062935)(Kociba et al., 1974, 062929)(Argus et al., 1973, 062912)(Argus et al., 1965, 017009) (see summary Table 4-17 in the *Toxicological Review of 1,4-Dioxane* (US EPA, 2010, #####)).

In the available chronic studies, Kociba et al. (1974, 062929) 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, 062929) reported toxic effects of heptocellular degeneration and necrosis in the liver, while liver lesions reported in other studies (JBRC, 1998, 196240)(Argus et al., 1973, 062912) appeared to be related to the carcinogenic process. Kociba et al. (Kociba et al., 1974, 062929) also reported renal tubule epithelial cell degenerative changes and necrosis in the kidney which was supported by data in NCI (1978, 062935) and Argus et al. (1973, 062912); 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, 062929) was chosen as the principal study for the derivation of the RfD.

Kociba et al. (1974, 062929) 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 the 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, 062929) 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 PODs 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, 062935) and liver hyperplasia (JBRC, 1998, 196240). The $BMDL_{10}$ values of 22.3 mg/kg-day and 23.8 mg/kg-day from the NCI (1978, 062935) and JBRC (1998, 196240) studies, respectively, are within a factor of two of the NOAEL (9.6 mg/kg-day) observed by Kociba et al. (1974, 062929).

___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 of 10 is 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 necessasry, 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, 062929) 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, 062924). This developmental study indicates that the developing fetus may be a target of toxicity. An 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, 062929) study represents the most sensitive effect and dataset observed in a chronic bioassay.

Kidney toxicity as evidenced by glomerulonephritis (Argus et al., 1973, 062912)(Argus et al., 1965, 017009) and degeneration of the cortical tubule (NCI, 1978, 062935)(Kociba et al., 1974, 062929) 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, 062929).

Rhinitis and inflammation of the nasal cavity were reported in both the NCI (1978, 062935) (mice only, dose ≥ 380 mg/kg-day) and JBRC (1998, 196240) studies (≥ 274 mg/kg-day in rats, >278 mg/kg-day in mice). JBRC (1998, 196240) eported 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, 062924).

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 theRfD is medium. Confidence in the principal study (Kociba et al., 1974, 062929) 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 – US 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* (US 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).

__I.B. Reference Concentration (RfC) for Chronic Inhalation Exposure

Substance Name - 1,4-Dioxane
CASRN – 123-91-1
Section I.B. Last Revised -- 00/00/0000

NOTE: During the development of this assessment, new data regarding the toxicity of 1,4-dioxane through the inhalation route of exposure became available. The IRIS Program will evaluate the more recently published 1,4-dioxane inhalation data for the potential to derive an RfC in a separate assessment. A description of the studies that were available at the time that this assessment was under development are described below.

Inhalation studies for 1,4-dioxane evaluated in this assessment were not adequate for the determination of an RfC value. Only one subchronic study (Fairley et al., 1934) and one chronic inhalation study (Torkelson et al., 1974) were identified. In the subchronic study, rabbits, guinea pigs, rats, and mice (3–6/species/group) were exposed to 1,000, 2,000, 5,000, or 10,000 ppm of 1,4-dioxane vapor for 1.5 hours two times a day for 5 days, 1.5 hours for one day, and no exposure on the seventh day. Animals were exposed until death occurred or were sacrificed after various durations of exposure (3-202.5 hours). Detailed dose-response information was not provided; however, severe liver and kidney damage and acute vascular congestion of the lungs were observed at concentrations ≥ 1,000 ppm. Kidney damage was described as patchy degeneration of cortical tubules with vascular congestion and hemorrhage. Liver lesions varied from cloudy hepatocyte swelling to large areas of necrosis.

Torkelson et al. (1974) performed a chronic inhalation study in which male and female Wistar rats (288/sex) were exposed to 111 ppm 1,4-dioxane vapor for 7 hours/day, 5 days/week for 2 years. Control rats (192/sex) were exposed to filtered air. No significant effects were observed on BWs, survival, organ weights, hematology, clinical chemistry, or histopathology. Because Fairley et al. (1934) identified a free-standing LOAEL only, and Torkelson et al. (1974) identified a free-standing NOAEL only, neither study was sufficient to characterize the inhalation risks of 1,4-dioxane. A route extrapolation from oral toxicity data was not performed because 1,4-dioxane inhalation causes direct effects on the respiratory tract (i.e., respiratory irritation in humans, pulmonary congestion in animals) (Wirth and Klimmer, 1936; Fairley et al., 1934; Yant et al., 1930), which would not be accounted for in a cross-route extrapolation. In addition, available kinetic models are not suitable for this purpose (see Appendix B of the *Toxicological of 1,4-Dioxane* (US EPA, 2010, ####).

An inhalation assessment for 1,4-dioxane was not previously available on IRIS.

_II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name - 1,4-Dioxane
CASRN – 123-91-1
Section II. Last Revised -- 00/00/0000

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, 2005, 086237) and the *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (U.S. EPA, 2005, 088823). 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 $\mu g/m^3$ 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, 062935). The linearized multistage extra risk procedure was used for linear low dose extrapoloation. An inhalation unit risk (IUR) of 1.5×10^{-5} $(\mu g/m^3)^{-1}$ was not previously derived.

__II.A. Evidence for Human Carcinogenicity

___II.A.1. Weight-Of-Evidence Characterization

Under the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005, 086237), 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]; mesothiolomas of the peritoneum, mammary, and nasal tumors have also been observed in rats following 2 years of oral exposure to 1,4- dioxane).

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 (Kano et al., 2009, 594539)(JBRC, 1998, 196240)(Yamazaki et al., 1994, 196120)(NCI, 1978, 062935)(Kociba et al., 1974, 062929)(Argus et al., 1973, 062912)(Hoch-Ligeti and Argus, 1970, 029386)(Hoch-Ligeti et al., 1970, 062926)(Argus et al., 1965, 017009). Additionally, mesothiolomas of the peritoneum (Kano et al., 2009, 594539)(JBRC, 1998, 196240)(Yamazaki et al., 1994, 196120), mammary (Kano et al., 2009, 594539)(JBRC, 1998, 196240)(Yamazaki et al., 1994, 196120), and nasal tumors (Kano et al., 2009, 594539)(JBRC, 1998, 196240)(Yamazaki et al., 1994, 196120)(NCI, 1978, 062935)(Kociba et al., 1974, 062929)(Argus et al., 1973, 062912)(Hoch-Ligeti et al., 1970, 062926) 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, 062914)(Thiess et al., 1976, 062943).

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 (Lundberg et al., 1987, 062933)(King et al., 1973, 029390). Dose-response and temporal data support the occurrence of cell proliferation and hyperplasia prior to the development of liver tumors (JBRC, 1998, 196240)(Kociba et al., 1974, 062929) 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, 1998, 196240)(Kociba et al., 1974, 062929) 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 (Kano et al., 2008; JBRC, 1998a; 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 (mesothiolomas), 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 asses the evidence of carcinogenicity of 1,4-dioxane (see Section 4.1 in the *Toxicological Review of 1,4-Dioxane*, (USEPA, 2010 #####). In each case, the cohort size and number of reported cases were of limited size (Buffler et al., 1978, 062914)(Thiess et al., 1976, 062943).

___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 (Kano et al., 2009, 594539)(JBRC, 1998, 196240)(Yamazaki et al., 1994, 196120)(NCI, 1978, 062935)(Kociba et al., 1974, 062929). With the exception of the NCI (1978, 062935) study, the incidence of nasal cavity tumors was generally lower than the incidence of liver tumors in exposed rats. The Kano et al. (2009, 594539) 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, 062935) bioassay. The Kociba et al. (1974, 062929) study also used three dose groups and low exposures; 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, 594539) 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.

___II.A.4. Supporting Data for Carcinogenicity

Several carcinogenicity bioassays have been conducted for 1,4-dioxane in mice, rats, and guinea pigs (Kano et al., 2009, 594539)(JBRC, 1998, 196240)(Yamazaki et al., 1994, 196120)(NCI, 1978, 062935)(Kociba et al., 1974, 062929)(Torkelson et al., 1974, 094807)(Argus et al., 1973, 062912)(Hoch-Ligeti and Argus, 1970, 029386)(Hoch-Ligeti et al., 1970, 062926)(Argus et al., 1965, 017009). Liver tumors have been observed following drinking water exposure in male Wistar rats (Argus et al., 1965, 017009), male guinea pigs (Hoch-Ligeti and Argus, 1970, 029386), male Sprague Dawley rats (Argus et al., 1973, 062912)(Hoch-Ligeti et al., 1970, 062926), male and female Sherman rats (Kociba et al., 1974, 062929), female Osborne-Mendel rats (NCI, 1978, 062935), male and female F344/DuCrj rats (Kano et al., 2009, 594539)(JBRC, 1998, 196240)(Yamazaki et al., 1994, 196120), male and female B6C3F_1 mice (NCI, 1978, 062935), and male and female Crj:BDF$_1$ mice (Kano et al., 2009, 594539)(JBRC, 1998, 196240)(Yamazaki et al., 1994, 196120). In the earliest cancer bioassays, the liver tumors were described as hepatomas (Argus et al., 1973, 062912)(Hoch-Ligeti and Argus, 1970, 029386)(Hoch-Ligeti et al., 1970, 062926)(Argus et al., 1965, 017009); however, later studies made a distinction between hepatocellular carcinoma and hepatocellular adenoma (Kano et al., 2009, 594539)(JBRC, 1998, 196240)(Yamazaki et al., 1994, 196120)(NCI, 1978, 062935)(Kociba et al., 1974, 062929). Both tumor types have been seen in rats and mice exposed to 1,4-dioxane. Kociba et al. (1974, 062929) 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 (1998, 196240) 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, 062912)(Hoch-Ligeti et al., 1970, 062926), Osborne-Mendel rats (NCI, 1978, 062935), Sherman rats (Kociba et al., 1974, 062929), and F344/DuCrj rats (Kano et al., 2009, 594539)(JBRC, 1998, 196240)(Yamazaki et al., 1994, 196120) Most tumors were characterized as squamous cell carcinomas. Nasal tumors were not elevated in B6C3F_1 or Crj:BDF$_1$ mice. JBRC (1998, 196240) 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, 062935) 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, 094807).

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 (Lundberg et al., 1987, 062933)(Bull et al., 1986, 194336)(King et al., 1973, 029390) (see Section 4.2.3 in the *Toxicological Review of 1,4-Dioxane*).

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, 594539) study (also (JBRC, 1998, 196240)(Yamazaki et al., 1994, 196120)). Female rats dosed with 429 mg/kg-day in drinking water for 2 years also showed a statistically significant increase in mammary gland adenomas (Kano et al., 2009, 594539)(JBRC, 1998, 196240)(Yamazaki et al., 1994, 196120). A significant increase in the incidence of these tumors was not observed in other chronic oral bioassays of 1,4-dioxane (NCI, 1978, 062935)(Kociba et al., 1974, 062929).

__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 0.1 $(mg/kg\text{-}day)^{-1}$ is based on the incidence of hepatocellular adenomas and carcinomas in female mice exposed to 1,4-dioxane in drinking water for 2 years. 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* (USEPA, 2010, XXXX). The rat $BMDL_{50}$ of 32.94 mg/kg-day represents the POD used to calculate the $BMDL_{HED}$ of 4.96 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 – 4.96 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 mg/kg-day) = 7×10^{-2} per mg/kg-day

The slope factor for 1,4-dioxane should not be used with exposures exceeding the point of departure ($BMDL_{50HED}$ = 4.96 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, 594539) 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 $BMDL_{10}$ much lower than the response level at the lowest dose in the study (Kano et al., 2009, 594539). Thus, the log-logistic model was also run for BMRs of 30 and 50%. Using a higher BMR resulted in BMDLs 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
References – Kano et al. (2009, 594539)

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

Tumor	Dose (mg/kg-day)			
	0	**66**	**278**	**967**
Hepatocellular adenoma or carcinoma	5/50	35/50[a,b]	41/50[a,b]	46/49[a,b]

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

Source: Kano et al. (2009, 594539)

Oral SF using linear low-dose extrapolation approach and route-to-route 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	0, 66, 278, 967	49.90	32.94	7.51	4.96	0.10

hepatocellular adenoma or carcinoma	mg/kg-day					

___II.B.3. Addittional Comments

Supplementary information not required.

___II.B.4. Discussion of Confidence

Relevance to humans. The oral CSF is 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 the liver adenomas and carcinomas observed in animal models due to exposure to 1,4-dioxane are not plausible in humans. Liver adenomas and carcinomas were considered as a plausible outcome 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 mesothiolomas of the peritoneal cavity (Kano et al., 2009, 594539). 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, 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 are not available to support a carcinogenic MOA for 1,4-dioxane. In the absence of a MOA(s) for the observed tumor types due to 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, 594539)(NCI, 1978, 062935)(Kociba et al., 1974, 062929), 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* 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, 2006, 194567):

- 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 χ^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, 194567) 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, 594539). A BMR of 50% was used because it is proximate to the response at the lowest dose tested and the $BMDL_{50}$ was derived by applying appropriate parameter constraints, consistent with recommended use of BMDS in the external review draft BMD technical guidance document (U.S. EPA, 2000, 194567).

The human equivalent oral CSF estimated from liver tumor datasets with statistically significant increases ranged from 4.2×10^{-4} to 0.18 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, 062929) and the female mouse liver adenoma and carcinoma dataset (Kano et al., 2009, 594539).

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 *2005 Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005, 086237). 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, 594539) 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 quantified 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, both species and sexes reported from the Kano et al. (2009, 594539) 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 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 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.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

NOTE: During the development of this assessment, new data regarding the toxicity of 1,4-dioxane through the inhalation route of exposure became available. The IRIS Program will evaluate the more recently published 1,4-dioxane inhalation data for the potential to derive an inhalation unit risk in a separate assessment. A description of the studies that were available at the time that this assessment was under development are described below.

Inhalation studies for 1,4-dioxane evaluated in this assessment were not adequate for the determination of an inhalation unit risk. No treatment-related tumors were noted in a chronic inhalation study in rats; however, only a single exposure concentration was used (111 ppm 1,4-dioxane vapor for 7 hours/day, 5 days/week for 2 years) (Torkelson et al., 1974). A route extrapolation from oral bioassay data was not performed (see Section 5.2). In addition, available kinetic models are not suitable for this purpose (see Appendix B of the *Toxicological Review of 1,4-Dioxane* (US EPA, 2010 ####).

__II.D. EPA Documentation, Review, And Contacts (Carcinogenicity Assessment)

___II.D.1. EPA Documentation

Source Document – US 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* (US EPA, 2010, #####).

___II.D.2. EPA Review

Agency Completion Date -- __/__/__ *[note: Leave BLANK until completion is reached]*

___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).

_III. [reserved]
_IV. [reserved]
_V. [reserved]

_VI. Bibliography

1,4-Dioxane
CASRN – 123-91-1
Section VI. Last Revised -- 00/00/0000

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__VI.B. Inhalation RfC References

None

__VI.C. Carcinogenicity Assessment References

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VII. Revision History

1,4-Dioxane
CASRN – 123-91-1
File First On-Line 08/22/1988

Date	Section	Description
08/22/1988	II.	Carcinogen summary on-line
06/01/1989	II.D.3.	Primary and secondary contacts changed
02/01/1990	VI.	Bibliography on-line
09/01/1990	II.	Text edited
09/01/1990	III.A.	Health Advisory on-line
09/01/1990	VI.D.	Health Advisory references added
08/01/1991	VI.C.	Citations clarified
01/01/1992	IV.	Regulatory Action section on-line

04/01/1997	III., IV., V.	Drinking Water Health Advisories, EPA Regulatory Actions, and Supplementary Data were removed from IRIS on or before April 1997. IRIS users were directed to the appropriate EPA Program Offices for this information.
10/28/2003	II.D.2.	Screening-Level Literature Review Findings message has been added.
02/09/2004	I.,II.	This chemical is being reassessed under the IRIS Program.
00/00/0000	I., II., IV.,	RfD and cancer assessment updated

_VIII. Synonyms

1,4-Dioxane
CASRN – 123-91-1
Section VIII. Last Revised -- 00/00/0000

- 123-91-1
- diethylene dioxide
- diethylene oxide
- dioxane, 1,4-
- p-dioxane
- dioxane
- dioxyethylene ether
- diethylene ether
- 1,4-diethylene dioxide