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

0326

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

Health assessment information on a chemical substance is included in IRIS only after a comprehensive review of chronic toxicity data by U.S. EPA health scientists from several Program Offices and the Office of Research and Development. The summaries presented in Sections I and II represent a consensus reached in the review process. Background information and explanations of the methods used to derive the values given in IRIS are provided in the Background Documents.

STATUS OF DATA FOR 1,4-Dioxane

File First On-Line 08/22/1988

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	no data	
Inhalation RfC Assessment (I.B.)	no data	
Carcinogenicity Assessment (II.)	on-line	09/01/1990

_I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

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

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Not available at this time.

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

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Not available at this time.

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_II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name -- 1,4-Dioxane
CASRN -- 123-91-1
Last Revised -- 09/01/1990

Section II 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 and from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in The Risk Assessment Guidelines of 1986 (EPA/600/8-87/045) and in the IRIS Background Document. IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment also utilize those Guidelines where indicated (Federal Register 61(79):17960-18011, April 23, 1996). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

_II.A. Evidence for Human Carcinogenicity

__II.A.1. Weight-of-Evidence Characterization

Classification -- B2; probable human carcinogen.

Basis -- Induction of nasal cavity and liver carcinomas in multiple strains of rats, liver carcinomas in mice, and gall bladder carcinomas in guinea pigs.

__II.A.2. Human Carcinogenicity Data

Inadequate. Three epidemiologic studies on workers exposed to 1,4-dioxane are available. Theiss et al. (1976) reported 12 deaths among 74 workers exposed to dioxane. Two of the deaths were due to cancer: one lamellar epithelial carcinoma in a 66-year-old man and one myelofibrotic leukemia in a 71-year-old man. No statistically significant increase was noted based on these few cases of cancer. Among 165 production and processing workers exposed to dioxane (as well as vinyl chloride, perchloroethylene, methylene chloride, trichloroethylene and carbon tetrachloride), 12 deaths were reported (Buffler et al., 1976, cited in U.S. EPA, 1986b). Three of these deaths were due to cancer: one stomach cancer, one alveolar carcinoma, and one mediastinal malignancy. These deaths were not different from the expected numbers. In an unpublished report to NIOSH by Dernehl (1976, cited in U.S. EPA, 1986b), four cancers were reported among 80 dioxane workers. The cancers included a colonic cancer, a pulmonary cancer, a lymphosarcoma, and a glioblastoma. Again, the observed number of cancer cases was not different from the expected cancer deaths.

__II.A.3. Animal Carcinogenicity Data

Quantitative Estimate of Carcinogenic Risk from Oral Exposure

- Summary of Risk Estimates
- Dose-Response Data
- Additional Comments
- Discussion of Confidence

Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

- Summary of Risk Estimates
- Dose-Response Data
- Additional Comments
- Discussion of Confidence

EPA Documentation, Review and, Contacts

- Bibliography
- Revision History
- Synonyms

Sufficient. The NCI (1978) administered 1,4-dioxane (greater than or equal to 99.9% pure) in the drinking water to Osborne-Mendel rats (35 rats/sex/dose) and mice (50 mice/sex/dose) for a significant portion of their lifespan (110 weeks, rats; 90 weeks, mice). Male and female rats were given 530, 240, or 0 mg/kg/day and 640, 350, or 0 mg/kg/day, respectively. High- dose and matched control male rats were placed in the study 1 year after the study began to replace two original groups of male rats that had died during an air-conditioning failure. Male and female treated rats had a statistically significant elevated incidence of nasal cavity squamous cell carcinomas and treated female rats had a statistically significant elevated incidence of liver adenomas, both dose-related. Male and female mice treated with 830, 720 or 0 mg/kg/day and 860, 380, or 0 mg/kg/day, respectively, developed a statistically significant elevated incidence of liver carcinomas and liver carcinomas or adenomas, both dose-related. Although the survival rate of treated rats and female mice was decreased compared with controls, the NCI concluded that sufficient numbers of treated animals survived.

Kociba et al. (1974) administered 1%, 0.1%, 0.01% or 0% 1,4-dioxane in the drinking water to male and female Sherman rats for up to 716 days (60 rats/sex/treatment group). The incidences of hepatocellular carcinomas, liver cholangiomas, and nasal cavity squamous cell carcinomas showed a significant increase in the high-dose rats of both sexes. Similar administration of 0.5% to 2% 1,4-dioxane to male guinea pigs for 23 months induced gall bladder carcinomas (2/22) and liver hepatomas (3/22) (Hoch-Ligeti and Argus, 1970). Hoch-Ligeti et al. (1970) and Argus et al. (1973) treated male Sprague-Dawley rats with 1.8, 1.4, 1.0, 0.75, or 0% 1,4-dioxane in the drinking water for 13 months, followed by a 3-month observation period. Treatment-related hepatocellular carcinomas and nasal cavity carcinomas were observed at 1.8% and 1.4% 1,4-dioxane, and treatment-related nasal cavity carcinomas were observed at 1.0% and 0.75% 1,4-dioxane. Liver tumors (7/26) were induced in male Wistar rats after oral administration of 1% 1,4-dioxane in the drinking water for 63 weeks (Argus et al., 1965). One kidney transitional cell carcinoma and one myeloid leukemia were also observed in the treated animals. A lymphoid tissue lymphosarcoma was observed in 1 of 9 control rats.

In a 2-year inhalation study (Torkelson et al., 1974), male and female Wistar rats were exposed to 111 ppm or 0 ppm 1,4-dioxane vapor. Three replicate groups of 288 rats/sex served as the treated and control groups. Comprehensive gross and microscopic examination of the major organs and tissues revealed no treatment-related lesions.

__II.A.4. Supporting Data for Carcinogenicity

1,4-Dioxane was found to be a promoter in a two-stage skin carcinogenesis study in mice (King et al., 1973). A single dermal application of 50 ug of 7,12-dimethylbenzoanthracene (DMBA) was followed 1 week later by thrice-weekly paintings of 1,4-dioxane (unspecified concentration in acetone) for 60 weeks. Similar applications of 1,4-dioxane without DMBA initiation did not result in a significantly increased incidence of subcutaneous carcinomas.

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_II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure

__II.B.1. Summary of Risk Estimates

Oral Slope Factor -- 1.1E-2/mg/kg/day

Drinking Water Unit Risk -- 3.1E-7/ug/L

Extrapolation Method -- Linearized multistage procedure, extra risk

Drinking Water Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	3E+2 ug/L
E-5 (1 in 100,000)	3E+1 ug/L
E-6 (1 in 1,000,000)	3 ug/L

__II.B.2. Dose-Response Data (Carcinogenicity, Oral Exposure)

Tumor Type -- squamous cell carcinoma of the nasal turbinates
Test animals -- rat/Osborne-Mendel, male
Route -- drinking water
Reference -- NCI, 1978

Administered Dose (%)	Administered Dose (mg/kg)/day	Human Equivalent Dose (mg/kg)/day	Tumor Incidence
0	0	0	0/33
0.5	240	48	12/25
1.0	530	106	16/33

__II.B.3. Additional Comments (Carcinogenicity, Oral Exposure)

Transformed doses in mg/kg/day were provided by the study's author. NCI (1978) determined average daily doses from the mean consumption of dioxane solution per week at intervals during the second year of treatment. The length of exposure, experiment, and lifespan was 110 weeks for treated and control animals. The weight of the animals was assumed to be 0.55 kg from the study. The human weight was assumed to be 70 kg.

The unit risk should not be used if the water concentration exceeds 3E+4 ug/L, since above this concentration the slope factor may differ from that stated.

__II.B.4. Discussion of Confidence (Carcinogenicity, Oral Exposure)

The compound was administered at multiple dose levels by a relevant route of exposure. The animals were exposed for a significant portion of their lifespan, and comprehensive histologic examinations were performed. Although survival was affected by treatment, adequate numbers of rats were at risk for development of late-appearing tumors.

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_II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

Not available.

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_II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)

__II.D.1. EPA Documentation

Source Document -- U.S. EPA, 1986a,b

The values in the 1986 Reportable Quantities Document for 1,4-dioxane have received limited Agency review.

__II.D.2. EPA Review (Carcinogenicity Assessment)

Agency Work Group Review -- 05/13/1987, 02/03/1988

Verification Date -- 02/03/1988

Screening-Level Literature Review Findings -- A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the cancer assessment for 1,4-Dioxane conducted in August 2003 identified one or more significant new studies. IRIS users may request the references for those studies from the IRIS Hotline at hotline.iris@epa.gov or 202-566-1676.

__II.D.3. EPA Contacts (Carcinogenicity Assessment)

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 (internet address).

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

_VI. Bibliography

Substance Name -- 1,4-Dioxane
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_VI.A. Oral RfD References

None

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_VI.B. Inhalation RfD References

None

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_VI.C. Carcinogenicity Assessment References

Argus, M.F., J.C. Arcos and C. Hoch-Ligeti. 1965. Studies on the carcinogenic activity of

protein-denaturing agents: Hepatocarcinogenicity of dioxane. J. Natl. Cancer Inst. 35(6): 949-958.

Argus, M.F., R.S. Sohal, G.M. Bryant, C. Hoch-Ligeti and J.C. Arcos. 1973. Dose-response and ultrastructural alterations in dioxane carcinogenesis. Influence of methylcholanthrene on acute toxicity. Europ. J. Cancer. 9: 237-243.

Buffler, P.A., S.M. Wood, L. Suarez and D.J. Kilian. 1976. Mortality follow- up among workers exposed to 1,4-dioxane in the chemical industry. Unpublished report submitted to NIOSH by the Epidemiology Program, Dept. of Preventive Medicine and Community Health, The University of Texas Medical Branch, Galveston, Texas. December 17, 1976. (Cited in U.S. EPA, 1986b)

Dernehl, C.U. 1976. Epidemiology study of dioxane workers. Written communication to NIOSH. April, 1976. (Cited in U.S. EPA, 1986b)

Hoch-Ligeti, C. and M.F. Argus. 1970. Effects of carcinogens on the lung of guinea pigs. In: Conference on the Morphology of Experimental Respiratory Carcinogenesis, Gatlinburg, Tennessee, P. Nettesheim, M.G. Hanna, Jr. and J.W. Deatherage Jr., Ed. AEC Symposium Series No. 21, Springfield, VA, NTIS. p. 267-279.

Hoch-Ligeti, C., M.F. Argus and J.C. Arcos. 1970. Induction of carcinomas in the nasal cavity of rats by dioxane. Br. J. Cancer. 24: 164-167.

King, M.E., A.M. Shefner and R.R. Bates. 1973. Carcinogenesis bioassay of chlorinated dibenzodioxins and related chemicals. Environ. Health Perspect. 5: 163-170.

Kociba, R.J., S.B. McCollister, C. Park, T.R. Torkelson and P.J. Gehring. 1974. 1,4-Dioxane. I. Results of a 2-year ingestion study in rats. Toxicol. Appl. Pharmacol. 30: 275-286.

NCI (National Cancer Insitute). 1978. Bioassay of 1,4-Dioxane for Possible Carcinogenicity, CAS No. 123-91-1. NCI Carcinogenesis Tech. Rep. Ser. No. 80. DHEW Publication No. (NIH) PB-285-711.

Theiss, A.M., E. Tress and I. Fleig. 1976. Industrial-medical investigation results in the case of workers exposed to dioxane. Arbeitsmed. Sozialmed. Preventivmed. 11: 35-46.

Torkelson, T.R., B.K.J. Leong, R.J. Kociba, W.A. Richter and P.J. Gehring. 1974. 1,4-Dioxane. II. Results of a 2-year inhalation study in rats. Toxicol. Appl. Pharmacol. 30: 287-289.

U.S. EPA. 1986a. Reportable Quantities Document for 1,4-Dioxane (review draft). Prepared by the Carcinogen Assessment Group, Office of Health and Environmental Assessment, Washington, D.C. for the Office of Emergency and Remedial Response and Office of Solid Waste and Emergency Response, Cincinnati, OH.

U.S. EPA. 1986b. Evaluation of the Potential Carcinogenicity of 1,4-Dioxane (123-91-1) (review draft). Prepared by the Carcinogen Assessment Group, Office of Health and Environmental Assessment, Washington DC for the Office of Emergency and Remedial Response and Office of Solid Waste and Emergency Response, Cincinnati, OH. OHEA-C-073-97.

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_VII. Revision History

Substance Name -- 1,4-Dioxane
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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.

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_VIII. Synonyms

Substance Name -- 1,4-Dioxane
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Last Revised -- 08/22/1988

123-91-1
diethylene dioxide
diethylene oxide
1,4-Dioxane
Dioxane, 1,4-
p-dioxane

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