1,4-DIOXANE

Data were last reviewed in IARC (1976) and the compound was classified in *IARC Monographs* Supplement 7 (1987).

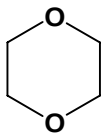
1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 123-91-1
Chem. Abstr. Name: 1,4-Dioxane
IUPAC Systematic Name: *para*-Dioxane
Synonym: 1,4-Diethylene dioxide

1.1.2 *Structural and molecular formulae and relative molecular mass*



$C_4H_8O_2$ Relative molecular mass: 88.11

1.1.3 *Chemical and physical properties of the pure substance*

(*a*) *Description*: Flammable liquid with faint pleasant odour (Budavari, 1996)
(*b*) *Boiling-point*: 101.1°C (American Conference of Governmental Industrial Hygienists, 1991)
(*c*) *Melting-point*: 11.8°C (American Conference of Governmental Industrial Hygienists, 1991)
(*d*) *Solubility*: Soluble in water and most organic solvents (Budavari, 1996)
(*e*) *Vapour pressure*: 4 Pa at 20°C; relative vapour density (air = 1), 3.30 (Verschueren, 1996)
(*f*) *Flash point*: 12.22°C , closed cup; 18.33°C, open cup (American Conference of Governmental Industrial Hygienists, 1991)
(*g*) *Explosive limits*: upper, 22%; lower, 2% by volume in air (American Conference of Governmental Industrial Hygienists, 1991)
(*h*) *Conversion factor*: $mg/m^3 = 3.60 \times ppm$

1.2 Production and use

Production of 1,4-dioxane in the United States in 1982 was approximately three thousand tonnes (United States National Library of Medicine, 1997).

1,4-Dioxane is used as a solvent in a wide range of organic products: lacquers; paints; varnishes; paint and varnish removers; wetting and dispersing agent in textile products, dye baths, and stain and printing compositions; cleaning and detergent preparations; cements; cosmetics; deodorants; fumigants; emulsions; and polishing compositions. It is also used as a stabilizer for chlorinated solvents (Lewis, 1993).

1.3 Occurrence

1.3.1 *Occupational exposure*

No data were available to the Working Group.

1.3.2 *Environmental occurrence*

1,4-Dioxane has been detected in ambient air samples at low levels at several sites in the United States (United States National Library of Medicine, 1997).

1.4 Regulations and guidelines

The American Conference of Governmental Industrial Hygienists (ACGIH) (1997) has recommended 90 mg/m^3 as the threshold limit value (TLV) for occupational exposures to 1,4-dioxane in the workplace air. Until 1981, the ACGIH TLV was 180 mg/m^3 (American Conference of Governmental Industrial Hygienists, 1991). Similar values have been used as standards or guidelines in many countries (International Labour Office, 1991).

No international guideline for 1,4-dioxane in drinking-water has been established (WHO, 1993).

2. Studies of Cancer in Humans

In a prospective mortality study of 165 workers who had been exposed to low concentrations of 1,4-dioxane since 1954, seven deaths had occurred in the manufacturing department by 1975, two of which were from cancer. Expected numbers, based on Texas mortality rates, were 4.9 and 0.9, respectively. In the processing department, five deaths were observed versus 4.9 expected, of which one was from cancer (0.8 expected) (Buffler *et al.*, 1978).

3. Studies of Cancer in Experimental Animals

1,4-Dioxane was tested in rats and guinea-pigs by oral administration: it produced malignant tumours of the nasal cavity and liver in rats and tumours of the liver and gall-bladder in guinea-pigs. It was also active as a promoter in a two-stage skin carcino-

genesis study in mice. No carcinogenic effect was observed in one inhalation study in rats (IARC, 1976).

3.1 Oral administration

3.1.1 *Mouse*

Groups of 50 male and 50 female Crj:BDF_1 mice [age unspecified] were administered 1,4-dioxane (purity, > 99%) at 0, 500, 2000 or 8000 mg/L (ppm) in the drinking-water for 104 weeks. Survival of the two high-dose female groups was reduced. 1,4-Dioxane increased the incidence of hepatocellular adenomas and carcinomas combined in males from 22/50 in controls, to 36/50 low-dose, 45/50 mid-dose and 44/50 high-dose [$p < 0.01$ for all comparisons, Fisher's exact test] and in females from 4/50 in controls, to 36/50 low-dose, 50/50 mid-dose and 47/50 high-dose [$p < 0.01$ for all comparisons, Fisher's exact test]. One nasal cavity tumour occurred in a high-dose female (Yamazaki *et al*., 1994).

3.1.2 *Rat*

Groups of 50 male and 50 female F344/DuCrj rats [age not given] were administered 1,4-dioxane (purity > 99%) at 0, 200, 1000 or 5000 mg/L (ppm) in the drinking-water for 104 weeks. Survival of exposed males and females was reduced. In males, combined hepatocellular adenoma and carcinoma occurred in 0/50 controls, 2/50 low-dose, 4/50 mid-dose and 38/50 high-dose animals [$p < 0.01$, Fisher's exact test]. In females, combined hepatocellular adenomas and carcinomas occurred in 1/50 controls, 0/50 low-dose, 5/50 mid-dose and 48/50 high-dose rats [$p < 0.01$, Fisher's exact test]. Mesotheliomas of the peritoneum were found in 28/50 high-dose males compared with 2/50 controls [$p < 0.01$, Fisher's exact test]. The incidence of subcutaneous fibromas and mammary fibroadenomas in high-dose males was greater than in the control group (12/50 and 4/40 versus 5/50 and 1/50, respectively). In females, nasal cavity tumours were found in 7/50 high-dose rats compared with 0/50 controls [$p < 0.05$, Fisher's exact test], and mammary adenomas were found in 16/50 high-dose rats compared with 6/50 controls [$p < 0.01$, Fisher's exact test] (Yamazaki *et al*., 1994).

3.2 Intraperitoneal injection

Mouse: Groups of 30 male A/J mice, six to eight weeks of age, were administered 1,4-dioxane [purity unspecified] by intraperitoneal injection three times per week for eight weeks for total doses of 0, 400, 1000 and 2000 mg/kg bw. The high dose increased the multiplicity of lung tumours to 0.97 per mouse ($p < 0.05$) compared with 0.28 per mouse in controls given vehicle alone (Maronpot *et al*., 1986).

In a mouse-lung adenoma assay, 1,4-dioxane produced a significant increase in the incidence of lung tumours in males given an intermediate intraperitoneal dose; no such increase was noted in males given a lower or higher intraperitoneal dose or in females given three intraperitoneal doses or in either males or females given 1,4-dioxane orally (Stoner *et al.*, 1986).

3.3 Administration with known carcinogens

Rat: Groups of 8–11 male Sprague-Dawley rats and 19 controls, weighing 200 g, were administered 1,4-dioxane (purity, 99.5%) by gavage once a day on five days per week for seven weeks at a dose of 0, 100 or 1000 mg/kg bw beginning five days after partial hepatectomy and injection of a single dose of 30 mg/kg bw *N*-nitrosodiethylamine (NDEA) to initiate hepatocarcinogenesis. The high dose increased the multiplicity of hepatic foci to 4.7 per cm^2 ($p < 0.01$) compared with 1.3 per cm^2 with NDEA initiation alone. In two other groups of rats, 100 or 1000 mg/kg 1,4-dioxane alone did not induce foci (Lundberg *et al*., 1987).

4. Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms

4.1 Absorption, distribution, metabolism and excretion

The toxicology of 1,4-dioxane has been reviewed and evaluated comprehensively (DeRosa *et al*., 1996), including a full summary of its disposition in animals and humans. 1,4-Dioxane is rapidly absorbed and metabolized and does not accumulate in the body, but the saturation of metabolism at high doses is of toxicological relevance.

4.1.1 *Humans*

(*a*) *Inhalation exposure*

Young *et al*. (1977) exposed four volunteers to 50 ppm [180 mg/m^3] 1,4-dioxane vapour for 6 h. It was rapidly taken up, with plasma levels reaching a plateau after 3 h. The major metabolite, β-hydroxyethoxyacetic acid (HEAA), was detected during the exposure period. At the end of the exposure, plasma levels of 1,4-dioxane fell with a half-life of 59 min. HEAA plasma levels reached their peak 1 h after the end of the exposure and fell thereafter with a half-life of 48 min. The absorption rate of 1,4-dioxane under these conditions was 76.1 mg/h and the total dose was 5.4 mg/kg. The dominant route of elimination was oxidation to HEAA, which is rapidly cleared in the urine; 47% of the dose was excreted as HEAA during exposure and excretion was complete within 8 h of the end. The excretion half-life of HEAA was 2.7 h and its renal clearance was 121 mL/min, which indicates clearance by glomerular filtration, as creatinine clearance in these subjects was 124 mL/min. Renal clearance of 1,4-dioxane was 0.34 mL/min, compared with its metabolic clearance of 75 mL/min.

During workplace exposures of 1.6 ppm [5.8 mg/m^3] 1,4-dioxane for 7.5 h, at the end of the workday, the levels of HEAA were 118-fold those of 1,4-dioxane (urinary concentrations of 414 and 3.5 μmol/L, respectively), showing rapid and very extensive metabolism (Young *et al*., 1976).

(*b*) *Dermal absorption*

The penetration of 1,4-dioxane through human skin is poor. In-vitro studies show that 3.2% of an applied dose passes through excised skin under occlusion and only 0.3% when not occluded (ECETOC, 1983).

4.1.2 *Experimental systems*

Young *et al*. (1978) exposed rats by inhalation to 50 ppm [180 mg/m^3] 1,4-dioxane for 6 h, resulting in an estimated absorbed dose of 71.9 mg/kg which was recovered as 6.8 μg 1,4-dioxane and 21.3 mg HEAA in the 0–48 h urine. These data are consistent with quantitative absorption of 1,4-dioxane after inhalation. These authors also administered orally 10, 100 or 1000 mg/kg bw [^{14}C]1,4-dioxane to rats. In each case, absorption was complete within 24 h. Of the low dose, 99% was excreted in the urine within 24 h; this fell to 86% of the 100-mg/kg bw and 76% of the 1000 mg/kg bw dose within 72 h. This reduction in urinary excretion was compensated by exhalation as unchanged 1,4-dioxane at a rate of 0.43% at 10 mg/kg bw, 5% at 100 mg/kg bw and 25% at 1000 mg/kg bw.

The principal route of metabolism of dioxane is C-oxidation, giving a lactone which exists principally in the open-chain form of HEAA. The proportion detected as the lactone (1,4-dioxane-2-one) depends upon the analytical techniques used (Braun & Young, 1977; Woo *et al*., 1978). A small percentage of the dose (2–3%) is excreted as $^{14}CO_2$, presumably arising from β-oxidation of HEAA.

Young *et al*. (1978) also gave rats oral daily doses of 10 or 1000 mg/kg bw [^{14}C]1,4-dioxane for 17 days. Urine was collected for 20 days and 99% and 82% of the 10 and 1000 mg/kg doses were recovered, respectively, with 1% and 9% exhaled as dioxane and 4% and 7% as $^{14}CO_2$.

The single-dose data show that the formation of HEAA is saturated as the dose is increased, throwing emphasis upon alternate pathways of elimination. Comparison of the single- and repeated-dose data suggests that the conversion of 1,4-dioxane to HEAA is induced by repeated administration.

The saturation of the clearance of 1,4-dioxane as a function of dose was shown clearly after intravenous administration of 3, 10, 30, 100 and 1000 mg/kg bw to rats (Young *et al*., 1978). At 3 and 10 mg/kg, the elimination half-life of 1,4-dioxane was 1.1 h but, as the dose increased, this became progressively longer. The clearance decreased from 3.33 mL/min at 3 mg/kg bw to 0.25 mL/min at 100 mg/kg bw, this being due to decreased metabolic clearance. At 10 mg/kg bw, 5% of a dose of [^{14}C]1,4-dioxane was excreted unchanged in urine and expired air, while at 1000 mg/kg, excretion of unchanged 1,4-dioxane rose to 38%. The major metabolite HEAA accounted for 92% of the 10 mg/kg dose and 60% at 1000 mg/kg bw.

These findings are complemented by those of Woo *et al*. (1977a), who gave rats 1000, 2000, 3000 or 4000 mg/kg bw [^{14}C]1,4-dioxane by intraperitoneal injection and found that saturation of the formation of HEAA occurred at about 3000 mg/kg.

The metabolism of 1,4-dioxane to HEAA has the characteristics of a mixed-function oxidase-mediated reaction (Woo *et al*., 1977b, 1978) and the administration of 1,4-

dioxane to rats resulted in increased hepatic microsomal aniline hydroxylase and aminopyrine *N*-demethylase activities (Dietz *et al*., 1982).

4.2 Toxic effects

4.2.1 *Humans*

In a cohort of workers exposed to various concentrations of 1,4-dioxane at the workplace (0.02–47.8 mg/m^3), Thiess *et al*. (1976) observed no clinical effects or changes in mortality related to the exposure.

4.2.2 *Experimental systems*

In a study by Kociba *et al*. (1974), rats of each sex received 0.01, 0.1 or 1% 1,4-dioxane in the drinking-water for up to 716 days. At 16 months, about 50% of the 1% dose group survived. Histopathological examination of the animals revealed degenerative and necrotic alterations in the liver parenchyma and in renal tubules. These changes were observed to a lower extent in the 0.1% dose group. No increased DNA repair was found in the liver or in nasoturbinate or maxilloturbinate nasal epithelial cells isolated from male Fischer 344 rats receiving 2% or 1% 1,4-dioxane in the drinking-water. The dose of 1% 1,4-dioxane in the drinking-water for five days did not increase relative liver weight or hepatic palmitoyl coenzyme A-reductase activity (Goldsworthy *et al*., 1991). While a single dose of 1000 mg/kg bw 1,4-dioxane given by gavage did not enhance hepatic DNA synthesis, administration in the drinking-water for two weeks led to an approximately two-fold increase in the hepatic labelling index. Similarly, Stott *et al*. (1981) reported a 1.5-fold increase in hepatic DNA synthesis, and a minimal centrilobular hepatocellular swelling in male Sprague-Dawley rats given 1000 mg/kg bw 1,4-dioxane daily by gavage over 11 weeks; the relative liver weight was enhanced in these animals, while gavage of 10 mg/kg bw did not result in such effects in the liver. In female Sprague-Dawley rats treated orally with 850, 2550 or 4200 mg/kg bw 1,4-dioxane, 21 and 4 h before killing, Kitchin and Brown (1990) found a marked increase in hepatic ornithine decarboxylase activity, whereas alanine aminotransferase activity and the level of reduced glutathione in the liver were unchanged. Doses of 2550 and 4200 mg/kg bw resulted in significant induction of total hepatic cytochrome P450.

4.3 Reproductive and developmental effects

4.3.1 *Humans*

No data were available to the Working Group.

4.3.2 *Experimental systems*

In Sprague-Dawley rats administered 1,4-dioxane by gavage (0, 0.25, 0.5 and 1 mL/kg bw per day) on days 6–15 of gestation, no effect on implantation number, number of live fetuses, postimplantation loss or the rate of malformations was found (Giavini *et al*., 1985). At 1 mL/kg bw per day, embryotoxicity and slight maternal toxicity, manifested by reduced weight gain, were observed.

4.4 Genetic and related effects

The toxicity (including genotoxicity) of 1,4-dioxane has been reviewed (DeRosa *et al*., 1996).

4.4.1 *Humans*

In lymphocytes obtained from six workers employed in 1,4-dioxane production and exposed to unspecified airborne levels of the compound for 6–15 years, no increase in chromosomal aberrations was found relative to that observed in an equal number of controls (Thiess *et al.*, 1996).

4.4.2 *Experimental systems* (see Table 1 for references)

1,4-Dioxane with or without metabolic activation did not induce differential DNA repair in *Escherichia coli* K-12 *uvrB/rec A* and was not mutagenic in *Salmonella typhimurium* or in L5178Y mouse lymphoma cells. In Chinese hamster ovary CHO cells, it did not cause chromosomal aberrations, although it did cause a slight increase in sister chromatid exchange in the absence of metabolic activation. It has also been reported to cause morphological transformation of BALB/c 3T3 mouse cells.

Oral administration of 1,4-dioxane to rats caused DNA strand breaks in liver cells. However, no covalent DNA binding was detected in rat liver. No induction of unscheduled DNA synthesis was observed in rat hepatocytes after either in-vivo treatment or in-vitro cell treatment with 1,4-dioxane, even when the animals had previously been exposed to 1% 1,4-dioxane for one week. In the same study, no induction of unscheduled DNA synthesis in rat nasal epithelial cells was observed.

Of three studies on the induction of bone-marrow micronuclei, one was negative for male C57BL/6 and CBA mice, one was inconclusive for male B6C3F_1 mice, while the third gave a clear positive result for male and female C57BL/6 mice and a negative result for male BALB/c mice, suggesting overall possible weak, strain-specific clastogenic activity.

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Exposure to 1,4-dioxane may occur during its manufacture and its use as a solvent in a wide range of organic products. It has been detected in ambient air.

5.2 Human carcinogenicity data

Deaths from cancer were not elevated in a single, small prospective study of workers exposed to low concentrations of dioxane.

5.3 Animal carcinogenicity data

1,4-Dioxane was tested for carcinogenicity by oral administration in mice, rats and guinea-pigs. It produced an increased incidence of hepatocellular adenomas and

Table 1. Genetic and related effects of 1,4-dioxane

Test system	Result[a]		Dose (LED or HID)[b]	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
ERD, *Escherichia coli* K12 *uvrB/recA* strains, differential toxicity	–	–	101315	Hellmér & Bolcsfoldi (1992)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	51500	Stott *et al*. (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	5000	Haworth *et al*. (1983)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	NG	Khudoley *et al*. (1987)
SA3, *Salmonella typhimurium* TA1530, reverse mutation	–	–	NG	Khudoley *et al*. (1987)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	51500	Stott *et al*. (1981)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	5000	Haworth *et al*. (1983)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	NG	Khudoley *et al*. (1987)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	51500	Stott *et al*. (1981)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	5000	Haworth *et al*. (1983)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	NG	Khudoley *et al*. (1987)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	51500	Stott *et al*. (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	51500	Stott *et al*. (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	5000	Haworth *et al*. (1983)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	NG	Khudoley *et al*. (1987)
SCN, *Saccharomyces cerevisiae* D61M, aneuploidy	–	NT	4.75% in air	Zimmermann *et al*. (1985)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations	–		35000 ppm feed	Yoon *et al*. (1985)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations	–		50000 ppm inj	Yoon *et al*. (1985)

Table 1 (contd)

Test system	Result[a]		Dose (LED or HID)[b]	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
DIA, DNA strand breaks, cross-links or related damage, rat hepatocytes *in vitro*	+	NT	26.4	Sina *et al*. (1983)
URP, Unscheduled DNA synthesis, rat primary hepatocytes *in vitro*	–[c]		88	Goldsworthy *et al*. (1991)
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus *in vitro*	–	–	5000	McGregor *et al*. (1991)
SIC, Sister chromatid exchange, Chinese hamster ovary CHO cells *in vitro*	(+)	–	10520	Galloway *et al*. (1987)
CIC, Chromosomal aberrations, Chinese hamster ovary CHO cells *in vitro*	–	–	10520	Galloway *et al*. (1987)
TBM, Cell transformation, BALB/c 3T3 mouse cells	+	NT	2000	Sheu *et al*. (1988)
DVA, DNA strand breaks, Sprague-Dawley rat liver cells *in vivo*	+		2550 po × 1	Kitchin & Brown (1990)
UPR, Unscheduled DNA synthesis, male Sprague-Dawley rat hepatocytes *in vivo*	–		1000 po × 1	Goldsworthy *et al*. (1991)
UVR, Unscheduled DNA synthesis, male Fischer 344 rat nasal epithelial cells *in vivo*	–[c]		1000 po × 1	Goldsworthy *et al*. (1991)
MVM, Micronucleus test, male and female C57BL/6 mouse bone-marrow cells *in vivo*	+		900 po × 1	Mirkova (1994)
MVM, Micronucleus test, male BALB/c mouse bone-marrow cells *in vivo*	–		5000 po × 1	Mirkova (1994)
MVM, Micronucleus test, male $B6C3F_1$ mouse bone-marrow cells *in vivo*	?		2000 ip × 3	McFee *et al*. (1994)

Table 1 (contd)

Test system	Result[a]		Dose (LED or HID)[b]	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
MVM, Micronucleus test, male C57BL/6 mouse bone-marrow cells *in vivo*	–		3600 po × 1	Tinwell & Ashby (1994)
MVM, Micronucleus test, male CBA mouse bone-marrow cells *in vivo*	–		1800 po × 1	Tinwell & Ashby (1994)
BVD, Binding (covalent) to DNA, rat liver cells *in vivo*	–		1000 po × 1	Stott *et al*. (1981)

[a] +, positive; (+), weak positive; –, negative; NT, not tested; ?, inconclusive

[b] LED, lowest effective dose; HID, highest ineffective dose; in-vitro tests, µg/mL; in-vivo tests, mg/kg bw/day; NG, not given; inj, injection; po, oral; ip, intraperitoneal

[c] With or without pretreatment with 1% dioxane in drinking-water for one week

carcinomas in mice, tumours of the nasal cavity, liver subcutaneous tissues, mammary gland and peritoneal mesotheliomas in rats and tumours of the liver and gall-bladder in guinea-pigs. No increase in tumours was seen in rats following inhalation exposure. In the mouse-lung adenoma assay, intraperitoneal injection of 1,4-dioxane increased the incidence of lung tumours in males; no such effect was seen following oral administration. In a two-stage liver foci assay in rats, 1,4-dioxane showed promoting activity.

5.4 Other relevant data

1,4-Dioxane is rapidly absorbed upon inhalation or after oral administration, but its penetration of skin is poor. The major metabolite is β-hydroxyethoxyacetic acid, which is rapidly excreted. In rats, the elimination of 1,4-dioxane and its metabolites is progressively delayed as doses are increased, indicating saturation of metabolism.

No clinical signs or changes in mortality were found in a cohort of exposed workers. In rats, 1,4-dioxane produces degenerative and necrotic changes in liver and renal tubules. High doses can significantly increase the total hepatic cytochrome P450 content.

No reproductive effects of 1,4-dioxane exposure of rats have been reported.

Most of the broad of tests for genotoxic activity have produced negative results, but positive results were obtained in a cell transformation assay and conflicting results were obtained in mouse bone-marrow cell tests for micronucleus induction.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of 1,4-dioxane.

There is *sufficient evidence* in experimental animals for the carcinogenicity of 1,4-dioxane.

Overall evaluation

1,4-Dioxane is *possibly carcinogenic to humans (Group 2B)*.

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