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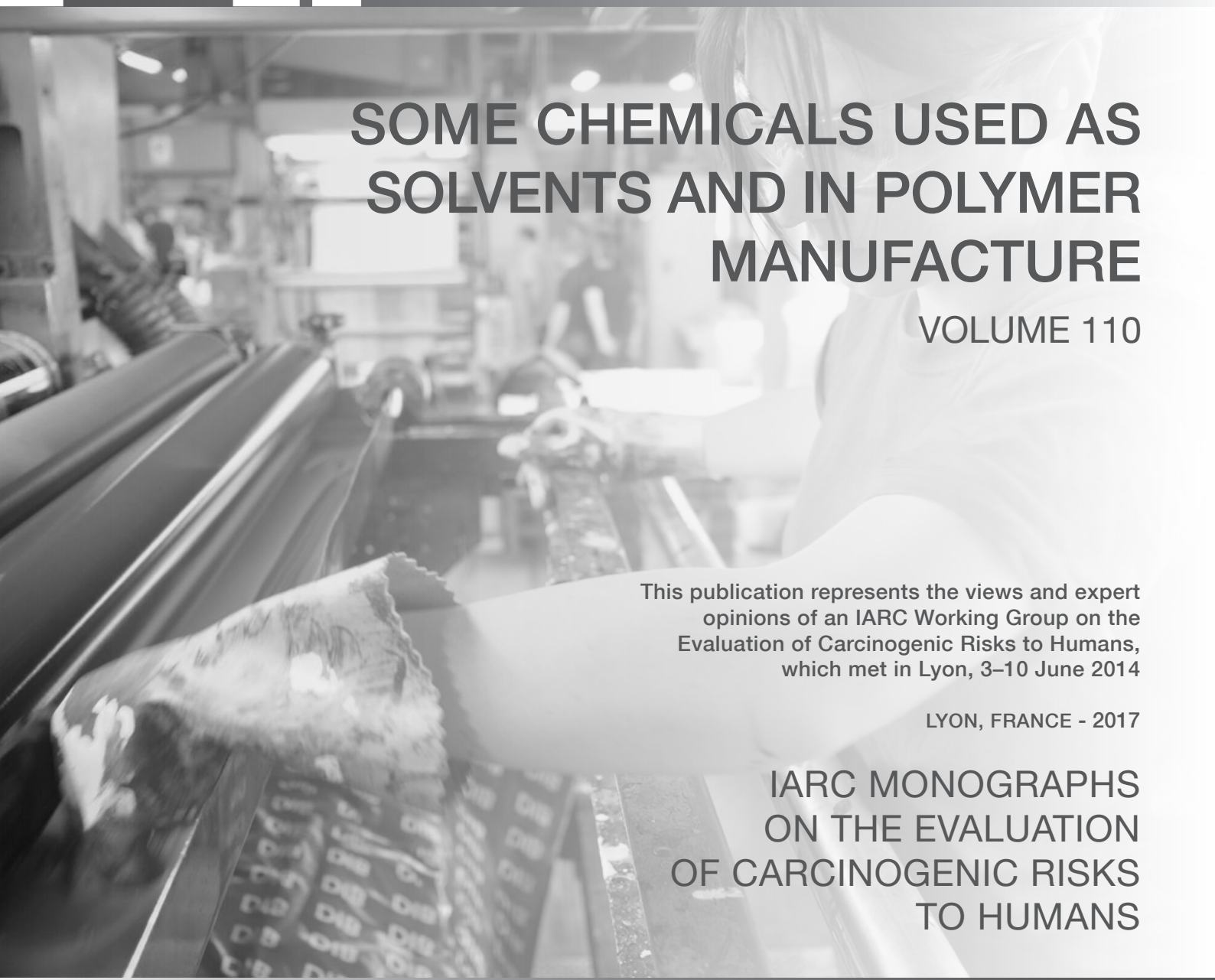

SOME CHEMICALS USED AS SOLVENTS AND IN POLYMER MANUFACTURE

VOLUME 110

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International Agency for Research on Cancer

World Health Organization

1,3-PROPANE SULTONE

1,3-Propane sultone was reviewed previously by the Working Group in 1973, 1987, and 1998 (IARC, 1974, 1987, 1999). New data have since become available, and these have been incorporated, and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Identification of the agent

1.1.1 Nomenclature

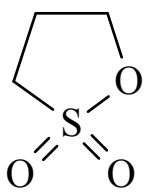
Chem. Abstr. Serv. Reg. No.: 1120-71-4

Chem. Abstr. Serv. Name: 1,2-Oxathiolane, 2,2-dioxide

IUPAC Systematic Name: Oxathiolane 2,2-dioxide

Synonyms: 3-Hydroxy-1-propanesulfonic acid sultone; 3-hydroxythietane-1,1-dioxide; 1,2-oxathiolane 2,2-dioxide; 1-propanesulfonic acid-3-hydroxy-gamma-sultone; propane sultone; propanesultone

1.1.2 Structural and molecular formulae, and relative molecular mass



Molecular formula: $C_3H_6O_3S$

Relative molecular mass: 122.14

1.1.3 Chemical and physical properties of the pure substance

Description: White crystalline solid or colourless liquid; foul odour above 31 °C (HSDB, 2014)

Boiling point: 180 °C at 40 HPa (30 mmHg) (Sigma-Aldrich, 2012)

Melting point: 30–33 °C (Sigma-Aldrich, 2012)

Specific gravity: 1.392 at 25 °C (Sigma-Aldrich, 2012)

Solubility: Readily soluble in ketones, esters and aromatic hydrocarbons; soluble in water (100 g/L) (HSDB, 2014); insoluble in aliphatic hydrocarbons (IARC, 1974)

Volatility: Vapour pressure, 0.27 mmHg at 25 °C; vapour density relative to air, 4.2 (NTP, 2011)

Stability: Hydrolyses to 3-hydroxy-1-propanesulfonic acid (IARC, 1974)

Octanol/water partition coefficient: log $k_{ow,}$ −0.28 (NTP, 2011)

Conversion factor: Assuming normal temperature (25 °C) and pressure (101 kPa), 1 mg/m^3 = 4.99 ppm, calculated from: mg/m^3 = (relative molecular mass/24.45) × ppm.

1.1.4 Technical products and impurities

One commercial-grade formulation of 1,3-propane sultone was reported to contain 99% active ingredient, 0.2% water, and 0.8% acid (as 3-hydroxy-1-propanesulfonic acid) (IARC, 1974).

1.1.5 Analysis

Two methods have been described for the determination of 1,3-propane sultone in workplace air. In the first, 1,3-propane sultone is preconcentrated from air in a wash bottle containing methyl-isobutylketone as absorbent. 1,3-Propane sultone is then determined by gas chromatography with sulfur selective detection. Alternatively, 1,3-propane sultone is collected by drawing air through an impinger, the inner wall of which being coated with 2-mercaptobenzothiazole (sodium salt) as a sink. In this way, 1,3-propane sultone is preconcentrated in the form of the sodium salt of 2-mercaptobenzothiazole-*S*-propanesulfonic acid, which is extracted by high-perfomance liquid chromatography (HPLC) with ultraviolet detection (Oldeweme & Klockow, 1986; Royal Society of Chemistry, 1989).

The United States Environmental Protection Agency (EPA) has developed a method (EPA-TO-15) for the analysis of a wide range of volatile organic compounds in air, including 1,3-propane sultone. The method involves sampling air, by vacuum or pumping, into an evacuated canister, which has a passivated, chemically inert inner surface. A known volume of sample is then directed from the canister through a solid multisorbent concentrator, where the analyte is concentrated before analysis by thermal desorption and analysis by gas chromatography/mass spectrometry (EPA, 1999).

1.2 Production and use

1.2.1 Production

1,3-Propane sultone can be produced commercially by dehydrating gamma-hydroxypropanesulfonic acid, which is prepared from sodium hydroxypropanesulfonate. This sodium salt can be prepared by the addition of sodium bisulfite to allyl alcohol (Li et al., 2013).

1,3-Propane sultone was produced in Germany and in the USA in the 1950s and 1960s (IARC, 1974). In 1974, the only producer of 1,3-propane sultone in the USA manufactured less than 500 kg annually (IARC, 1974). In 2009, 1,3-propane sultone was produced by one manufacturer each in Europe and China, and was available from 28 suppliers, including 13 suppliers in the USA (NTP, 2011). Reports filed in 1986, 1990, and 2002 under the Toxic Substances Control Act Inventory Update Rule of the EPA indicated that production plus imports of 1,3-propane sultone in the USA totalled 10 000 to 500 000 lb [~4.5 to 227 tonnes] (NTP, 2011).

1.2.2 Use

1,3-Propane sultone has been used as an intermediate to introduce the propylsulfonate group into molecules, and to confer water solubility and an anionic character (IARC, 1999).

Although the industrial use of 1,3-propane sultone was largely discontinued in the 1960s (Bolt & Golka, 2012), the compound has more recently been used for the manufacture of products for the galvanotechnical and photographic industry (Oldeweme & Klockow, 1986), and also for chemical synthesis in the laboratory (Geddes, 2000; Kirschner & Green, 2005; Smith & Zharov, 2008; Kumar et al., 2012).

A recent patent cites use of 1,3-propane sultone in the preparation of a pharmaceutical intermediate (Wei et al., 2012). 1,3-Propane sultone has also been proposed as an electrolyte additive to improve cyclability safety of lithium

ion batteries (Park et al., 2009; Han et al., 2012). It has also been used in the preparation of hydroxyl sulfonate surfactants for use in enhanced oil recovery, both in micellar polymer flooding and in foam treatment (Rist & Carlsen, 2005). 1,3-Propane sultone has been used to prepare ultrathin antifouling coatings with stable surface zwitterionic functionality (Yang & Gleason, 2012).

1,3-Propane sultone has been used as a chemical intermediate in the production of fungicides, insecticides, cation-exchange resins, dyes, vulcanization accelerators, and variety of other chemicals (IARC, 1999).

In the European Union, under the Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) regulations, 1,3-propane sultone is registered for use as an additive for electrolysis, manufacture of fine chemicals, manufacture of bulk, large-scale chemicals, and formulations of preparations, substances, and mixtures (ECHA, 2015). 1,3-Propane sultone is also registered for the following uses at industrial sites: (a) as a transported isolated intermediate: 1,3-propane sultone is used as a pre-product in the manufacture of aqueous polyurethane dispersions, and of light-sensitive dyes for photographic and radiographic films; (b) as an onsite isolated intermediate: 1,3-propane sultone is used to manufacture sulfopropylated substances by complete conversion with amines, mercaptanes, alcoholates, and carboxylates; (c) in scientific research and development; and (d) in the manufacture of batteries and accumulators.

The only permitted consumer use of 1,3-propane sultone in Europe is in sealed batteries, where use does not infringe the restriction for use by non-professionals since batteries are articles with no intended release of the substance and not covered by the REACH regulations (ECHA, 2015).

1.3 Occurrence and exposure

1.3.1 Environmental occurrence

(a) Natural occurrence

1,3-Propane sultone is not known to occur naturally.

(b) Air, water, soil, or food

No data were available on levels of 1,3-propane sultone in air, water, soil, or food.

In moist air, 1,3-propane sultone will hydrolyse to form 3-hydroxy,1-propane sulfonic acid. In the atmosphere, it will react with photochemically produced hydroxyl radicals (half-life, 8 days) (NTP, 2011).

In water or a moist environment, 1,3-propane sultone will also rapidly hydrolyse to 3-hydroxy-1-propanesulfonic acid. 1,3-Propane sultone may occur in the waste streams of industrial facilities where it is manufactured or used, but is not expected to persist for long periods of time (IARC, 1974).

1.3.2 Occupational exposure

There are few data available on occupational exposure to 1,3-propane sultone. An exposure study of 1,3-propane sultone from 1972 by the Government of Japan shows a low level of exposure. Out of two reported companies with six types of jobs and 85 workers, 8-hour time-weighted average (TWA) exposure was less than 0.007 mg/m^3. In 2008, the Government of Japan required companies using ≥ 500 kg of 1,3-propane sultone to report the amount used and job types involved (MHLW, 2010).

The routes of potential human exposure to 1,3-propane sultone are ingestion, inhalation, and dermal contact (NTP, 2011). Workers involved in the formulation of compounds made from 1,3-propane sultone or the production of its end products are at the greatest risk of potential exposure (IARC, 1974).

1.3.3 Exposure of the general population

There were no data available on levels of exposure to 1,3-propane sultone in humans.

The Toxic Chemical Release Inventory of the EPA reported that 332 lbs [~150 kg] of 1,3-propane sultone was released to the environment in the USA in 2012 (TRI-Explorer, 2012).

1.4 Regulations and guidelines

The American Conference of Governmental Industrial Hygienists has recommended that occupational exposure by all routes to 1,3-propane sultone be carefully controlled to levels that are as low as possible (ACGIH, 2001).

The United States National Institute of Occupational Safety and Health has recommended that occupational exposures to 1,3-propane sultone be limited to the lowest feasible concentration (NIOSH, 2005).

In Ontario, Canada, under Regulation 833, occupational exposure by all routes to 1,3-propane sultone in the workplace is required to be carefully controlled to levels as low as possible (Ontario Ministry of Labor, 2013). There were no published limit values for 1,3 propane sultone in countries of the European Union, or elsewhere in the world.

The Scientific Committee on Occupational Exposure limits (SCOEL) of the European Commission has categorized 1,3-propane sultone in SCOEL Group A, as a genotoxic carcinogen without a threshold. Therefore, a health-based occupational exposure limit cannot be deduced. For humans, any contact with 1,3-propane sultone is to be avoided. Dermal absorption can contribute substantially to concern regarding health effects. Therefore, a skin notation is warranted (SCOEL, 2013).

In Japan, the Industrial Safety and Health Act requires enclosure systems during manufacturing, use, and waste treatment, as well as appropriate personal protective equipment to avoid skin contact; no exposure limit values have been established (MHLW, 2011).

2. Cancer in Humans

Only one study of cancer in humans exposed to 1,3 propane sultone was available to the Working Group. Bolt & Golka (2012) describe the occurrence of cancer among 55 employees at a factory in Germany that manufactured 1,3-propane sultone in 1952–1963; the last stocks were used as of 1977. A list of exposed workers was registered in 2007 as required by law, and those who developed cancer were eligible for compensation. As of 2010, cancer had been observed in 20 of the exposed workers. Among the 24 tumours reported were several rare cancers, including one cancer of the duodenum, and one malignant Schwannoma (a peripheral nerve sheath tumour, also known as neurosarcoma). The reported tumours included two glioblastomas (cancers of the brain were previously reported in experimental animals exposed to 1,3 propane sultone). Two cancers of skin (one basal cell, the other type unspecified) were also observed. No data on the expected numbers of all cancers were presented. [Without comparative data on the number of cancers expected, it is difficult to interpret the findings of this study, which is essentially a case series among an exposed population.]

3. Cancer in Experimental Animals

The carcinogenicity of 1,3-propane sultone in experimental animals was previously reviewed by the Working Group (IARC, 1999).

3.1 Mouse

1,3-Propane sultone was tested for carcinogenicity in one study in male and female mice treated by skin application, and in one study in female mice treated by subcutaneous injection.

See Table 3.1

Table 3.1 Studies of carcinogenicity with 1,3-propane sultone in mice

Strain (sex) Duration Reference	Dosing regimen, Animals/group at start	Incidence of tumours	Significance	Comments
Skin application				
CF1 (M) ≥ 78 wk Doak et al. (1976)	Single dose of toluene, single dose of 1,3-propane sultone 2.5% w/v in toluene, 10 doses of 2.5% w/v in toluene every other day, single dose of 25% w/v in toluene. Painted on shaved back skin, then observed for ≥ 78 wk 48 mice/group	*Skin tumours* 0/48, 0/48, 3/48 (6%), 29/36 (80%)* Benign: 0/48, 0/48, 1/48 (2%), 13/36 (36%)* Malignant: 0/48, 0/48, 2/48 (4%), 16/36 (44%)* *Systemic tumours* 29/48 (60%), 34/48 (71%), 47/48 (98%)*, 28/36 (78%) Lymphoreticular: 4/48 (8%), 10/48 (21%), 22/48 (46%)*, 12/36 (33%) Lung: 23/48 (48%), 27/48 (56%), 34/48 (71%), 24/36 (67%)	*[$P < 0.05$]	Purity, > 99.9% Most skin tumours were epidermal, but C3H mice developed mainly fibrosarcomas Systemic tumours were lymphoreticular, lung, mammary gland, uterine, and other sites
CF1 (F) ≥ 78 wk Doak et al. (1976)	Single dose of toluene, single dose of 1,3-propane sultone at 2.5% w/v in toluene, 10 doses of 2.5% w/v in toluene every other day, single dose of 25% w/v in toluene. Painted on shaved back skin then observed for ≥ 78 wk 48 mice/group	*Skin tumours* 0/48, 1/48 (2%), 2/48 (4%), 26/46 (56%)* Benign: 0/48, 0/48, 2/48 (4%), 18/46 (39%)* Malignant: 0/48, 1/48 (2%), 0/48, 8/46 (17%)* *Systemic tumours* 29/48 (60%), 42/48 (87%)*, 48/48 (100%)*, 36/46 (78%) Lymphoreticular: 9/48 (19%), 13/48 (27%), 36/48 (75%)*, 20/46 (43%) Lung: 17/48 (35%), 25/48 (52%), 32/48 (67%)*, 26/46 (56%)	*[$P < 0.05$]	Purity, > 99.9% Most skin tumours were epidermal, but C3H mice developed mainly fibrosarcomas Systemic tumours were lymphoreticular, lung, mammary gland, uterine, and other sites
CF1 (M) 56 wk Doak et al. (1976)	0 or 2.5% 1,3-propane sultone w/v in benzene painted on shaved back skin, 2 × per wk for 4 wk, then in toluene painted on shaved back skin, 2 × per wk for 52 wk 25 mice/group	*Skin tumours* 0/22, 15/21 (71%)* Benign: 0/22, 6/21 (28%)* Malignant: 0/22, 9/21 (43%)* *Systemic tumours* 7/22 (32%), 18/21 (86%)* Lymphoreticular: 0/22, 12/21 (57%)* Lung: 4/22 (18%), 9/21 (43%)	*[$P < 0.05$]	Purity, > 99.9% Most skin tumours were epidermal, but C3H mice developed mainly fibrosarcomas Systemic tumours were lymphoreticular, lung, mammary gland, uterine, and other sites

Table 3.1 (continued)

Strain (sex) Duration Reference	Dosing regimen, Animals/group at start	Incidence of tumours	Significance	Comments
CF1 (F) 56 wk Doak et al. (1976)	0 or 2.5% 1,3-propane sultone w/v in benzene painted on shaved back skin 2 × per wk for 4 wk, then in toluene painted on shaved back skin 2 × per wk for 52 wk 21–25 mice/group	*Skin tumours* 0/25, 3/24 (12%) Benign: 0/25, 3/24 (12%) Malignant: 0/25, 0/24 *Systemic tumours* 7/25 (28%), 18/24 (75%)* Lymphoreticular: 3/25 (12%), 17/24 (71%)* Lung: 4/25 (16%), 2/24 (8%) Uterine or mammary gland (combined): 1/25 (4%), 2/24 (8%)	*[$P < 0.05$]	Purity, > 99.9% Most skin tumours were epidermal, but C3H mice developed mainly fibrosarcomas Systemic tumours were lymphoreticular, lung, mammary gland, uterine, and other sites
C3H (M) 56 wk Doak et al. (1976)	0 or 2.5% 1,3-propane sultone w/v in benzene painted on shaved back skin 2 × per wk for 4 wk, then in toluene painted on shaved back skin 2 × per wk for 52 wk 25 mice/group	*Skin tumours* 0/25, 20/22 (91%)* Benign: 0/25, 2/22 (9%) Malignant: 0/25, 18/22 (82%)* *Systemic tumours* 13/25 (52%), 18/22 (82%) Lymphoreticular: 1/25 (4%), 2/22 (9%) Lung: 0/25, 5/22 (23%)*	*[$P < 0.05$]	Purity, > 99.9% Most skin tumours were epidermal, but C3H mice developed mainly fibrosarcomas Systemic tumours were lymphoreticular, lung, mammary gland, uterine, and other sites
C3H (F) 56 wk Doak et al. (1976)	0 or 2.5% 1,3-propane sultone w/v in benzene painted on shaved back skin 2 × per wk for 4 wk, then in toluene painted on shaved back skin 2 × per wk for 52 wk 25 mice/group	*Skin tumours* 0/21, 6/25 (24%)* Benign: 0/21, 2/25 (8%) Malignant: 0/21, 4/25 (16%) *Systemic tumours* 4/21 (19%), 17/25 (68%)* Lymphoreticular: 0/21, 2/25 (8%) Lung: 0/21, 1/25 (4%) Uterine or mammary gland (combined): 2/21 (9%), 18/25 (72%)*	*[$P < 0.05$]	Purity, > 99.9% Most skin tumours were epidermal, but C3H mice developed mainly fibrosarcomas Systemic tumours were lymphoreticular, lung, mammary gland, uterine, and other sites
CBah (Hairless strain) (M) 56 wk Doak et al. (1976)	0 or 2.5% 1,3-propane sultone w/v in benzene painted on shaved back skin 2 × per wk for 4 wk, then in toluene painted on shaved back skin 2 × per wk for 52 wk 25 mice/group	*Skin tumours* 0/24, 20/23 (87%)* Benign: 0/24, 2/23 (9%) Malignant: 0/24, 18/23 (78%)* *Systemic tumours* 2/24 (8%), 3/23 (13%) Lymphoreticular: 0/24, 2/23 (9%) Lung: 0/24, 0/23	*[$P < 0.05$]	Purity, > 99.9% Most skin tumours were epidermal, but C3H mice developed mainly fibrosarcomas Systemic tumours were lymphoreticular, lung, mammary gland, uterine, and other sites

Table 3.1 (continued)

Strain (sex) Duration Reference	Dosing regimen, Animals/group at start	Incidence of tumours	Significance	Comments
CBah (Hairless strain) (F) 56 wk Doak et al. (1976)	0 or 2.5% 1,3-propane sultone w/v in benzene painted on shaved back skin 2 × per wk for 4 wk, then in toluene painted on shaved back skin 2 × per wk for 52 wk 25 mice/group	*Skin tumours* 0/25, 18/25 (72%)* Benign: 0/25, 3/25 (12%) Malignant: 0/25, 15/25 (60%)* *Systemic tumours* 1/25 (4%), 6/25 (24%)* Lymphoreticular: 0/25, 2/25 (8%) Lung: 0/25, 0/25 Uterine or mammary gland (combined): 0/25, 5/25 (20%)*	*[$P < 0.05$]	Purity, > 99.9% Most skin tumours were epidermal, but C3H mice developed mainly fibrosarcomas Systemic tumours were lymphoreticular, lung, mammary gland, uterine, and other sites
Subcutaneous injection				
ICR/Ha Swiss (F) 63 wk Van Duuren et al. (1971)	1,3-Propane sultone at 0, 0.3 mg/0.05 mL in distilled water injected into the left flank 1 × per wk 30 mice/group	*Injection-site tumours* 0/30, 21/30 (70%)* Fibrosarcoma: 0/30, 7/30 (23%)* Epithelial tumours: 0/30, 9/30 (30%)*	*[$P \leq 0.01$]	Purity, 91% Injection-site tumours were: 1 papilloma, 7 adenoacanthomas, 1 undifferentiated carcinoma, 2 spindle cell sarcomas, 7 fibrosarcomas and 3 adenosarcomas

F, female; M, male; wk, week

3.1.1 Skin application

In a first experiment, groups of 48 male and 48 female CF1 mice (age, 6 weeks) were treated with a single dose of 1,3-propane sultone at 0 (toluene only), 2.5% weight/volume (w/v), or 25% w/v in toluene, or with 10 doses at 2.5% w/v every second day, and observed for up to 78 weeks. For each application, approximately 0.1 mL of the test solution was painted on the shaved back skin of mice. The incidence of malignant skin tumours of epidermal origin was significantly higher in male and female mice receiving a single dose at 25% w/v. The incidence of lymphoreticular tumours was significantly higher in male and female mice receiving 10 doses at 2.5% w/v. The incidence of tumours of the lung was significantly increased in female mice receiving 10 doses at 2.5% w/v (Doak et al.,1976)

In another experiment, groups of 20–25 male and female CF1, C3H, and hairless CBah Swiss mice (age, 6 weeks) were given 1,3-propane sultone (purity, > 99.9% [measurement method not reported]) at 0 (control) or 2.5% w/v in benzene by skin application, twice per week for 4 weeks. Beginning on week 5, 1,3-propane sultone was applied twice per week for 52 weeks (56 weeks in total) at concentrations of 0 (control) or 2.5% w/v in toluene. For each application, approximately 0.05–0.1 mL of the test solution was painted on the shaved back skin of mice. Benzene was replaced by toluene because of possible hazard to staff at the animal facility.

Most tumours of the skin observed were of epidermal origin in CF1 and CBah mice, while in C3H male mice the predominant tumour type at the painting site was dermal fibrosarcoma. The systemic tumours observed were lymphoreticular, lung, uterine, mammary gland (in females), and other sites In CF1 male mice, the incidences of malignant skin tumours and of lymphoreticular tumours (mainly lymphoreticular cell sarcomas [possibly malignant lymphomas]) were significantly increased. In C3H and CBah male mice, the incidence of malignant skin tumours was significantly increased. In C3H male mice, the incidence of lung tumours was significantly increased. [The Working Group noted that the biological behaviour of the lung tumours (i.e. benign versus malignant) was not indicated.] In female CF1 mice, incidence of lymphoreticular tumours was significantly increased, but the incidence of skin tumours was not. In female C3H mice, the incidence of skin tumours was significantly increased. In female CBah mice, the incidences of uterine or mammary gland tumours (combined) and skin tumours were significantly increased (Doak et al.,1976). [The Working Group noted the unusual grouping of tumours of the uterus and mammary gland.]

3.1.2 Subcutaneous injection

Groups of 30 female ICR/Ha Swiss mice (age, 6–8 weeks) were injected subcutaneously with 1,3-propane sultone (purity, 91%), at a dose of 0.3 mg/0.05 mL in distilled water in the left flank, once per week for 63 weeks. Controls received distilled water only. At 63 weeks, the incidence of benign and malignant tumours (combined) (21 out of 30: 1 papilloma, 7 adenoacanthomas, 1 undifferentiated carcinoma, 2 spindle cell sarcomas, 7 fibrosarcomas, 3 adenosarcomas) at the injection site was significantly increased compared with the control group (0 out of 30). The incidences of fibrosarcoma and epithelial tumours were significantly increased (Van Duuren et al., 1971).

3.2 Rat

1,3-Propane sultone was tested for carcinogenicity in two studies in male and female rats treated by gavage. [The Working Group considered two other studies by Gupta et al. (1981) and Druckrey et al. (1970) to be inadequate for the evaluation of the agent due to the lack of controls.]

See Table 3.2

Table 3.2 Studies of carcinogenicity in rats given 1,3-propane sultone by gavage

Strain (sex) Duration Reference	Dosing regimen, Animals/group at start	Incidence of tumours	Significance[a]	Comments
CD (M) 60–61 wk Ulland et al. (1971)	0, 28 mg/kg bw, 2 × per wk, for 60 wk (lower dose) or 56 mg/kg bw, 2 × per wk, discontinued at wk 32 (higher dose) 26 mice/group	Brain glioma: 0/6, 12/26 (46%)*, 16/26 (61%)**	*$P < 0.01$ **$P < 0.001$	Purity, NR The data for this study may have been included in the study by Weisburger et al. (1981)
CD (F) 60–61 wk Ulland et al. (1971)	0, 28 mg/kg bw, 2 × per wk, for 60 wk (lower dose) or 56 mg/kg bw, 2 × per wk, discontinued at wk 32 (higher dose) 26 mice/group	Brain glioma: 1/6 (17%), 15/26 (58%)*, 13/26 (50%)** Mammary gland: 0/6, 7/26 (27%), 13/26 (50%)*	*[$P < 0.01$] **[$P < 0.05$][a]	Purity, NR The data for this study may have been included in the study by Weisburger et al. (1981)
CD (M) 60 wk Weisburger et al. (1981)	0, 28 mg/kg bw, 2 × per wk for 60 wk (lower dose) or 56 mg/kg bw, 2 × per wk, discontinued at wk 32 (higher dose) 26 mice/group	Cerebrum, malignant glioma: 0/16, 10/26 (38%)*, 11/26 (42%)* Cerebellum, malignant glioma: 1/16 (6%), 6/26 (23%)*, 11/26 (42%)**	*$P < 0.05$	Purity, 91% Gliomas were described as astrocytomas by the authors
CD (F) 60 wk Weisburger et al. (1981)	0, 28 mg/kg bw, 2 × /wk for 60 wk (lower dose) or 56 mg/kg bw, 2 × /wk, discontinued at wk 32 (higher dose) 26 mice/group	Cerebrum, malignant glioma: 0/16, 12/26 (42%)*, 12/26 (42%)* Cerebellum, malignant glioma: 0/16, 8/26 (31%)**, 4/26 (15%) Mammary gland, adenocarcinoma: 0/16, 6/26 (23%)**, 13/26 (50%)*	*$P < 0.01$ **$P < 0.05$	Purity, 91% Gliomas were described as astrocytomas by the authors

[a] Fisher exact test

bw, body weight; F, female; M, male; NR, not reported; wk, week

Oral administration

In a first report, groups of 26 male and 26 female CD rats (age, 6 weeks) were given 1,3-propane sultone at a dose of 28 mg/kg bw by gavage, twice per week, for 60 weeks (lower dose), or 56 mg/kg bw (higher dose), twice per week, for 32 weeks. Control groups of 6 males and 6 females were given water for 61 weeks.

At 60–61 weeks, the incidence of brain glioma was significantly increased in males in the groups at the lower and higher doses. The incidences of tumours of the mammary gland, squamous cell carcinoma of the ear canal, leukaemia, adenocarcinoma of the small intestine, and other tumours were increased, but without statistical significance. In females, the incidence of brain glioma was significantly increased in the groups at the lower and higher doses. The incidence of tumours of the mammary gland was significantly increased in the group at the higher dose. The incidences of squamous cell carcinomas of the ear canal, leukaemia, adenocarcinoma of the small intestine, and other tumours were increased, but without statistical significance (Ulland et al., 1971). [The Working Group noted that the results of this report may also have been included in the report of the study by Weisburger et al. (1981) (see below).]

In a second report, groups of 26 male and 26 female weanling CD rats [specific age not reported] were quarantined for 7–10 days, and given 1,3-propane sultone (purity, 91%) at a dose of 28 mg/kg bw by gavage, twice per week, for 60 weeks (lower dose), or 56 mg/kg bw, twice per week for 32 weeks (higher dose). Two groups of 16 males and 16 females served as matched controls. Weighted mean doses were calculated as 28 mg/kg bw for the group at the lower dose, and 29.9 mg/kg bw for the group at the higher dose.

In males, at 60 weeks, the incidences of cerebrum malignant glioma [described as astrocytoma by the authors] and of cerebellum malignant glioma [described as astrocytoma by the authors] were significantly increased compared with controls at both doses. In females, the incidence of cerebrum malignant glioma was significantly increased at both doses, and the incidence of cerebellum malignant glioma was significantly increased at the lower dose. The incidence of adenocarcinoma of the mammary gland was significantly increased at both doses (Weisburger et al., 1981).

4. Mechanistic and Other Relevant Data

4.1 Toxicokinetic data

No studies were available on the toxicokinetics and metabolism of 1,3-propane sultone. [The Working Group noted that, in view of its chemical reactivity, it may be anticipated that 1,3-propane sultone is hydrolysed within the organism to 3-hydroxy-1-propane sulfonic acid.]

4.2 Genetic and related effects

4.2.1 Humans

No data were available to the Working Group.

4.2.2 Experimental systems

See Table 4.1

(a) In vivo

Groups of Sprague-Dawley rats were given 1,3-propane sultone as a single intravenous injection at a dose of 30.5 mg/kg bw Robbiano & Brambilla (1987). Within 1 hour after dosing, 1,3-propane sultone induced DNA fragmentation in the brain, indicated by increased DNA alkaline-elution rates.

To evaluate a new glycosylphosphatidylinositol *Pig-a* gene mutation assay in rats

Table 4.1 Genetic and related effects of 1,3-propane sultone

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
DNA adducts, *N*-7 alkylation of guanosine and guanine in DNA, acellular system, in vitro	+	NT	24.5	Hemminki (1983)
DNA strand breaks, male Sprague-Dawley rat brain cells, in vivo	+	NA	30.5 iv × 1	Robbiano & Brambilla (1987)
Prophage, *umu* gene induction, SOS repair test, DNA strand breaks, cross-links or related damage	+	NT	16	Nakamura et al. (1987)
Gene mutation (*Pig-a*), male Sprague-Dawley rats, in vivo	+ [d]	NA	12.5 oral × 28 days	Dertinger et al. (2011a, b)
Salmonella typhimurium TA100, or TA1535 reverse mutation	+	NT	5 µg/plate	Simmon (1979a)
Salmonella typhimurium TA100, reverse mutation	+	NT	6	Bartsch et al. (1983)
Salmonella typhimurium TA1535, reverse mutation	+	NT	5 µg/plate	Simmon (1979a)
Salmonella typhimurium TA1536, TA1537, TA1538 or TA98, reverse mutation	–	NT	5 µg/plate	Simmon (1979a)
Saccharomyces cerevisiae, homozygosis by mitotic recombination or gene conversion	+	+	1000	Simmon (1979b)
Hordeum species (barley), mutation	+	NA	611	Kaul & Tandon (1981)
Hordeum species (barley), mutation	+	NA	975	Singh & Kaul (1985)
Hordeum species (barley), chromosomal aberrations	(+)	NA	611	Kaul & Tandon (1981)
Chromosomal aberrations, human lymphocytes, in vitro	+	NT	122	Kaul (1985)
Chromosomal aberrations, Chinese hamster Don lung fibroblasts, in vitro	+	NT	12	Abe & Sasaki (1977)
Chromosomal aberrations, Chinese hamster lung Don cells, in vitro	+	NT	63	Ishidate (1988)
Micronuclei in peripheral blood cells, male Sprague-Dawley rats, in vivo	+	NA	12.5 ip × 1	Torous et al. (2000)
Micronucleated reticulocytes, male Sprague-Dawley rats, in vivo	+ [c]	NA	25 oral × 28 days	Dertinger et al. (2011a, b)
Sister-chromatid exchange, human lymphocytes, in vitro	+	NT	61	Kaul (1985)
Sister-chromatid exchange, Chinese hamster Don lung fibroblasts, in vitro	+	NT	1.2	Abe & Sasaki (1977)
Cell transformation, human newborn foreskin epithelial cells, in vitro	+	NT	7.5	Milo et al. (1981)

Table 4.1 (continued)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Cell transformation, C3H 10T½ CL8 mouse cells, in vitro	(+)	NT	50	Oshiro et al. (1981)
Cell transformation, Syrian hamster embryo cells, clonal assay, in vitro	–	NT	10	Pienta et al. (1977)
Poly(ADP-ribose)polymerase induction, primary human newborn foreskin fibroblasts, in vitro	+	NT	5	Sharma et al. (1994)
Host-mediated assay, *Salmonella typhimurium* TA1530 and TA1538 in Swiss-Webster mice, in vivo (alkaline elution assay)	+	NA	12 im × 1	Simmon (1979a)

[a] +, positive; (+), weak positive; –, negative; NA, not applicable; NT, not tested
[b] LED, lowest effective dose; HID, highest ineffective dose; in-vitro tests, µg/mL; in-vivo tests, mg/kg bw per day; im, intramuscular; ip, intraperitoneal
[c] LED was 20 mg/kg bw per day in a 3-day study
[d] LED was 80 mg/kg bw per day in a 3-day study

in vivo, Dertinger et al. (2011a, b) used 1,3-propane sultone as a positive control. Mutagenicity was assessed in male Sprague-Dawley rats treated with 1,3-propane sultone for 3 (doses: 0, 20, 40, or 80 mg/kg bw per day) or 28 consecutive days (doses: 0, 12.5, 25, or 50 mg/kg bw per day). 1,3-Propane sultone increased the frequencies of *Pig-a* mutation and of micronucleated reticulocytes in both the 3-and 28-day studies in a dose-dependent manner.

Groups of male Sprague-Dawley rats were given a single intraperitoneal dose of 1,3-propane sultone (12.5, 25, or 50 mg/kg bw) as a positive control to test whether modifications to a flow-cytometric scoring procedure for measuring micronucleated reticulocytes could be applied to enumerate micronuclei in rat peripheral blood (Torous et al., 2000). In circulating blood cells isolated from rats exposed to 1,3-propane sultone in vivo, there was a dose-dependent increase in the frequency of micronucleated reticulocytes 24 or 48 hours after dosing.

(b) In vitro

Hemminki (1983) reacted 1,3-propane sultone (200 mM) [24.5 µg/mL] with guanosine or DNA at physiological pH. The main reaction product was *N-7*-alkylated guanosine, accounting for more than 90% of total products. Two minor putative adducts were *N-1* and O^6 alkyl derivatives.

The genotoxicity of 1,3-propane sultone has been previously evaluated by IARC (1999). 1,3-Propane sultone caused DNA damage and mutation in bacterial and mitotic recombination in yeast. It induced mutations and chromosomal aberrations in plant cells. In cultured mammalian cells, 1,3-propane sultone induced chromosomal aberrations (including in human lymphocytes), sister-chromatid exchange (including in human lymphocytes), and cell transformation in all except one study.

In primary human neonatal foreskin fibroblasts exposed to propane sultone, there was a four- to eight-fold induction of poly(ADP-ribose)polymerase (PADPR) activity compared with untreated controls. Poly(ADP)ribosylation is considered to be involved in DNA repair and to represent an early response to DNA damage (Sharma et al., 1994). [The Working Group noted that the given concentration of 41 nM, equivalent to 5 ng/mL, was unusually low.]

(c) Interaction with proteins/histones

1,3-Propane sultone reacts with proteins, as demonstrated for histones (Wagner & Blevins, 1993). In human foreskin fibroblastic cells exposed to 1,3-propane sultone for 3, 12, or 24 hours, electrophoresis of the histone fractions resolved multiple forms of histones H1, H3, and H4. Propane sultone (0.1 mM) induced a broadening of the H2A and H2B bands after a 24-hour exposure, demonstrating histone modification.

4.3 Other effects relevant to carcinogenicity

Ippen & Mathis (1970) reported on cases of "protracted chemical burns" in chemical workers exposed to 1,3-propane sultone by dermal contact.

4.4 Mechanistic considerations

1,3-Propane sultone, as an inner hydroxyalkyl sulfonic acid ester, is a directly alkylating agent and does not require metabolic activation to induce genotoxicity. It reacts with DNA nucleosides and with proteins (Hemminki, 1983; Wagner & Blevins, 1993). Upon hydrolysis, 1,3-propane sultone is likely to be converted to the strongly acidic hydroxyalkyl sulffonic acid. The available data on 1,3-propane sultone demonstrate conclusively that it is a strong direct genotoxicant (Table 4.1). 1,3-Propane sultone has been used as a positive control for a variety of genotoxicity assays (Sharma et al., 1994; Dertinger et al., 2011a, b), indicating that it is widely recognized

as a genotoxic agent. Reactivity of 1,3-propane sultone with histones (Wagner & Blevins, 1993) suggests that additional epigenetic mechanisms may operate.

5. Summary of Data Reported

5.1 Exposure data

1,3-Propane sultone is an alkylating agent that has been produced in small quantities since the 1950s by the dehydration of gamma-hydroxypropanesulfonate. It is used as an intermediate to introduce the propylsulfonate group into molecules, and to confer water solubility and an anionic character. Although the industrial use of 1,3-propane sultone was largely discontinued in the 1960s, it has been used more recently in the manufacture of lithium batteries, and for chemical synthesis in the laboratory. Workers involved in the formulation of compounds made from 1,3-propane sultone are at the greatest risk of potential exposure.

5.2 Human carcinogenicity data

Only one case series among 55 employees at a factory in Germany that manufactured 1,3-propane sultone in 1952–1963 was available to the Working Group. The number of expected cancers was not presented, precluding interpretation of this study.

5.3 Animal carcinogenicity data

There were two studies of carcinogenicity with 1,3-propane sultone in mice: one study in males and females treated by skin application, and one study in females treated by subcutaneous injection. When administered by skin application, 1,3-propane sultone increased the incidences of benign and malignant skin tumours and lymphoreticular (lympho-haematopoietic system) tumours in males and females. When administered by subcutaneous injection, 1,3-propane sultone increased the incidences of fibrosarcoma and epithelial tumours.

There were two reports of studies of oral administration (gavage) in male and female rats. In these reports, 1,3-propane sultone increased the incidence of malignant glioma of the cerebrum and malignant glioma of the cerebellum in male and female rats. 1,3-Propane sultone also increased the incidence of adenocarcinoma of the mammary gland in female rats in one report, and of tumours of the mammary gland in the other report.

5.4 Mechanistic and other relevant data

1,3-Propane sultone is an alkylating agent that reacts directly with DNA and proteins. DNA reactivity is evident in a variety of assays for genotoxicity, including those in experimental animals and with human cells in vitro. A secondary non-genotoxic effect involving interaction with histones may also contribute to carcinogenicity. Because 1,3-propane sultone does not require metabolic activation and reacts directly with DNA and other macromolecules, it is likely that this mechanism operates both in experimental animals and in humans.

Overall, the mechanistic data for 1,3-propane sultone are *strong*, because the genotoxicity and mutagenicity of this compound are very well established, and are consistent across different experimental systems.

6. Evaluation

6.1 Cancer in humans

There is *inadequate evidence* in humans for the carcinogenicity of 1,3-propane sultone.

6.2 Cancer in experimental animals

There is *sufficient evidence* in experimental animals for the carcinogenicity of 1,3-propane sultone.

6.3 Overall evaluation

1,3-Propane sultone is *probably carcinogenic to humans (Group 2A).*

6.4 Rationale

In making this overall evaluation, the Working Group took into account that 1,3-propane sultone is a strong, direct-acting alkylating agent that reacts with DNA and proteins and that, as a result, is genotoxic in virtually all test systems examined, both in vitro and in vivo. Results of studies of cancer in experimental animals are consistent with this mechanism because tumours arose both at the site of exposure and at distant sites. In the absence of adequate data on cancer in humans, the overall evaluation of 1,3-propane sultone was upgraded from *Group 2B* to *Group 2A* on the basis of strong evidence for genotoxicity.

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