Recommendation from the Scientific Committee on Occupational Exposure Limits for 1,3-Propane sultone

SCOEL/SUM/189
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Employment, Social Affairs and Inclusion

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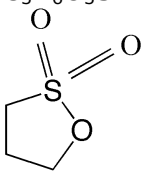
8-hour TWA:	Not feasible to derive a health-based limit (see Recommendation)
STEL (15-min):	Not feasible to derive a health-based limit (see Recommendation)
BLV:	Not feasible to derive a health-based limit (see Recommendation)
Notation:	Skin
Additional categorisation:	SCOEL carcinogen group A (genotoxic carcinogen without threshold)

Criteria documents used: This evaluation is based on DFG 1976, 1985, IARC 1999, and NTP 2011.

1. Substance identification, physico-chemical properties

Chemical name:	1,3-Propane sultone
Synonyms:	1,2-oxathiolane, 2,2-dioxide; 3-hydroxy-1-propane-sulphonic acid gamma-sultone
Molecular formula:	$C_3H_6O_3S$
Structural formula:	
EC No.:	214-317-9
Annex I Index No.:	016-032-00-3
CAS No.:	1120-71-4
Molecular weight:	122.14 g/mol
Boiling point (0.039 bar):	180 °C
Melting point:	31 °C
Vapour pressure (25 °C):	0.27 mm Hg
Specific gravity	1.393
Log K_{ow}	- 0.28
Water solubility (25 °C)	171 g/l
Vapour density (air = 1)	4.2
Conversion factors: (20 °C, 101.3 kPa)	1 ppm = 5.076 mg/m^3 1 mg/m^3 = 0.197 ppm

EU classification:

Carc. 1B	H350	May cause cancer
Acute Tox. 4	H312	Harmful in contact with skin.
Acute Tox. 4	H302	Harmful if swallowed

2. Occurrence/use and occupational exposure

1,3-Propane sultone is used as a chemical intermediate to introduce the sulphopropyl group into molecules and to confer water solubility and an anionic character. It is used as a chemical intermediate in the production of fungicides, insecticides, cation-exchange resins, dyes, vulcanisation accelerators, detergents, lathering agents, bacteriostats, and a variety of other chemicals and as corrosion inhibitor for mild (untempered) steel (IARC 1999, NTP 2011). Occupational exposure may therefore occur upon industrial or laboratory handling of the compound. Potential routes of exposure are ingestion, inhalation and dermal contact (NTP 2011).

3. Health significance

1,3-Propane sultone is a highly reactive alkylating agent. It is acutely toxic, irritating to the skin and highly carcinogenic, both locally and systemically.

3.1. Toxicokinetics

There are no studies into toxicokinetics and metabolism of 1,3-propane sultone (DFG 1976, 1985). In view of its chemical reactivity, it may be anticipated that the compound is hydrolysed to 3-hydroxy-1-propane sulphonic acid. The water-soluble sulphonate could be excreted in the urine.

Hemminki (1983) reacted guanosine and DNA at physiological pH. The main product was the *N*-7-alkyl guanosine, accounting for more than 90 % of total products (Figure 1). Two minor putative adducts were the *N*-1 and O^6 alkyl derivatives. This was seen in conjunction with the direct genotoxicity and carcinogenicity of 1,3-propane sultone.

1,3-Propane sultone is reactive with proteins, as demonstrated for histones (Wagner and Blevins 1993).

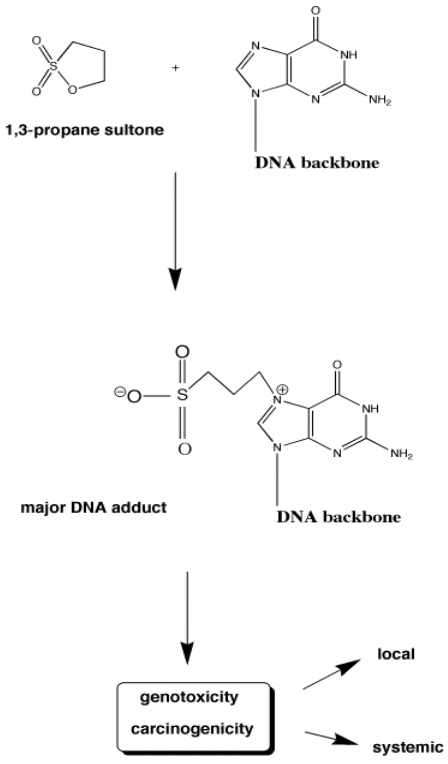


Figure 1. Reactivity of 1,3-propane sultone with guanosine and DNA (Hemminki 1983).

3.2. Acute toxicity

3.2.1. Human data

Data were not available.

3.2.2. Animal data

Inhalation

When rats were exposed for 4 hours to saturated vapour of 1,3-propane sultone, no signs of toxicity were reported (DFG 1976, 1985). [This must be seen in conjunction with the low vapour pressure of the substance.]

Oral

Oral LD_{50} values reported for rats were 157 mg/kg and 350 mg/kg (two different experiments), for mice 500–750 mg/kg (DFG 1976, 1985).

Dermal

A dermal LD_{50} reported for rabbits was 660 mg/kg (DFG 1976).

3.3. Irritation and corrosivity

Owing to its chemical reactivity 1,3-propane sultone is irritating and corrosive to the skin of animals and humans (DFG 1976).

Ippen and Mathies (1970) described cases of caustic "protracted chemical burns" after dermal contact with 1,3-propane sultone. The clinical picture was similar to that after contact with epoxides, notably epichlorohydrine. There may be a latency time of a few hours, during which the clinical picture develops.

3.4. Sensitisation

Although data are scarce, the possibility of skin sensitisation has been noted by DFG (1985).

3.5. Repeated dose toxicity

Because of the very strong carcinogenicity, repeated dose experiments with 1,3-propane sultone were primarily conducted under the aspect of carcinogenicity (see Section 3.7).

3.6. Genotoxicity

3.6.1. In vitro

The genotoxicity of 1,3-propane sultone has been documented and evaluated by IARC (1999). According to this evaluation, 1,3-propane sultone causes DNA damage and mutation in bacteria and induces mitotic recombination in yeast. It induces mutations and chromosomal aberrations in plant cells. In cultured mammalian cells, it induces chromosomal aberrations, sister chromatid exchanges and, according to single studies, cell transformation in C3H 10T½ cells, but not in Syrian hamster embryo cells. DNA strand breaks are induced in brain cells from rats injected with 1,3-propane sultone.

3.6.2. In vivo – human data

There were no human data on genotoxicity of 1,3-propane sultone.

3.6.3. In vivo – animal data

Robbiano and Brambilla (1987) administered a series of genotoxic carcinogens to Sprague-Dawley rats at equimolar doses. The compounds, including 1,3-propane sultone, which were carcinogenic to the brain, induced DNA fragmentation in rat brain, as indicated by increased rates of sister chromatid exchange.

Torous *et al* (2000) applied 1,3-propane sultone intraperitoneally to male Sprague-Dawley rats. In circulating blood cells, there was a dose-dependent increase of micronucleated reticulocytes.

An international collaborative trial was established to systematically investigate a rat *in vivo* Pig-a gene mutation assay (Dertinger *et al* 2011a). In order to evaluate this new method, the mutagenic response was determined of male Sprague Dawley rats treated for 3 or 28 consecutive days with several doses of 1,3-propane sultone. Pig-a mutant frequencies were supplemented with peripheral blood micronucleated reticulocyte counts. 1,3-Propane sultone increased Pig-a mutation and micronucleated reticulocyte frequencies in the 3- and 28-day studies. While the greatest induction of micronucleated reticulocyte counts was observed in the 3-day study, the highest Pig-a responses were found with 28 days of treatment (Dertinger *et al* 2011b).

3.7. Carcinogenicity

3.7.1. Human data

In one chemical company in Germany, 1,3-propane sultone had been manufactured in limited amounts in the 1950s and 1960s, and for a few purposes until the 1970s. The production and use of 1,3-propane sultone was discontinued after recognition of its carcinogenicity in experimental animals. The group of workers handling the compound occupationally comprised 55 persons in total; these persons were later subjected to medical surveillance by the ODIN service for the organisation of post-exposure medical examinations in Germany (Radek 1998). A first review of data from this group (Bolt and Golka 2004) pointed to long tumour latency times and revealed the occurrence of several malignancies at sites similar to those observed in animal experiments. A follow-up revealed that 20 of the 55 persons were diseased with malignancies in 2006 (Bolt and Golka 2012). Again, the types of malignancies were surprisingly consistent with the results from the animal (rodent) studies. As cerebral gliomas were a major type of tumours in animals induced by 1,3-propane sultone experimentally, the occurrence of two glioblastoma cases within the exposed group appeared remarkable. Three intestinal malignancies were recorded within the cases observed; noteworthy was one case of a duodenal carcinoma, normally being a very rare human malignancy. Also a malignant schwannoma that was observed represented an extremely rare human malignancy. Two haematopoietic/lymphatic malignancies were observed. There was 1 case of a renal cell carcinoma and 6 cases of lung cancer. The data were interpreted to provide a clear indication of carcinogenicity of 1,3-propane sultone in humans. A total of 12 cases with various neoplasms were legally compensated within the period of 1985–2010 as having contracted an occupational disease (Berufskrankheit), based on the "opening clause" of § 9 (2) SGB VII of legislation in Germany (Bolt and Golka 2012).

3.7.2. Animal data

(Evaluation of IARC 1999)

Oral administration

Initial range-finding studies in rats pointed to a variety of target sites of carcinogenicity, including mammary gland, brain (glioma) and intestine (Druckrey *et al* 1970, Van Duuren *et al* 1971, Ulland *et al* 1971).

On this basis, 1,3-propane sultone (purity 91 %) was administered orally by gavage to groups of 26 male and 26 female weanling Sprague-Dawley rats at doses of 28 and 56 mg/kg bw per day twice per week for 60 or 32 weeks. The animals were then observed without further dosing up to 60 weeks. Two groups of rats, one consisting of 16 males and 16 females and one of 26 males and 26 females, were used as matched and pooled controls. Survival at 52 weeks among male and female rats, respectively, was 62 % and 39 % in the 28-mg/kg bw group, and 15 % and 23 % in the 56-mg/kg bw group. Administration of the high dose was stopped at week 32 because numerous mammary tumours had developed in the females from week 18 and there was high mortality among the males. Significant increases in the incidence of certain tumours were found. The incidences in the matched control, low-dose and high-dose groups, respectively, were: male rats - malignant glioma (cerebrum), 1/16, 10/26 and 11/26: malignant glioma (cerebellum), 0/16, 6/26 and 11/26; and female rats - malignant glioma (cerebrum), 1/16, 12/26 and 12/26; malignant glioma (cerebellum), 0/16, 8/26 and 4/26; mammary adenocarcinoma, 0/16, 6/26 and 13/26 (Weisburger *et al* 1981, see Table 1).

Subcutaneous administration

Eighty random-bred male albino rats (weighing 70–140 g) were divided into groups of 5 or 10 (no controls) and given 1–7 subcutaneous injections of 1,3-propane sultone at doses of 62, 125 or 166 mg/kg bw. Multiple doses were given at 15-day intervals. Neoplastic lesions varying from well differentiated to anaplastic adenocarcinomas were seen in the lungs of 17/73 rats 21–25 weeks after injection of 1,3-propane sultone (Gupta *et al* 1981). [IARC (1999) noted limited reporting of these data.]

Skin application

Groups of 25 male and 25 female mice of each of three strains (CF1, C3H and CBah, a hairless strain), six weeks of age, were treated twice weekly by painting with approximately 0.05–0.1 ml benzene per mouse for 4 weeks and then toluene for 1 year or with 2.5 % w/v 1,3-propane sultone (purity, 99.9 %) in the same solvents and for the same time; control groups were left untreated. In the control groups, survival at the end of the experiment (58 weeks) was at least 60 %. No CF1 or C3H mice survived exposure to 1,3-propane sultone for 58 weeks and only 12 % of the CBah mice survived to this time. No skin tumours were seen in the untreated or solvent control groups, whereas, in the 1,3-propane sultone-treated groups of male and female mice, respectively, the numbers of tumour-bearing mice were: CF1, 15/21, 3/24; C3H, 20/22, 6/25; CBah, 20/23, 18/25. In addition, there was a higher proportion of CF1 mice with lymphoreticular neoplasms: untreated control males, 1/24, females, 1/23; solvent control males, 0/22, females, 3/25; 1,3-propane sultone-treated males, 12/21, females, 17/24. No significant increase in these neoplasms was seen in either the C3H or the CBah strains of mice (Doak *et al* 1976).

Groups of 48 male and 48 female CF1 mice were painted with either approximately 0.05–0.1 ml per mouse of toluene or 1,3-propane sultone in toluene administered as a single application of 2.5 % or 25 % (w/v), or as 10 applications of a 2.5 % (w/v) solution on alternate days. The experiment was terminated after 78 weeks. No skin tumours were found in the toluene controls of either sex, whereas in the 1,3-propane

Table 1. Oral carcinogenicity bioassay with 1,3-propane sultone in rats (Charles River CD) (Weisburger *et al* 1981).

Daily dose (mg/kg)	Duration (weeks)	Malignancies	Incidences			
			Controls		Treated	
			m	f	m	f
28	60	Malignant glioma, brain	1/26	1/26	10/26	12/26
		Malignant glioma, cerebellum	0/26	0/26	6/26	8/26
		Mammary carcinoma	-	0/26	-	6/26
		Leukaemia	0/26	0/26	0/26	2/26
		Small bowel carcinoma	0/26	0/26	3/26	2/26
56	32	Malignant glioma, brain	1/26	1/26	11/26	12/26
		Malignant glioma, cerebellum	0/26	0/26	11/26	4/26
		Mammary carcinoma	-	0/26	-	13/26
		Leukaemia	0/26	0/26	4/26	3/26
		Small bowel carcinoma	0/26	0/26	3/26	1/26

m= males, f = females.

sultone-treated groups, the numbers of tumour-bearing mice were: single application of 2.5 %, 0/48 males and 1/48 females; 10 applications of 2.5 %, 3/48 males and 2/48 females; single application of 25 %, 29/36 males and 26/46 females (Doak *et al* 1976).

3.8. Reproductive toxicity

There were no data on reproductive toxicity of 1,3-propane sultone.

4. Recommendations

1,3-Propane sultone is an alkylating chemical, which is highly reactive towards DNA and proteins. Owing to its chemical reactivity it is directly mutagenic and carcinogenic. In experimental animals, 1,3-propane sultone induces malignant tumours locally and systemically. Even a single subcutaneous dose of 10 mg/kg elicited local sarcomas in 4/15 rats after a mean latency time of 500 day (Druckrey *et al* 1970). Systemically, target sites for malignancies are the brain, the mammary gland (in females), the intestine, the haematopoietic system and the kidneys (Table 1).

In one chemical company in Germany, 1,3-propane sultone was manufactured in limited amounts in the 1950s and 1960s, and for a few purposes until the 1970s. The production and use was discontinued after recognition of its carcinogenicity in experimental animals. The group having handled the compound occupationally comprised 55 persons in total. A follow-up revealed that 20 out of the 55 persons were diseased with malignancies in 2006. All the experimental tumour sites (except mammary cancer, as there were only males in the cohort) were represented in the German cohort of exposed employees (Section 3.7.1). Taken together, the present data point to carcinogenicity in humans and to an extreme carcinogenic potency of 1,3-propane sultone.

Based on this body of data, 1,3-propane sultone is categorised in the SCOEL Group A of carcinogens, as a genotoxic carcinogen without a threshold. Therefore, a health-based OEL cannot be deduced. Because of the limited quantitative data, a formal quantitative cancer risk assessment cannot be performed. However, it must strictly be enforced that any contact of humans with 1,3-propane sultone is avoided.

When applied locally to the skin, 1,3-propane sultone is irritant and caustic ("chemical burns"). Dermal and oral LD_{50} values are found at a similar order of magnitude (Section 3.2.2), and repeated skin application has led to systemic malignancies (Section 3.7.2). This clearly indicates that dermal absorption can contribute substantially to concern regarding health effects. Therefore, a skin notation is warranted.

There were no data on biological monitoring.

The present Recommendation was adopted by SCOEL 12 June 2013.

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