



EUROPEAN COMMISSION
Employment, Social Affairs and Inclusion DG

Employment and Social Legislation, Social Dialogue
Health, Safety and Hygiene at Work

Luxembourg,
EMPL B3/AMo/zp ARES (2012)

SCOEL Contact Points

Subject: Activities of the Scientific Committee on Occupational Exposure Limits (SCOEL)

Dear Sir or Madam,

In the context of cooperation and transparency concerning the Commission's activities in the establishment of OELs, I send you the provisional SCOEL recommendations on the substances:

SCOEL/SUM/145	- 4-Aminotoluene	CAS: 106-49-0
SCOEL/SUM/189	- 1,3-Propane sultone	CAS: 1120-71-4

The purpose of sending these documents is to allow interested parties to submit additional information, if necessary or to contribute to the scientific discussion. There are four main areas where SCOEL welcomes scientific comments, namely:

- Are there any important or critical published papers that have not been taken into consideration?
- Has any of the scientific data been misinterpreted?
- Is the approach taken consistent with SCOEL's methodology?
- Are you aware of any other relevant information?

I would therefore be grateful to receive any scientific comments or data that you may have on these substances on 20 April 2012 at the latest to:

Employment, Social Affairs and Inclusion DG
Health, Safety and Hygiene at Work
European Commission
Ms. Jill Järnberg – SCOEL Scientific Secretary
Euroforum Building - Room EUFO 2191A
L-2920 LUXEMBOURG

Comments should be addressed directly to: Ms. Jill Järnberg (e-mail: jill.jarberg@ec.europa.eu) with copy to Ms. Zofia Podolan (e-mail: zofia.podolan@ec.europa.eu).

Yours faithfully,

A handwritten signature in black ink, appearing to read 'C. Constantinou', with a stylized flourish at the end.

Costas CONSTANTINOU
Head of Unit

C.c.: SCOEL Members
Members of AC Working Party on Chemicals



Recommendation from the Scientific Committee on Occupational Exposure Limits for 4-Aminotoluene (*p*-toluidine)

*SCOEL/SUM/145
September 2012*

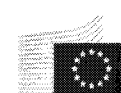


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Recommendation from the Scientific Committee on Occupational Exposure Limits for 4-Aminotoluene (*p*-Toluidine)

8-hour TWA:	1 ppm
STEL (15-min):	2 ppm
Notation:	"Skin"

Substance identification

Chemical name: 4-Aminotoluene

Synonyms: *p*-Toluidine, 4-toluidine, 4-methylaniline, *p*-methylaniline

Molecular formula: C₇H₉N

Structural formula:



EC No.: 203-403-1

Annex I Index No.: 612-160-00-4

CAS No.: 106-49-0 (for *p*-toluidine hydrochloride: 540-23-8)

Molecular formula:

Molecular weight: 107.15

Conversion factor 1 ppm = 4.46 mg/m³;

(20 °C, 101 kPa): 1 mg/m³ = 0.224 ppm

EU classification:

Carc. 2	H351	Suspected of causing cancer
Acute Tox. 3 *	H331	Toxic if inhaled
Acute Tox. 3 *	H311	Toxic in contact with skin
Acute Tox. 3 *	H301	Toxic if swallowed
Eye Irrit. 2	H319	Causes serious eye irritation
Skin Sens. 1	H317	May cause an allergic skin reaction
Aquatic Acute 1	H400	Very toxic to aquatic life

This evaluation is based on Greim (2004), Henschler (1990), ACGIH (2001), ECB (2000), NLM (1991, 2005, 2006), the references cited in these reviews and additional references from a database search performed in 2012.

Physico-chemical properties

4-Aminotoluene (4AT) is a white solid. 4AT has a melting point of 44 °C and a boiling point of 200 °C. The vapour pressure at 20 °C is 0.26 hPa. 4AT is slightly soluble in water (11 g/l at 20 °C and pH = 7) and very soluble in alcohol, ether, acetone, oils and dilute acids. A log P_{ow} of 1.39 is reported. The pK_a is 5.1, the density 1.046 g/cm³ at 20 °C. The substance has a flash point of 87 °C (closed cup) (ACGIH 2001, ECB 2000, NLM 2005).



1. Occurrence/use and occupational exposure

4AT is used as an intermediate in the synthesis of dyes and other organic chemicals, in the preparation of ion exchange resins and as a reagent for the detection of lignin, nitriles and phloroglucinol (ACGIH 2001, NLM 2005).

2. Health significance

2.1. Toxicokinetics

2.1.1. Human data

There were no data available (for limited biological monitoring data, see Section 2.1.3).

2.1.2. Animal data

Data regarding toxicokinetics following inhalation or dermal uptake were not available. The structural analogue 2-aminotoluene (2AT, *o*-toluidine) was demonstrated to rapidly penetrate the human skin *in vitro* (Luersen *et al* 2006).

Quantitative data on oral absorption were not available. Seventy-two hours after oral (gavage) administration of 500 mg/kg ¹⁴C-4AT in male rats, the radioactivity was detectable in all organs with the highest concentrations occurring in fat, liver, skin, kidneys and blood. The lowest concentrations were found in brain, testes, bone marrow and muscle. The level of DNA binding was about 1.2-fold higher for 4AT than for 2-aminotoluene (2AT). Similar, but smaller differences were seen for binding to RNA and protein. The area under the plasma concentration curve for 4AT was about 1.8-fold lower than that for 2AT. Both isomers were eliminated from plasma with a half-life of 12–14 hours (Brock *et al* 1990).

4AT caused a decrease in aryl hydrocarbon hydroxylase activity, aminopyrine demethylase activity and cytochrome P450 content in the liver of Wistar rats after i.p. administration of 75 mg/kg × day on 3 consecutive days. Microsomal epoxide hydrolase and cytosolic GSH-transferase activity were increased. No significant effects were seen in lung and kidneys. 4-Hydroxymethylaniline and 4-aminobenzaldehyde were identified as metabolites of 4AT in microsomal preparations from rabbit liver. Binding of 4AT or its corresponding nitroso metabolite to haemoglobin (Hb) was observed in female rats after oral treatment with 0.6 mmol/kg (64 mg/kg) (Henschler 1990).

2-Amino-5-methylphenol was identified as a urinary metabolite of 4AT in rats. Only small amounts of unchanged 4AT appear in urine. After a single oral administration of 500 mg/kg, excretion amounted to 2.5 % in 24-hour urine of male rats (Cheever *et al* 1980). Similar results were observed in a subchronic study with male rats receiving 40, 80 and 160 mg/kg bw × day with the diet (Jodynis-Liebert and Bennisir 2005, see Section 2.5.2). The excretion of 4AT in 24-hour urine as determined on one day at weeks 1–4 and every second week thereafter showed a dose-dependent increase of the absolute amount and was about 2–6 %, 2.3–4.3 % and 1.3–3.6 % of the administered dose levels (as read from figures). At each dose, there was a tendency for an increase of excretion during the first weeks.

2.1.3. Biological monitoring

4AT was detected in blood and urine of non-occupationally exposed smokers and non-smokers. No differences in urinary 4AT-concentration could be detected between non-



smokers and smokers. The mean level of Hb adducts of 4AT in blood of male cigarette smokers was - depending on the type of tobacco smoked - 50–100 % higher than in that of non-smokers (Henschler 1990). In theory, the induction of methaemoglobin(MHb)emia might be used for biological monitoring. However, this requires a measurement immediately after blood sampling. As the MHb-reductase is active in erythrocytes, measurement results of MHb will change upon sample storage.

2.2. Acute toxicity

2.2.1. Human data

Smyth (1931) noted that toluidine (isomer not specified) causes strangury, haemoglobinuria and anaemia with symptoms similar to aniline poisoning, but with less pronounced methaemoglobinemia. It is also reported, but without supporting details, that 40 ppm toluidines (176 mg/m³, all isomers, no detailed data) will cause severe intoxication within 60 minutes and that 10 ppm (44 mg/m³) may lead to symptoms of illness "if exposure continues for more than a short time" (Goldblatt 1955).

2.2.2. Animal data

Valid data on the inhalation toxicity of 4AT were not available.

For oral administration (no details available), LD₅₀s of 620–794 mg/kg, 330–794 mg/kg and 270 mg/kg are reported for rats, mice or rabbits, respectively. For 4AT × HCl, rat LD₅₀ values of 1 285 mg/kg and 2 951 mg/kg are reported (ECB 2000). An LD₅₀ of 890 mg/kg is reported for dermal application in rabbits (ACGIH 2001).

As with other anilines and similar aromatic amines, methaemoglobinaemia has been observed following administration of 4AT. Oral (gavage) administration of 200 mg/kg caused a MHb level of 21.7 % within one hour in rats; MHb levels of up to 40 % were observed 2–6 h after dermal application of 0.25–1.25 % 4AT (ECB 2000).

The MHb forming ability of a series of aniline derivatives was compared in cats. At single equimolar intravenous doses (0.25 mmol/kg), 4AT caused a mean MHb level of 39.6 % and was by a factor of 2 less potent than aniline (72.3 % MHb) (McLean *et al* 1969). MHb formation was slow in anaesthetised dogs after i.v. administration of 0.77 mmol/kg AT hydrochloride (111 mg/kg) and reached a MHb level of about 13 % after 8 hours (Kiese 1963).

2.3. Irritation and corrosivity

2.3.1. Human data

4AT has an aromatic, wine-like odour (NLM 2005). A value of 0.33 ppm (1.5 mg/m³) is reported as olfactory threshold without any details (Falcy and Malard 2005).

2.3.2. Animal data

No data were available regarding respiratory irritation

Skin

It is reported that 4AT caused no irritation requiring labelling in a standard test according to OECD guideline 404 (ECB 2000).



Eyes

In a standard test according to OECD guideline 405, 4AT was irritating to the eyes of rabbits (ECB 2000).

2.4. Sensitisation

2.4.1. Human data

No data were available regarding sensitisation to 4AT. However, cross-reactivity to 4AT has been observed in epicutaneous tests with patients showing sensitisation to *p*-phenylenediamine (Kleniewska 1975).

2.4.2. Animal data

4AT was tested in an occlusive epicutaneous test with guinea pigs. Induction was carried out with 2 % 4AT in vaseline without adjuvant every second day for a total of four times. For the challenge reaction, 10 animals/group were treated with 0.1, 0.5, 1 and 2 % 4AT in vaseline. Sensitisation (slight erythema) was observed in 0, 4, 6 and 8 of the animals. Further testing revealed cross-reactivity in animals sensitised to *p*-phenylenediamine (Kleniewska and Maibach 1980).

2.5. Repeated dose toxicity

2.5.1. Human data

Methaemoglobinemia has been observed in occupationally exposed workers (Section 2.7).

2.5.2. Animal data

Inhalation

There were no data available.

Oral

In a sub-acute feeding study, 10 male rats/group were fed diets containing 0, 165, 825 or 1 650 ppm 4AT (0, 13.8, 66.8, 125.7 mg/kg/day). There were no mortality and no clinical signs of 4AT poisoning. Body weight gain was reduced at the highest dose and the relative liver weight was increased in mid- and high-dose animals. No gross lesions were observed at necropsy (Industrial Bio-Test Laboratories 1973). In a further study, male rats received 4AT at doses of 0, 40, 80 and 160 mg/kg bw/day in two kinds of diet with 4 % or 14 % fat for 1 or 3 months (Jodynys-Liebert and Bennisir 2005). After 3 months, body weight gain was significantly and markedly lower at the highest dose in both diet groups and at the middle dose in the high-fat group. The MHB level in blood was between 1.2 and 1.5 % in controls and significantly increased at all dose levels in all groups after 1 and 3 months; MHB reached 3.7 and 3.6 % after one and 6.6 % and 4.2 % after 3 months at the lowest dose. In another experiment of the same working group (Malik-Brys and Senczuk 1995), a MHB-level of 7.5 % was reached at the same 4AT doses after 6 months. The concentration of reduced glutathione in the liver significantly increased at all dose levels in all groups after 1 and 3 months. In parallel, hepatic lipid peroxidation increased compared to controls; the increase was lower at the highest dose. Alanine aminotransferase was slightly (< 1.8-fold) increased, especially after 3 months of high-fat diet. 4AT had no effect on blood urea nitrogen (BUN), serum aspartate aminotransferase and sorbitol dehydrogenase. Other parameters were not investigated. No consistent differences between 4AT and 2AT on the assessed parameters were evident except that 2AT but not 4AT caused an increase in BUN. No valid NOAEL can be derived from these



studies, as only selected parameters were investigated and morphology was not included.

Dermal

Liver cell necrosis was observed in rats in a carcinogenicity study with subcutaneous application of 4AT (Steinhoff and Dycka 1981, see Section 2.7.2).

2.6. Genotoxicity

2.6.1. In vitro

4AT or its hydrochloride did not induce mutations in the vast majority of tests with *Salmonella typhimurium* strains G46, TA98, TA100, TA1535, TA1537 and TA1538 and in *Escherichia coli* strains WP2, WP2 uvrA, C3706 and D3052 in the presence or absence of exogenous metabolic activation system. A positive response with 4AT hydrochloride was observed in one study with *S. typhimurium* strain TA100 in the presence of S9 mix from induced hamster liver. 4AT did not induce DNA repair in *E. coli* pol A. No mitotic crossing-over was induced in *Saccharomyces cerevisiae* D3, no mitotic gene conversion in *S. cerevisiae* D4 and no strand breaks in V79 Chinese hamster fibroblasts. 4AT caused DNA damage in human lung cells and unscheduled DNA synthesis in rat hepatocytes (NLM 200, Henschler 1990, ECB 2000).

4-Methylphenylhydroxylamine, a probable metabolite of 4AT *in vivo*, was mutagenic in *S. typhimurium* strain TA98 with S9 mix and without S9 mix in TA100 in a fluctuation test in *E. coli* WP2 uvrA. Also, 4-methylphenylhydroxylamine induced mitotic crossing over in *S. cerevisiae* D4 (Henschler 1990).

2.6.2. In vivo – Human data

There were no data available.

2.6.3. In vivo – Animal data

4AT gave a positive response in a *Drosophila* "wing spot"- test at the highest feeding dose (5 mM) (ECB 2000). An increase in DNA strand breaks was observed in liver and kidney of male mice after i.p. administration of 35 mg/kg (Henschler 1990).

2.7. Carcinogenicity

2.7.1. Human data

Among 81 persons (62 men and 19 women, aged 22–55 years) employed in production of 2AT and 4AT were 4 cases of bladder papilloma. Thirty-five of the workers were in production, 18 were fitters and 10 were cleaning personnel (no other details given); 9 persons had been exposed for less than 1 year, 31 between 1 and 5 years, 20 between 6 and 10 years, and 21 for more than 10 years. Concentrations of 4AT in the air were not given; for 2AT air levels were 0.7–28.6 mg/m³, 6–9 mg/m³ in most samples [about 1–2 ppm]. Cystoscopic examination of 75 of the 81 workers revealed 2 cases of bladder papilloma, one being a 23-year-old worker who had been exposed for 1 year and 8 months only to 4-AT, and the other was a 49-year-old worker exposed to both substances for 23 years. Methaemoglobinaemia (6–19 %) was diagnosed in 20 persons. Of 16 employees who had been exposed for between 12 and 17 years, 6 had developed bladder tumours (4 carcinomas, 1 papilloma, 1 multiple papilloma) (Khlebnikova *et al* 1970). The problem of the study is the co-exposure with the known carcinogen 2AT and the lack of specific exposure data on 4AT. Therefore, it is very difficult to draw specific conclusions on 4AT from this study.

2.7.2. Animal data

Carcinogenicity studies with inhalation exposure were not available.

4AT hydrochloride was fed to 25 male CD rats/group at concentrations of 1 000 and 2 000 ppm in the diet for 18 months. The higher dose is reported to represent the maximum tolerated dose (MTD). A number of other aromatic amines and nitro compounds were also tested in this study and for every 5 test substances a control group of 100 animals was used. There were no signs of toxicity and no increase in the incidence of any tumour (Weisburger *et al* 1978).

In the same study, male and female CD-1 mice (25/ sex and group) were fed diets containing 4AT hydrochloride at either 1 000 ppm for 6 months followed by 500 ppm for 12 months or at 2 000 ppm for 6 months followed by 1 000 ppm for 12 months. The dose was adjusted since the MTD had been exceeded. Mice (n = 25) of each sex served as matched controls and groups of 99 males and 102 females as pooled controls. All animals were observed for 21 months. There was a significant increase in hepatic adenomas in males at both dose levels (low dose: 8/17, high dose: 9/19) and in females (unspecified "liver tumours") at the higher dose (3/17) (Weisburger *et al* 1978).

In the same study, the isomeric 2AT (*o*-toluidine) was clearly carcinogenic in male rats (subcutaneous fibromas and fibrosarcomas, bladder carcinomas, multiple tumours, pituitary and adrenal adenomas) and in male and female mice (haemangiosarcomas and haemangiomas). No clear effect was seen for 3AT (*m*-toluidine; Weisburger *et al* 1978).

In a further unpublished study, Sprague-Dawley rats were treated with 0, 25 and 75 mg/kg of 4AT by subcutaneous injection in peanut oil once a week for 24 months. 4AT treatment caused a decrease in body weight gain but no decrease in survival time. The number of malignant tumours at the site of injection was slightly increased at both dose levels in males and females. Also, the incidence of benign liver tumours was increased at the high dose (especially in females) (Steinhoff and Dycka 1981).

4AT caused no papillomas or carcinomas at the site of application after treatment of female mice with one drop of a 20 % solution of 4AT in dioxane on the skin of the back twice a week for 12 weeks (Henschler 1990).

2.8. Reproductive toxicity

2.8.1. Human data

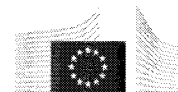
There were no data available.

2.8.2. Animal data

Oral administration of 200 mg/kg/day is reported to inhibit DNA synthesis in mouse testicular tissue (ACGIH 2001). Further data were not available.

3. Recommendation

Methaemoglobin (MHb) formation is the critical non-neoplastic effect in animals and humans exposed to 4AT. However, quantitative data on the formation of MHb after inhalation of 4AT were not available. MHb levels reached between 4.2 % and 6.6 % after 3 months of feeding 40 mg/kg/day of 4AT in rats and were only marginally further increased after 6 months (Jodynys-Liebert and Bennasir 2005). Comparison of equimolar intravenous doses of 4AT and aniline in cats indicates that the ability of 4AT



to induce MHb formation is lower and about half as high as the ability of aniline (McLean *et al* 1969). Depending on the concentration of MHb, methaemoglobinemia may have serious health effects in humans. By analogy to tolerable levels of CO-Hb in carbon monoxide exposed persons, a MHb level of 4-5 % has been considered tolerable (Bolt *et al* 1985). Thus, 40 mg/kg/day 4AT may eventually be regarded as the LOAEL concerning MHb induction in rats. However, it is important to note that the induction of MHb is highly variable across species, and that an assessment of morphology was not included in these studies.

4AT was not mutagenic or genotoxic in most *in vitro* tests with bacterial or eukaryotic test systems including mammalian cells. DNA damage was observed in human lung cells and unscheduled DNA synthesis in rat hepatocytes. The *in vivo* database is very limited. A mutagenic response was obtained in a *Drosophila* test. Strand breaks in liver and kidney of mice and DNA binding in various tissues of rats have been detected. Additionally, haemoglobin adducts of 4AT have been observed in humans. 4-Methylphenylhydroxylamine, the metabolite of 4AT which is involved in methaemoglobin formation and haemoglobin binding, is mutagenic in bacterial test systems. In summary, a genotoxic potential of 4AT *in vivo* cannot be ruled out.

The database with respect to carcinogenic effects in humans is very limited. Two cases of bladder papillomas and 6 cases of bladder tumours were identified in an examination of 81 workers with occupational exposure to 4AT and, most of them, to 2AT. The latter (*o*-toluidine) is an established human bladder carcinogen (Khlebnikova *et al* 1970).

Several older animal carcinogenicity studies have been performed in the 1970s. Weekly subcutaneous injections of 4AT over a period of 2 years led to an increase in malignant tumours at the site of application in both males and females and in benign liver tumours in females. No tumours at the site of application occurred after dermal application of a solution of 4AT to the skin of mice. 4AT was not carcinogenic in an 18-month feeding study with male rats, but in the same study, feeding of 4AT caused a slight increase of liver tumours in male and female mice. From the report it appears likely that these were benign (hepatic adenomas). In the same study, 2AT was clearly carcinogenic under similar conditions (Section 3.7.2). Therefore, although the possibility of metabolic formation of genotoxic *N*-oxidation products in humans may raise some concern for a genotoxic potential of 4AT, there is no experimental or epidemiological proof of carcinogenicity. Compared to its structural isomer 2AT (*o*-toluidine), a carcinogenic potential of 4AT, if such a potential exists, must be much lower.

For setting an OEL, the key health effect of 4-AT is methaemoglobinaemia. The experimental data in cats of McLean *et al* (1969; Section 3.2.2) show that the 4AT is by a factor of 2 less potent in this respect than aniline. This ratio is also supported by early industrial experience in humans (Smyth 1931, Goldblatt 1955; Section 3.2.1). For aniline, SCOEL has derived an OEL of 0.5 ppm, based on the induction of methaemoglobinaemia in humans (SCOEL SUM/153; Aug 2010). In consequence of this derivation for aniline, a provisional OEL of 1 ppm can be proposed for 4AT.

As the induction of methaemoglobin by aromatic amines is dependent on metabolic *N*-oxidation, which is a time-dependent process, it may be anticipated that a short-term (15 min) excursion of exposure by a factor of 2 has no practically relevant effect on methaemoglobin formation, if the 8h-TWA is observed, a STEL of 2 ppm can be recommended for 4AT.

These values may be revised, if new data on MHb formation in humans by either 4AT or the reference compound aniline become available.



Other assignments

Given the acute toxicity of 4AT after dermal exposure of rats and rabbits and by analogy with other aromatic amines, especially aniline and 2AT, which penetrate the skin, a "skin" notation is applied.

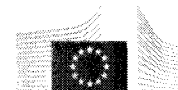
No data were available regarding sensitisation to 4AT in humans. However, para-group cross-reactivity has been observed in patients sensitised to *p*-phenyldiamine. A sensitising potential of 4AT and para-group cross reactivity has also been observed in guinea pigs (Kleniewska 1975, Kleniewska and Maibach 1980).

There were no data on developmental or reproductive toxicity in humans or animals.

The present Recommendation was adopted by SCOEL on XX Month, Year.

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

*SCOEL/SUM/189
September 2012*

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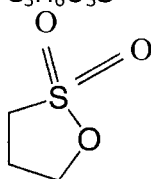
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Recommendation from the Scientific Committee on Occupational Exposure Limits for 1,3-Propane sultone

8-hour TWA:	Not feasible to derive a health-based limit (see Section 3. Recommendation)
STEL (15-min):	Not feasible to derive a health-based limit (see Section 3. Recommendation)
BLV:	Not feasible to derive a health-based limit (see Section 3. Recommendation)
Notation:	Skin
SCOEL carcinogen group:	A (genotoxic carcinogen without threshold)

Substance identification and 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:	1 ppm = 5.076 mg/m ³
(20 °C, 101.3 kPa)	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

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

1. 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 handling of the compound. Potential routes of exposure are ingestion, inhalation and dermal contact (NTP 2011).

2. 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.

2.1. Toxicokinetics

There were no studies into the 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).

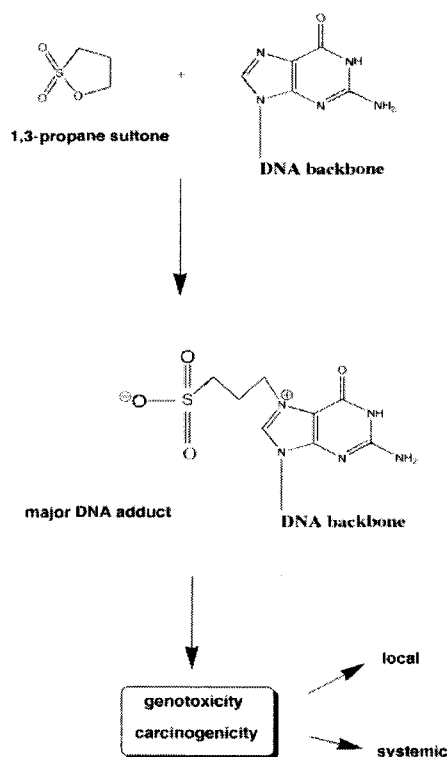


Figure 1. Reactivity of 1,3-propane sultone with guanosine and DNA (Hemminki 1983).

2.2. Acute toxicity

2.2.1. Human data

Data were not available.

2.2.2. 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 LD₅₀ values reported were 157 mg/kg and 350 mg/kg (two different experiments) for rats and 500–750 mg/kg for mice (DFG 1976, 1985).

Dermal

A dermal LD₅₀ reported for rabbits was 660 mg/kg (DFG 1976).

2.3. 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.

2.4. Sensitisation

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

2.5. 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 2.7).

2.6. Genotoxicity

2.6.1. 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.

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).

2.6.2. In vivo – human data

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

2.6.3. 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.

2.7. Carcinogenicity

2.7.1. Human data

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 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 of the 55 persons revealed that 20 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 one 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).

2.7.2. Animal data

In 1999, 1,3-Propane sultone was classified by IARC as *possibly carcinogenic to humans (Group 2B)* based on sufficient animal data:

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 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 four weeks and then toluene for one 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 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 tumour was found in the toluene controls of either sex, whereas in the 1,3-propane 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).

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.

2.8. Reproductive toxicity

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

3. Recommendation

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.

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 2.7.1). 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 LD₅₀ values are found at a similar order of magnitude

(Section 2.2.2), and repeated skin application has led to systemic malignancies (Section 2.7.2). Therefore, a skin notation is warranted.

There were no data on biological monitoring.

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