Butane-1-thiol

(CAS No: 109-79-5)

Health-based Reassessment of Administrative Occupational Exposure Limits

Committee on Updating of Occupational Exposure Limits,
a committee of the Health Council of the Netherlands

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1 Introduction

The present document contains the assessment of the health hazard of butane-1-thiol by the Committee on Updating of Occupational Exposure Limits, a committee of the Health Council of the Netherlands. The first draft of this document was prepared by AAE Wibowo, Ph.D. (Coronel Institute, Academic Medical Centre, Amsterdam, the Netherlands).

In December 1997, literature was searched in the databases Medline, Chemical Abstracts, Current Contents, and Embase, starting from 1966, 1970, 1970, and 1988 respectively, and using the following keywords: butanethiol, butyl mercaptan, thiobutyl alcohol, mercaptobutane, and 109-79-5. HSELINE, CISDOC, MHIDAS, NIOSHTIC (covering the period 1985/87 until 1997), and Poltox (Toxline, Cambridge Sc Abstr, FSTA; covering information until 1994), databases available from CD-ROM, were consulted as well.

In December 1998, the President of the Health Council released a draft of the document for public review. Comments were received from the following individuals and organisations: A Aalto (Ministry of Social Affairs and Health, Tampere, Finland), P Wardenbach, Ph.D. (Bundesanstalt für Arbeitsschutz und Arbeitsmedizin, Dortmund, Germany). These comments were taken into account in deciding on the final version of the document.

An additional literature search in February 2005 did not result in information changing the committee's conclusions.

2 Identity

Name	: butane-1-thiol
Synonyms	: butanethiol; 1-butanethiol; *n*-butyl mercaptan; thiobutyl alcohol; 1-mercaptobutane; butyl sulfhydrate
molecular formula	: $C_4H_{10}S$
structural formula	: CH_3-CH_2-CH_2-CH_2-SH
CAS number	: 109-79-5

3 Physical and chemical properties

molecular weight	: 90.2
boiling point	: 98°C
melting point	: -116°C
flash point	: 1.7°C (open cup); 2°C (closed cup)
vapour pressure	: at 25°C: 6 kPa
solubility in water	: not soluble (at 25°C: 0.06 g/100 mL)
log $P_{octanol/water}$	: 2.28 (experimental); 2.25 (estimated)
conversion factors	: at 20°C, 101.3 kPa: 1 mg/m^3 = 0.27 ppm 1 ppm = 3.76 mg/m^3

Data from ACG02, NLM04, http://www.syrres.com/esc/est_kowdemo.htm.

Butane-1-thiol is a colourless to yellow liquid, with a strong, garlic-, cabbage- or skunklike odour. The odour threshold ranges from 0.0001 to 0.001 ppm (0.0004 to 0.004 mg/m^3). The readily noticeable level is about 0.1 to 1 ppm (0.4 to 3.8 mg/m^3) (Far94, Kat30, NIO78).

4 Uses

Butane-1-thiol is used as a chemical intermediate in the production of insecticides and herbicides. It is also used as a gas odorant (ACG02).

5 Biotransformation and kinetics

The committee did not find data on the absorption of butane-1-thiol following inhalation, oral, or dermal exposure. From acute toxicity studies in experimental animals, it can be deduced that uptake by these routes is possible.

The committee found hardly any data on distribution, metabolism, and excretion of butane-1-thiol.

The metabolism of butane-1-thiol may proceed through the 2 pathways as proposed by NIOSH for ethanethiol. In the one way, the sulphur atom of the thiol is metabolised by oxidation and is excreted for the major part in the urine as inorganic sulphate. The carbon moiety enters the carbon metabolic pool and is excreted ultimately as CO_2. In the other way, the thiol is methylated into a sulphide that is converted into a sulphoxide and a sulphone by subsequent oxidations (NIO78). Metal-catalysed auto-oxidation into disulphides and reduction of the disulphides formed into thiols may occur as well. In this redox cycle, thiyl radicals and ‘active oxygen’ species are involved (Mun98).

Using liver microsomal fractions from phenobarbital-pretreated male Sprague-Dawley rats *in vitro*, lipophilic thiol compounds were bound as ligands by at least 2 species of oxidised cytochrome P450 (Nas76).

Abou-Donia et al. reported that the half-life of butane-1-thiol in plasma of the hen was 8 days after a single oral administration of 100 mg/kg bw (Abo79).

6 Effects and mechanism of action

Human data

Katz and Talbert performed a series of experiments to study odour thresholds of amongst others certain thiols including butane-1-thiol by exposing subjects at vapour concentrations ranging from '1 part in 10 to 1 part in 1013' for various periods. In addition to the determination of odour intensities, nasal and eye irritation were noted. The 6 volunteers involved described the odour of butane-1-thiol as skunklike and disagreeable but did not experience significant irritation of eyes, nose, or throat (Kat30).

Gobbato and Terribile described a case of acute butane-1-thiol intoxication in 7 workers accidentally exposed for ca. 1 hour to concentrations later estimated to be in the range of 50 to 500 ppm (188 to 1880 mg/m^3). Effects were severe in one worker and mild in the others. All workers experienced asthenia, muscular weakness, and malaise and 6 sweating, nausea, vomiting, and headache. Other symptoms such as neck pains, dizziness, inebriation, confusion, anxiety, agitation, and blurred vision were seen occasionally. Six workers recovered within a day but the most severely affected individual, remaining unconscious for 20 minutes immediately after the exposure, suffered profound weakness, dizziness, nausea and vomiting, drowsiness, and depression (Gob68).

Animal data

Irritation and sensitisation

Fairchild and Stokinger stated that most thiol compounds, among which butane-1-thiol, were irritating to the mucous membranes of experimental animals within approximately 15 minutes after exposure to high (not specified) vapour concentrations. Corneal opacities or cloudiness in the eyes often occurred in mice just prior to or after death from exposure to butane-1-thiol (Fai58).

Citing unpublished reports, Farr and Kirwin reported that the degree of skin irritation induced by butane-1-thiol varied from none to slight (Far94). Cirstea studied the skin-sensitising capacity of butane-1-thiol in guinea pigs. The compound (20% solution in acetone) was applied daily for 10 days or until signs of contact dermatitis, such as erythema, induration, and eczematous crusts, were noted. The results showed that butane-1-thiol did not have skin-sensitising capability (Cir72).

Citing unpublished information, Farr and Kirwin reported iridal and moderate to slight conjunctival irritation during the first 24 hours and through 72 hours after instillation, respectively, from one study and marked irritation lasting for up to 4 days from another study (Far94). Slight to moderate eye irritation was observed for a number of thiols among which butane-1-thiol (Fai58).

Acute toxicity

Acute 4-hour inhalation LC_{50} values of butane-1-thiol were 4020 and 2500 ppm (15,115 and 9400 mg/m^3) in rats and mice, respectively (observation time: 15 days). Animals died from respiratory arrest (Fai58). In other, unpublished, rat studies, a 4-hour LC_{50} of 6060 ppm (22,786 mg/m^3) was found while exposure to 54,000 ppm (203,040 mg/m^3) was lethal to all rats within 97 minutes (Far94). For dogs, a 30-minute LC_{50} of 770 ppm (2895 mg/m^3) was listed (NIO04).

The acute dermal LD_{50} of butane-1-thiol in rabbits was considered to be greater than 34,600 mg/kg bw (Far94).

Acute oral LD_{50} values of butane-1-thiol in rats were 1500 (observation time: 15 days) (Fai58) and 1800 mg/kg bw (Far94); for mice, a value of 3000 mg/kg bw was listed (NIO04). The acute intraperitoneal LD_{50} in rats was 399 mg/kg bw (Fai58).

All routes of administration gave essentially identical symptoms, namely restlessness, increased respiration, incoordination, muscular weakness, skeletal muscle paralysis in most cases, heavy to mild cyanosis, lethargy and/or sedation, respiratory depression followed by coma and death in cases of lethal doses (Fai58, Far94). Animals surviving single near-lethal doses by intraperitoneal and, in particular, by oral administration, and sacrificed at various times within 20 days post-treatment, frequently showed pathological changes that, although inconsistent, were indicative of liver and kidney damage. In mice, the liver showed changes consisting of cloudy swelling, fatty degeneration, and necrosis; the kidneys showed varying degrees of cloudy swelling, and the lungs displayed capillary engorgement, patchy oedema, and occasional haemorrhage (Fai58).

Abou-Donia et al. studied the symptomatology and histology of the central and peripheral nervous system of hens (n=3/group) after single oral doses of 100, 400, or 1000 mg/kg bw of butane-1-thiol (in gelatine capsule) at the end of a 30-day test period. Animals administered 1000 mg/kg bw suffered from body weight loss not found at the other doses. At doses of 400 and 1000 mg/kg bw, the hens developed dose-dependent clinical signs of late acute effects consisting of haemolysis of red blood cells, darkening and drooping of the comb, loss of appetite, weakness, emaciation, paralysis, and death. The behaviour of hens given 100 mg/kg bw was not different from that of the controls. No histological changes of the brain, spinal cord, sciatic nerve, and liver were present in any of the hens. It can be concluded that the no-observed-adverse-effect level (NOAEL) for a single oral dose of burane-1-thiol is 100 mg/kg bw in hens. Biochemical analyses at this dose level (100 mg/kg bw) showed that there was a slight increase of acetylcholinesterase activity in the brain and an initial increase of butyrylcholinesterase activity in plasma (Abo79). In a separate study on the effects of butane-1-thiol on haematology end points in hens (n=5), a single oral dose of butane-1-thiol of 500 mg/kg bw caused formation of Heinz bodies and extensive erythrocyte deformation and lysis in blood samples taken 24 and 48 hours after treatment. The haemoglobin concentration, packed cell volume, erythrocyte number, and glucose-6-phosphate dehydrogenase activity were significantly lower than in the controls, while the methaemoglobin level was significantly higher. In experiments on the effects on plasma butyryl-cholinesterase and brain acetylcholinesterase in hens (n=3/group) given single oral doses of butane-1-thiol of 100, 400, or 500 mg/kg bw, there were dose-dependent increases of plasma butyrylcholinesterase activity starting at post-treatment day 1, reaching a maximum at day 21, and returning to control levels at day 28, the day of sacrifice. Brain acetylcholinesterase activity was not affected at day 28 in hens given 500 mg/kg bw butane-1-thiol (Abd83).

Repeated-dose toxicity

In a study designed to provide dose ranging information for setting exposure levels for a 90-day inhalation toxicity study, rats (Charles Rivers CD; n=10/sex/group) were exposed whole body to vapour concentrations of butane-1-thiol of ca. 200, 1100, and 1900 ppm (752, 4136, 7144 mg/m^3), 6 hours/day, 5 days/week, for 2 weeks. In the 1900-ppm group, all animals died or were sacrificed after 6 days of exposure, animals showing tremors, dyspnoea, excessive lachrymation, urine-stained abdomen, brown material around eyes, nose, or head, and decreased body weight (gain). Post-mortem, organs were not

weighted. At macroscopic examination, primarily lung congestion was observed. Microscopic examination was performed on the kidneys only and showed tubular degeneration, ranging in severity from trace to severe, in 10/10 and 7/10 females. These changes were considered to be treatment related but also a possible secondary effect produced by the shock that preceded death. In the 1100-ppm group, one female animal was found dead after the last exposure day on study day 13. No signs of toxicity were observed in the animals of this group, but body weight (gain) was statistically significantly decreased after one and 2 weeks of exposure when compared to controls. In both male and female animals, relative spleen, kidney, heart, lung, and trachea weights were statistically significantly increased when compared to controls. Macroscopic examination showed dark-coloured kidneys; microscopic examination was not performed. In the 200-ppm group, no mortality, clinical signs, or effects on body weight (gain) were seen. Post-mortem examinations showed increased relative weights of kidneys in male and female rats and of lungs and trachea in males (Mil81).

In the subsequent 13-week study, rats (Charles Rivers CD; n=15/sex/group) were exposed whole body to vapour concentrations of butane-1-thiol of 9, 70, and 150 ppm (34, 263, 564 mg/m^3), 6 hours/day, 5 days/week, for 13 weeks. Mortality occurred in one high-concentration male (cause of death probably related to blood collection trauma) and one mid-concentration female animal (cause of death unknown). Body weight determinations and detailed observations for clinical signs of toxicity, both conducted at weekly intervals, did not show exposure-related effects in any of the exposed groups. Evaluations of various haematology and clinical chemistry parameters, performed before and after approximately 6 and 12 weeks of exposure, showed statistically significant changes only in haematology parameters in female animals including a dose-related decrease in erythrocyte counts in all exposed groups at weeks 6 and 12 and decreases in lymphocyte and segmented neutrophil counts in the high-concentration group at week 12. However, since the values observed were within the range of historical ‘normal’ values with the control values toward the high end of this range, Church considered the changes not toxicologically relevant. Statistically significant organ weight changes including increases in lung with trachea and in adrenal weights in (some of) exposed groups are summarised in Table 1.

Table 1 Changes in some organs weights in rats exposed to butan-1-thiol vapours, 6 hours/day, 5 days/week, for 13 weeks (Chu82).

	males (n=15/group)				females (n=15/group)			
	0	9[a]	70	150	0	9	70	150
absolute lung + trachea weight[b]	1.73	1.77	2.03**	1.78	1.37	1.34	1.41	1.31
relative lung + trachea weight[c]	0.38	0.40	0.46**	0.41**	0.52	0.53	0.53	0.53
absolute adrenal weight[d]	48	58**	57	51	62	69	68	61
relative adrenal weight[e]	1.04	1.32**	1.28**	1.19*	2.34	2.72*	2.53*	2.48

[a] Concentrations in mg/m^3.
[b] In g.
[c] As % body weight.
[d] In mg.
[e] As $\%x10^2$ body weight.

* $p<0.05$; ** $p<0.01$

However, in view of a lack of clear dose-response relationship and the absence of changes in the lungs of females, the committee questions the biological relevance of these findings.

Macroscopically, there were no treatment-related abnormalities in any of the exposure groups. At microscopic examination performed in the 150-ppm group only, lung lesions consisting of interstitial fibrosis were observed in 7/15 male and 12/15 female animals. These lesions were not seen in any of the control animals and were graded mainly as ‘trace’ or ‘mild’ (Chu82). Because the animals of the 10- and 70-ppm groups were not microscopically examined, the committee feels that this study does not allow definite conclusions with respect to, e.g., a NOAEL.

Szabo and Reynolds studied the ulcerogenic and adrenocorticolytic effects of some compounds, including butane-1-thiol, in female Sprague-Dawley rats. Butane-1-thiol was given to 5 rats at oral doses of 200 mg/kg bw for the first 2 days followed by 400 mg/kg bw for another 2 days. Autopsy was performed soon after the animal died or on the fifth day. The animals were examined for duodenal ulcers and adrenal necrosis. The criterion for ulcer was a lesion identifiable by gross examination. The results showed that butane-1-thiol did not induce duodenal ulcer, but adrenal necrosis occurred in 2/5 rats (Sza75).

The committee did not find data on the long-term toxicity, including carcinogenicity, of butane-1-thiol.

Mutagenicity and genotoxicity

Citing unpublished data, Farr and Kirwin reported that butane-1-thiol was found to be negative in the S. typhimurium mutation assay and in the Chinese hamster ovary sister chromatid exchange assay and weakly positive in the mouse lymphoma forward mutation assay (Far94).

Reproduction toxicity

Thomas et al. performed an inhalation reproduction toxicity study on butane-1-thiol in rats and mice. Groups of 25 pregnant Charles Rivers COBS CD rats and 25 pregnant Charles River CD-1 mice were whole body exposed to 0, 10, 68, and 152 ppm butane-1-thiol (0, 38, 255, and 570 mg/m^3), 6 hours/day, on gestational days 6 to19 and 6 to 16, respectively. Caesarean sections were performed on all rats and all surviving mice on gestational day 20 and 17, respectively. In rats, no mortality occurred. In the high-concentration animals, there was a slight increase in the incidence of hair loss on the limbs. In the groups exposed to 68 and 152 ppm, maternal body weight gains and adjusted mean body weight gains (at gestational day 20) were decreased when compared to controls while in the 10-ppm group, maternal body weight gains were similar and adjusted weights slightly lower. There were no biologically meaningful or statistically significant differences in developmental end points when comparing treated and control groups. In mice, 8 and 9 animals of the 68- and 152-ppm group, respectively, died. In these exposure groups, emaciation, unkempt appearance, red or brown staining of the perivaginal region, lethargy, and/or staining of hair were observed; severity and/or incidence increased dose relatedly. In the 68-ppm group, these effects were seen on gestational days 12-17 in 14 mice, 8 of which died. Unkempt appearance was seen in 2 mice of the 10-ppm group. There was a dose-dependent decrease in maternal and adjusted mean maternal body weight gains in all exposed groups. In 10 and 12 mice of the 10- and 68-ppm group, respectively, decreased body weight gains or weight losses were observed predominantly on gestational days 12-17, with a dose-related severity. Of the 16 gravid surviving dams of the 68-ppm group, 3 showed progressive weight losses resulting in terminal body weights lower than the initial weights while body weight gains of the remaining animals were similar to those of controls. In the 68- and 152-ppm groups, increases in mean post-implantation loss ($p<0.05$ and $p<0.01$, respectively) and in early resorptions per litter (not significant and $p<0.01$, respectively) occurred. A dose-related, not statistically significant increase of cleft palate incidence was observed in litters of the 10- and 68-ppm

group. The committee noted, however, that the incidence of cleft palate in the control litters was higher than historical control values. Total fetal abnormalities were statistically significantly different from controls at 68 ppm when using the fetus but not when using the litter as the unit of data analysis (i.e., the method recommended by relevant OECD guidelines) (Tho87). From this study, the committee concludes that the NOAELs for maternal and developmental toxicity are 38 (10 ppm) and 570 mg/m^3 (152 ppm; the highest concentration tested) in rats. In mice, the committee could not establish NOAELs since maternal toxicity and an increased incidence of cleft palate was found at 38 mg/m^3 (10 ppm), the lowest concentration tested.

7 Existing guidelines

The current administrative occupational exposure limit (MAC) for butane-1-thiol in the Netherlands is 1.5 mg/m^3 (0.5 ppm), 8-hour TWA.

Existing occupational exposure limits for butane-1-thiol in various countries are summarised in the annex.

8 Assessment of health hazard

The committee did not find human or experimental animal data on the kinetics of butane-1-thiol. However, similarly to ethanethiol, butane-1-thiol may be metabolised by 2 pathways either into sulphate and carbon dioxide or into sulphide, sulphoxide, and sulphone. Redox cycling (metal-catalysed auto-oxidation of the thiol into its dimer and reduction of the dimer into the thiol with formation of thiyl radicals and 'active oxygen' species) may occur as well.

Seven workers accidentally exposed to estimated concentrations of 50 to 500 ppm (188 to 1880 mg/m^3) for ca. 1 hour (almost) all experienced asthenia, muscular weakness, malaise, sweating, nausea, vomiting, and headache.

In experimental animals, butane-1-thiol was at most slightly irritating to the skin and moderately to markedly irritating to the eyes. There were no indications for a skin-sensitising potential.

Four-hour LC_{50} values were 4020 and 6060 ppm (15,115 and 22,786 mg/m^3) for rats and 2500 ppm (9400 mg/m^3) for mice, animals dying from respiratory arrest. In rabbits, the dermal LD_{50} was greater than 34,600 mg/kg bw. In these studies, signs indicative of central nervous system depression and cyanosis were observed.

In a 13-week inhalation study in which male and female rats were exposed whole body to vapour concentrations of butane-1-thiol of 9, 70, and 150 ppm

(34, 263, 564 mg/m^3) (6 hours/day, 5 days/week), there were no clinical signs or compound-related effects on survival, body weights, and haematology or clinical chemistry values in any of the exposed groups. Statistically significant increases in absolute and relative lung and adrenal weights were observed. Due to a lack of clear dose-response relationship and the absence of changes in the lungs of females, the committee questions the biological relevance of these findings. Post-mortem macroscopic and microscopic examinations performed only in the 150-ppm group, showed lung fibrosis. Because the animals exposed to 34 and 263 mg/m^3 (10 and 70 ppm) were not examined microscopically, the committee is of the opinion that this study is inappropriate as a basis for deriving a health-based recommended occupational exposure limit.

Butane-1-thiol was reported to be negative in an *in vitro* mutagenicity test in *S. typhimurium* and in a SCE test in Chinese hamster ovary cells and weakly positive in a mouse lymphoma mutation assay.

In rats exposed to 38, 255, and 570 mg/m^3 (10, 68, 152 ppm) on gestational days 6-19 (6 hours/day), no changes in developmental end points were observed when compared with controls. The NOAEL for maternal toxicity was 38 mg/m^3 (10 ppm) based on decreased maternal body weights at he next higher concentration. In mice, exposed to similar concentrations on gestational days 6-16, exposure to 38 mg/m^3 (10 ppm), the lowest level tested, induced both maternal (decreased body weights) as well as developmental toxicity (increased incidence of cleft palate, not statistically significant because of high incidence in control group).

The committee considers the toxicological database on butane-1-thiol too poor to justify recommendation of a health-based occupational exposure limit.

In view of the effects found in the dams in the reproduction toxicity study on mice (Tho87), the committee considers the present MAC-value of butane-1-thiol of 1.5 mg/m^3 (0.5 ppm), 8-hour time-weighted average (TWA), to be too high.

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Annex

Occupational exposure limits for butane-1-thiol in various countries.

country - organisation	occupational exposure limit		time-weighted average	type of exposure limit	note[a]	reference[b]
	ppm	mg/m^3				
the Netherlands						
- Ministry of Social Affairs and Employment	0.5	1.5	8 h	administrative		SZW05
Germany						
- AGS	0.5	1.9	8 h			TRG04
	0.5	1.9	15 min			
- DFG MAK-Kommission	0.5	1.9	8 h		[d]	DFG05
	1.0	3.8	15 min[c]			
Great Britain						
- HSE	-	-				HSE02
Sweden	-	-				Swe00
Denmark	0.5	1.5	8 h			Arb02
USA						
- ACGIH	0.5	-	8 h	TLV		ACG05
- OSHA	10	35	8 h	PEL		ACG04
- NIOSH	0.5	1.8	15 min[e]	REL		ACG04
European Union						
- SCOEL	-	-				EC05

[a] S = skin notation; which mean that skin absorption may contribute considerably to body burden; sens = substance can cause sensitisation.

[b] Reference to the most recent official publication of occupational exposure limits.

[c] Maximum number per shift: 4, with a minimum interval between peaks of 1 hour.

[d] Classified in pregnancy risk group C, i.e., there is no reason to fear a risk of damage to the embryo or fetus when MAK and BAT (Biological Tolerance Values for occupational exposures) values are observed.

[e] Ceiling value.