Benzenethiol

(CAS No: 108-98-5)

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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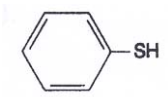
1 Introduction

The present document contains the assessment of the health hazard of benzenethiol 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, Embase, and Chemical Abstracts starting from 1966, 1988, and 1970, respectively, and using the following key words: benzenethiol, thiophenol, phenyl mercaptan, and 108-98-5. 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. The final literature search was carried out in Toxline and Medline in October 2003.

In October 2003, the President of the Health Council released a draft of the document for public review. No comments were received.

2 Identity

name	:	benzenethiol
synonyms	:	thiophenol; phenylthiol; phenylmercaptan; mercaptobenzene
molecular formula	:	C_6H_6S
structural formula	:	
CAS number	:	108-98-5

3 Physical and chemical properties

molecular weight	:	110.2
boiling point	:	168°C
melting point	:	-15°C
flash point	:	50°C (closed cup)
vapour pressure	:	at 19°C: 0.13 kPa
solubility in water	:	not soluble
log $P_{octanol/water}$	:	2.52
conversion factors	:	at 20°C, 101.3 kPa: 1 mg/m^3 = 0.22 ppm 1 ppm = 4.59 mg/m^3

Data from ACG99, NLM01.

Benzenethiol is a colourless liquid with an offensive, garlic-like odour. Air odour thresholds as low as 0.004 (0.9 ppb) (Amo83) and 0.001 mg/m^3 (0.3 ppb) (Rut86) have been reported. In an odour threshold study, a benzenethiol concentration of 3.2 mg/m^3 (0.72 ppm) was characterised as 'putrid', while no and very faint odour were reported at 0.000022 and 0.0012 mg/m^3 (0.005 and 0.3 ppb), respectively (Kat30).

4 Uses

Benzenethiol is used as a chemical intermediate for polymers and in the production of pesticides and pharmaceuticals. The compound is approved for use as a food additive under certain specified conditions (ACG99, NLM01).

5 Biotransformation and kinetics

From a dermal LD_{50} of 300 mg/kg bw in rats (see Section 6) (Fai58), the committee concludes that benzenethiol can be absorbed through the skin.

The committee did not find other quantitative or qualitative data on absorption.

Following single oral administration of doses of ^{35}S-labelled benzenethiol of 6 mg/kg bw to rats (n=2/sex), methylphenylsulphone, *o*- and *p*-hydroxy-methylphenylsulphone, conjugates of these hydroxy derivatives, and traces of methylphenylsulphoxide were identified in urine collected for 60 hours. Based on their own and other information, the authors suggested that, in vivo,

benzenethiol undergoes *S*-methylation to methylphenylsulphide, followed by oxidation to successively its corresponding sulphide, sulphoxide, and sulphone, and then hydroxylation of the sulphone ring and conjugation of the hydroxy derivatives (McB69).

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 benzenethiol by exposing subjects to 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 benzenethiol as very disagreeable and repulsive, and experienced a choking sensation in the throat, mucosal irritation, and headache. Eye, nose, and throat irritation occurred immediately after exposure, the eyes remaining irritated for hours. Already 'one inhalation' (not further specified) of benzenethiol at a concentration of 3.2 mg/m^3 (0.7 ppm) caused headache and irritation (Kat30). The committee did not find other human data on the toxic effects of benzenethiol.

Animal data

Irritation and sensitisation

In male and female rats exposed to concentrations of benzenethiol of 1100, 1560, and 2680 mg/m^3 (242, 343, 590 ppm) for one hour, ocular oedema and erythema and slight nasal discharge were reported (Bul69a). In male rats (n=7) and male mice (n=13), immediate irritation, as evidenced by preening, salivation, and lachrymation, was seen after starting exposure to a saturated atmosphere of benzenethiol (Haz51)*.

Fairchild and Stokinger found that instillation of 0.1 mL of the compound into the conjunctival sac of one eye of each of 3 rabbits produced moderate to severe redness, chemosis, and discharge for 3 to 4 days post-treatment. Diffuse

* The (theoretic) concentration in saturated air in ppm can be calculated using the formula: (vapour pressure in Pa x 10^6 ppm)/10^5 Pa. Using a vapour pressure of 260 Pa (at 25°C (NLM01); temperature of inhalation chamber was ca. 24°C), the committee estimates that these animals could have been exposed to, at most, 2600 ppm or (roughly) 12,000 mg/m^3)

corneal opacities occurred in 2 rabbits on the fourth day, involving three-quarters of the cornea (Fai58).

In an acute dermal toxicity study, 18-hour covered application of amounts of undiluted benzenethiol of 0.5 and 1.0 mL/kg (ca. 540 and 1080 mg/kg bw) to the clipped abdominal skin of rabbits (n=3/group) caused moderate to marked irritation generally accompanied by oedema, pigmentation, desquamation, coriaceous appearance, and necrosis. The effects generally deteriorated during the 8-day observation period and were still present at terminal sacrifice. Similar applications of 0.1 mL (ca. 110 mg/kg bw) for 5 successive days caused mild irritation as well as oedema, escharosis, coriaceous appearance, and necrosis. At sacrifice on day 11, all skins were 'normal' (Haz51). In another acute dermal toxicity study, application of doses of benzenethiol of 134-538 mg/kg to the clipped back skin of rabbits caused some inflammatory reaction that disappeared in 24 to 48 hours (Fai58). In a third study, application of 200 or 2000 mg/kg bw of neat benzenethiol to the skin of rabbits (n=4/group) caused severe skin burns classified as third degree (Bul69b). Benzenethiol was stated to be strongly irritating to the skin of guinea pigs after a 24-hour-covered contact (Rou68).

The committee did not find information on the possible skin sensitisation by benzenethiol.

Acute toxicity

When male and female rats were exposed to benzenethiol concentrations of 1100, 1560, and 2680 mg/m^3 (242, 343, 590 ppm) for one hour, mortality was observed in 0/10, 3/10, and 10/10 animals, respectively, resulting in an LC_{50} of 1900 mg/m^3 (418 ppm). Mortality intervals were 2-18 and 0.5-5 hours at the mid and high concentration, respectively. At the low level, acute depression was seen during the exposure time, while the higher levels produced dyspnoea, gagging, fasciculation, and cyanosis. Upon gross post-mortem examinations, no abnormalities were observed in the animals exposed to 1100 mg/m^3 (242 ppm) or in the survivors exposed to 1560 mg/m^3 (343 ppm). The treatment-related deaths exhibited haemorrhagic areas in the lungs (Bul69a). All male rats (n=7) and male mice (n=13) exposed to a saturated atmosphere of benzenethiol died within 40 and 55 minutes, respectively (see also footnote in Section 'Irritation and sensitisation') (Haz51).

Fairchild and Stokinger performed acute toxicity studies in which benzenethiol was administered by inhalation, dermal application, oral intubation, and intraperitoneal injection. The 4-hour LC_{50} values were ca. 150 and 130

mg/m^3 (33 and 29 ppm) for (Wistar-derived) rats and (Swiss-derived) mice, respectively, for a 15-day observation period. The dermal LD_{50} values, determined 4-8 hours after application to the clipped backs of the animals, were 300 and 134 mg/kg bw for rats and rabbits, respectively. In rats, the oral LD_{50} value was 46.2 mg/kg bw, determined 24 hours after administration (vehiculum: ethanol), while the intraperitoneal LD_{50} for a 15-day observation period was 9.8 mg/kg bw (25.2 mg/kg bw when determined 24 hours after injection). Symptomatology following lethal and maximum sublethal concentrations or doses was fairly uniform and included restlessness, increased respiration, incoordination, muscular weakness, skeletal muscle paralysis, heavy to mild cyanosis, lethargy and/or sedation, respiratory depression followed by coma and death, in cases of lethal doses. At macroscopic and microscopic post-mortem examination of the animals dying after these single exposures, generally, no lesions were seen. Animals surviving near-lethal oral or intraperitoneal doses and sacrificed 20 days after treatment frequently showed microscopic kidney and liver lesions. Animals dying several hours after being exposed to high concentrations of benzenethiol vapours had mild to severe hyperaemia of the trachea and the lungs. Generally, mice were more susceptible than rats (Fai58).

Eight days following 18-hour covered dermal application of an amount of benzenethiol of 0.5 mL/kg (ca. 540 mg/kg) to 3 rabbits, gross post-mortem examination showed slightly pale kidneys in one, a slightly granular liver in another, and red-coloured lungs and irritated intestines in the third rabbit. Following similar application of 1 mL (ca. 1080 mg/kg bw), one animal died within 24 hours, but the cause of death could not be determined because of advanced autolysis. At necropsy of the two other rabbits, pale and granular liver were seen in both animals as well as pale kidney and almost black spleen in one animal. The author did not indicate whether these effects should considered to be treatment related (Haz51). No mortality, signs of toxicity, or gross organ abnormalities were seen in 4/4 rabbits dermally treated with a single dose of 200 mg/kg bw. Following application of 2000 mg/kg bw, all 4 animals died between 0.5 and 1.5 hours post-treatment, exhibiting extreme excitation and cyanosis (Bul69b). In guinea pigs, dermal application of an amount of benzenethiol of 2 mL/kg (ca. 2160 mg/kg bw) caused deaths within 24 hours but no mortality occurred at dose of ca. 700 mg/kg bw (i.e., 0.65 mL/kg) (no more data presented) (Rou68).

Given in polyethylene glycol 200 by stomach tube to male and female Sprague-Dawley rats (n=7/sex/group), the oral LD_{50} was determined to be ca. 65 mg/kg bw for both males and females. During the 14-day observation period, there was no mortality at a single dose of ca. 54 mg/kg bw (i.e., 0.05 mL) while

9/16 animals died within 1 hour following administration of the next higher dose of ca. 81 mg/kg bw (i.e., 0,075 mL). Apart from some slight body weight depression, no signs of toxicity or organ abnormalities (gross post-mortem examination) was seen at doses of ca. 27 and 54 mg/kg bw. At doses of ca. 81 mg/kg bw and above, there were depression and laboured respiration, starting 5 to 30 minutes after dosing, and congested livers, kidneys, and adrenals and lung erythema in the treatment-related deaths (Hor66). Without presenting further information, the oral LD_{50} in rats was stated to be less than 50 mg/kg bw (Rou68). In male albino mice, single doses of 200, 300, or 500 mg/kg bw (in Wesson oil) caused mortality in 3/13, 8/13, and 13/13 animals, resulting in an oral LD_{50} of 267 mg/kg bw. In the low-dose group, animals died 5-7 days post-administration; in the mid- and high-dose group, all and 85% of the animals, respectively, within one day following administration. At all doses, there was depression with evidence of diarrhoea and some increased or irregular respiration. At 500 mg/kg bw, incoordination was also seen. Post-mortem examination results included no abnormalities in the survivors of the low-dose group, pale kidneys in the survivors of the mid-dose group, and haemorrhagic lungs, speckled and blanched livers, irritated intestines, and slightly granulated kidneys in the succumbed animals of the high-dose group (Haz51).

The committee notices the discrepancy between the oral LD_{50} in rats of 46.2 mg/kg bw (i.e., a dose that would kill 50% of the animals within 24 hours) reported above (Fai58) and the findings in the developmental toxicity studies in which repeated dosing of 50 mg/kg bw did not induce any mortality (Geo94).

Repeated-dose toxicity

Apart from a 4-day inhalation study, a 3-week intraperitoneal study, and the reproduction toxicity studies discussed below, no information was available on the effects (including potential carcinogenicity) of repeated exposure to benzenethiol or benzenethiol vapours.

Male rats (n=7) and mice (n=12) were exposed to benzenethiol vapours that were obtained by diluting air saturated with benzenethiol in such a way that '3.2% of the atmosphere within the chamber was saturated with benzenethiol vapour'*. Exposure was for 6 hours the first day, and for 8 hours daily on each of the 3 succeeding days, and terminal sacrifices were scheduled 3 days later. While 7 mice were found dead before starting the second exposure - the cause of death

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* Based on the assumptions and calculations presented in the footnote under Section 'Irritation and sensitisation', exposure could have been to a concentration as high as roughly 85 ppm or 400 mg/m^3.

was suggested to be cannibalism -, a second group of 13 mice was added. Among the rats, 2 died (during the night and 3 days, respectively, after the final exposure). During exposure, signs of irritation (preening, lachrymation, marked salivation), unthrifty appearance, lethargy, and decreased water and food consumption were observed. Post-mortem examination of the 2 deceased rats showed haemorrhagic lungs, marked intestinal irritation, and mottled livers and kidneys. In the surviving animals, gas-filled and irritated stomachs and intestines, congested and pale brown kidneys, small spleens, mottled livers, and markedly irritated eyes were seen while the lungs were unaffected. Two out of the 5 mice surviving the first exposure day, died during the second day, 2 during the fourth day, and one at post-exposure day 3. During exposure, effects observed were similar to those seen in rats. At autopsy, there were haemorrhagic lungs, marked intestinal irritation, and spotted kidneys and livers. In the added mouse group, one animal died after first exposure, 4 during or after the third exposure, and 6 during the 3-day period between the last exposure and terminal sacrifice. The effects seen in these animals and in those 2 that were terminally sacrificed were similar to those seen in the other mouse group (Haz51).

George et al. stated that in studies preliminary to a developmental study in rats, no signs of toxicity were observed in pregnant rats treated with 20 mg/kg bw/day on gestational days 6 through 15 or in non-pregnant rats given up to 40 mg/kg bw/day, for 6 consecutive days. At 50 mg/kg bw/day for 6 consecutive days, there was a 7% body weight decrease in non-pregnant rats (no more data presented) (Geo94). In similar studies in rabbits, pregnant animals were given 0.5, 1, 2, 5, or 10 mg/kg bw/day on gestational days 6 through 19, while non-pregnant animals were treated with 20, 40, or 50 mg/kg bw/day for 14 consecutive days. In none of the groups, effects on body weight were observed. Doses up to 40 mg/kg bw/day did not induce clinical signs. At 50 mg/kg bw/day, 1 or 2 non-pregnant rabbits were slightly sedated post-dosing on 2 days during the dosing period, and one of these animals died (on treatment day 10). Exposure of pregnant animals to 50 mg/kg bw starting on gestational day 6 caused excessive maternal toxicity. Six out of 13 animals died during the first treatment week, and the experiment was terminated by sacrificing the remaining animals at gestational day 14 (Nav94).

In a reproduction toxicity study using a continuous breeding protocol, parental rats (Spraque-Dawley; n=20/sex/group) were exposed to daily (7 days/week) oral (gavage) doses of benzenethiol of 9, 18, and 35 mg/kg bw, for 1 week housed individually and subsequently for 16 weeks housed as breeding pairs during which period animals were allowed to produce several litters. Thereafter (at day 112), pairs were separated. After rearing and weaning the final

litter, a crossover mating trail (in which high-dose males and females were paired with untreated females and males), and subsequent rearing and weaning, the F0 animals were sacrificed and post-mortem investigation was performed on the first 10 living animals/sex/group. Animals were kept exposed until sacrifice, i.e., males until study days 198-199 and females until day 217. In this part of the study, mortality was observed in 0, 1, and 2 males and 4, 2, and 5 females of the low-, mid-, and high-dose group, respectively, while there were no deaths in the control groups. Of these, one mid-dose male, one high-dose male, and one high-dose female died as a result of gavage errors and one low-dose and one high-dose female animal as a result of parturition difficulties; the cause of death of the other animals could not be determined. Clinical signs were observed in control and treated groups but at relatively low incidences (<20% per group) and without dose-related differences. Throughout this part of the study, body weights of male animals of the high-dose group were 7-15% less than those of controls while no effect on body weight was seen in high-dose females. At necropsy, absolute and relative liver and kidney weights were increased in all dose groups: relative liver weights of the low-, mid-, and high-dose animals by 20, 35, and 50 %, respectively, in males and by 11, 18, and 36%, respectively, in females; relative kidney weights by 30, 53, and 104%, respectively, in males and by 8, 5, and 20%, respectively, in females. Gross and microscopic post-mortem observations included a treatment-relatedly increased incidence of enlarged and pitted kidneys in male animals, increased incidences of renal tubular degeneration (30, 35, and 40%, respectively) in male and female animals, and centrilobular hepatocellular hypertrophy in mid- and high-dose male and in all treated female groups. In the F1 litter, selected from litters born after week 17 and, after a weaning period, exposed to the same dose levels as their respective parents for ca. 10 weeks, similar effects on body weight and liver and kidney were observed (Wol96a, Wol96b). From this study, the committee concludes that oral dose levels as low as 9 mg/kg bw/day (the lowest level tested) caused effects on liver and kidney (increased absolute and relative weights; renal tubular regeneration; centrilobular hepatocellular hypertrophy) of rats.

In the intraperitoneal study, 6 rats were given 9 injections of 3.5 mg/kg bw as a 2% v/v solution in ethanol over a 3-week period. One rat died on the seventh day. The remaining animals did neither show significant weight losses nor other signs of toxicity. Upon necropsy, fibrous thickening of the splenic capsule due to irritation caused by the repeated injections, enlargement of the spleen, hyperaemia of the adrenal medulla, and some mild kidney lesions were seen (Fai58).

Mutagenicity and genotoxicity

Benzenethiol was negative when tested in *S. typhimurium* strains TA100 with and without metabolic activation and TA98 with metabolic activation (not tested without S9) at concentrations of 25 to 500 µg/plate. Concentrations greater than 25 µg/plate caused poor survival in these tests (Lav79).

The committee did not find other data on the mutagenic and genotoxic potential of benzenethiol.

Reproduction toxicity

The potential fertility and reproductive effects of benzenethiol were assessed in Sprague-Dawley rats using the continuous breeding protocol. The compound was administered by gavage (vehicle: corn oil) at daily (7 days/week) doses of 9, 18, or 35 mg/kg bw to 20 animals/sex/group. Rats were individually housed for one week and then cohabited for 16 weeks. During cohabitation, litters were euthanised after evaluation on post-natal day 1. Litters born after week 17 were reared until post-natal day 21, and selected weanlings were administered the same dose levels as their respective parents. On post-natal day 81 (+10 days), F1 animals were cohabited within groups for one week and necropsied following delivery of the litters. Both in the parental F0 and F1 animals, toxicity was seen at all dose levels: increased absolute and relative liver and kidney weights and histological lesions at 9 mg/kg bw/day (see above under 'Repeated-dose toxicity').

As to male fertility indices, there were only a decreased epididymal sperm motility (by 5-6%) in the F0 mid- and high-dose group and a decreased right caudal epididymis weight in the high-dose group. However, this did not affect pregnancy outcome as was confirmed in a separate, crossover mating trial in which naive females were mated with high-dose males. Treatment did not affect fertility in the F0 females. In the male F1 generation, right testis weights were increased in the mid- and high-dose groups and, upon histological examination of the left testes, an increased incidence of inhibited spermiation (of the stage VIII-X tubules) was found in all treated groups. However, this did not affect pregnancy outcome. There were no fertility effects in F1 females.

As to the developmental aspects of this study, exposure of the F0 generation did not induce effects other than small, not clearly dose-related decreases in adjusted live pup weight by 4 ($p<0.05$) and 6% ($p<0.05$) in the low- and high-dose groups, respectively, and in the number of live pups by 7% (not significant) in the high-dose group. The females were the affected sex, since at the crossover

mating trial to determine the affected sex, the pups born to high-dose females (mated with untreated males) weighed 8-9% less than pups from untreated males and females, while no effects were observed in litters from benzenethiol-treated males and untreated females. In the F1 mating trial, no developmental effects were seen except for statistically significant decreases in mean live F2 pup weight by 9% and 12% in the mid- and high-dose groups, respectively. However, the statistical significance disappeared when adjusting for litter size. In addition, the females in these 2 dose groups littered about half a day earlier than the control group which may account for the pup weight decreases (Wol96a, Wol96b). The committee concludes that, in this study, the NOAELs for maternal and developmental toxicity were <9 and 35 mg/kg bw/day, respectively. The NOAELs for male and female fertility effects are <9 and 35 mg/kg bw, respectively.

The developmental toxicity of benzenethiol (purity: >99%) was examined in Sprague-Dawley rats (n=25/group) and New Zealand White rabbits (n=15-26/group). Rats were given oral (gavage) doses of 0, 20, 35, or 50 mg/kg bw/day on gestational days 6 through 15 (vehicle: corn oil). At 50 mg/kg bw, there was maternal toxicity as indicated by mortality (in 4/25), persistently decreased body weight and body weight gain, decreased food consumption during the treatment period, and, at necropsy on gestational day 20, decreased gravid uterine weights and increased relative and adjusted liver weights. Kidney weights were not affected. In the 2 other dose groups, there was a transient decrease in maternal body weight gain and food consumption during the first dosing period (gestational days 6-9). After dosing, rooting behaviour indicative of aversion to the taste or smell of the test substance was seen in all treatment groups. This behaviour was most prevalent and had an earlier onset at the mid and high doses and subsided after dosing was completed. At developmental toxicity evaluation, no significant differences between treated and control groups were found in the average number of corpora lutea per litter, the number of implantation sites per litter, the percent pre-implantation loss per litter, the percent late fetal deaths per litter, or in the incidence of visceral and skeletal malformations or variations. Embryo and fetal effects observed included post-implantation loss, decreased live litter size, decreased fetal body weight per litter, and an increased incidence of external malformations in the high-dose group and reduced female fetal body weight in the mid-dose group (Geo94, Geo95). The committee concludes that in this rat study, the NOAEL for developmental toxicity is 20 mg/kg bw/day, based on decreased female fetal body weights. The committee could not set a maternal

NOAEL since maternal body weight gain was affected in the first few treatment days at 20 mg/kg bw/day, the lowest dose tested.

Rabbits were given benzenethiol (in corn oil) at oral (gavage) doses of 0, 10, 30, or 50 mg/kg bw/day (replicate I) or 0, 10, 30, or 40 mg/kg bw (replicate II) on gestational days 6 through 19. Because of excessive mortality (46%) during the first treatment week of replicate I, the 50 mg/kg bw/day group was untimely terminated and replaced in the second replicate by 40 mg/kg bw/day. At sacrifice on day 30, a total of 24, 18, 20, and 9 pregnant animals of the control, 10, 30, and 40 mg/kg bw-group, respectively, were evaluated. In the maternal animals, one animal of the 10 and one of the 30 mg/kg bw/day-group died during the study. No consistent clinical signs were observed. Maternal relative food consumption during the end of the dosing period tended to be lower in the animals given 30 and 40 mg/kg bw/day, but food consumption before and after treatment did not differ from that in controls. In these groups, there was a transient dose-dependent decrease in maternal body weight gain during gestational days 12 through 15 (the same period in which the largest reductions in food consumption occurred), reaching statistically significance in the mid- and high-dose group. Overall maternal body weight gain during the dosing period (gestational days 6-19) tended to be lower in the treated animals. Because of the inconsistent nature and small size (generally less than 5%) of these body weight reductions, overall maternal weight gain during gestation and corrected weight gain did not differ across groups. At necropsy, gravid uterine weight, liver, and (right) kidney weights were not affected. Apart from a statistically significant increase in the percentage of female fetuses with variations per litter (mainly extra or rudimentary lumbar ribs) of the 40 mg/kg bw/day group, no differences between treated groups and controls were found in the developmental toxicity end points examined (Geo95, Nav94). The committee concludes that in this rabbit study, the NOAEL for developmental toxicity is 30 mg/kg bw/day, based on an increased incidence in the percentage of female fetuses with variations per litter (mainly extra or rudimentary lumbar ribs). The committee could not set a maternal NOAEL since maternal body weight gain was dose-dependently decreased during gestational days 12-15.

In vitro studies

In vitro experiments in human red blood cells have shown that benzenethiol can induce methaemoglobin formation (Amr89) and this group of compounds (e.g., aliphatic, aromatic, and heterocyclic thiols and disulphides) are described as

haemolytic agents (Mun89). There is no information whether it also occurs *in vivo*.

7 Existing guidelines

The current administrative occupational exposure limit (MAC) for benzenethiol in the Netherlands is 2 mg/m^3 (0.5 ppm), 8-hour TWA .

Existing occupational exposure limits for benzenethiol in some European countries and the USA are summarised in the annex.

8 Assessment of health hazard

The committee did not find qualitative data on the oral or inhalation absorption of benzenethiol. Although benzenethiol can be absorbed through the skin as indicated by a dermal LD_{50} value of 300 mg/kg bw in rats, no quantitative information was found. Following oral administration of labelled benzenethiol to rats, methylphenylsulphone, *o*- and *p*-hydroxy-methylphenylsulphone, conjugates of these hydroxy derivatives, and traces of methylphenylsulphoxide were identified in urine collected for 60 hours. This suggests that benzenethiol may undergo *S*-methylation to methylphenylsulphide, followed by oxidation to successively its corresponding sulphide, sulphoxide, and sulphone, and then hydroxylation of the sulphone ring and conjugation of the hydroxy derivatives.

Apart from an old study reporting headaches and eye, nose, and throat irritation in volunteers at 'one inhalation' of a concentration of 3.2 mg/m^3 (0.7 ppm), the committee did not find data on the effects of exposure to benzenethiol in man.

Liquid benzenethiol was very irritating to the eyes and skin of experimental animals. The committee could not assess the irritating potential of benzenethiol in experimental animals because only relatively high (>1000 mg/m^3) or poorly documented levels were used.

Acute toxicity studies showed rather varying results. In rats, the 1-hour LC_{50} was 1900 mg/m^3 (418 ppm), while 4-hour LC_{50} values were much lower: ca. 140 mg/m^3 (30 ppm) in both rats and mice. Dermal LD_{50} values of 300 and 134 mg/kg bw were reported for rats and rabbits, respectively, although in other rabbit experiments, no mortality occurred at doses of 200 or 540 mg/kg bw. Following oral administration, the LD_{50} in rats, determined 24 hours after treatment, was 42.6 mg/kg bw while in acute (with a 14-day observation period) and developmental studies, all rats survived doses up to 50 mg/kg bw. However, dose-response curves may be steep since in the aforementioned acute

experiment, a single dose of ca. 81 mg/kg bw caused the death of 9/16 animals within one hour. In mice, the oral LD_{50} was 267 mg/kg bw. When administering doses of 50 mg/kg bw/d to pregnant rabbits during organogenesis, 6/13 animals died with 5 days.

Apart from oral developmental toxicity studies, the committee did not find data from relevant repeated-dose toxicity studies. In one of these studies, which used a continuous breeding protocol, parental rats were given daily doses of 0, 9, 18, and 35 mg/kg bw for about 200 consecutive days, during which period several litters were produced and reared and weaned. In this study, no NOAEL could be established since liver and kidney effects (increased absolute and relative weights; renal tubular regeneration; centrilobular hepatocellular hypertrophy) were found in the parental animals at 9 mg/kg bw, the lowest level tested.

Apart from a negative result in a mutagenicity test in *S. typhimurium* strains TA100 (with and without metabolic activation) and TA98 (tested with metabolic activation only), the committee did not find data from mutagenicity or genotoxicity studies on benzenethiol.

In a reproduction toxicity rat study according to a continuous breeding protocol at doses of 9, 18, and 35 mg/kg bw, no effects were found on female fertility. Although some male fertility indices, among which a decreased epididymal sperm motility (by 5-6%), were impaired, pregnancy outcome was not affected. Treatment did not cause changes in developmental endpoints. The committee concluded that, in this study, the NOAELs for maternal and developmental toxicity were <9 and 35 mg/kg bw/day, respectively. The NOAELs for male and female fertility effects are <9 and 35 mg/kg bw, respectively. In developmental toxicity studies in rats and rabbits, the committee could not set NOAELs for maternal toxicity since maternal body weight gains were affected at the lowest doses tested, viz., 20 mg/kg bw in rats and 10 mg/kg bw in rabbits. Based on reduced female fetal body weight in rats and an increased incidence in the percentage of female fetuses with variations per litter (mainly extra or rudimentary lumbar ribs) in rabbits, the developmental NOAELs were 20 and 30 mg/kg bw in rats and rabbits, respectively.

The committee could take the oral reproduction toxicity study in which repeated dosing of 9 mg/kg bw, the lowest dose tested, induced effects on liver, kidneys, and epididymal sperm motility as a starting point in deriving a health-based occupational exposure limit. After adjusting for continuous exposure (7 days/week vs. 5 days/week for occupational exposure), and using a factor of 4 for scaling from rat to human based on caloric demand and an overall assessment factor of 36 - to account for the absence of a NOAEL, intra- and interspecies

variation, and the differences between experimental conditions and the exposure pattern of the worker, and the preferred-value approach, the committee could recommend a health-based occupational exposure limit of 0.5 mg/m^3. The committee is of the opinion that this level would protect workers from systemic effects. However, headache and irritation were found in volunteers after only very brief exposures to 3.2 mg/m^3 (0.7 ppm) indicating that benzenethiol is very irritating, offensively smelling compound. Because of lack of additional human data, the committee is not able to estimate which level would protect workers from irritation and to recommend a health-based occupational exposure limit.

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

Based on human (irritation) and experimental animal (systemic toxicity) data, the committee concludes that the current MAC value of 2 mg/m^3, 8-hour time-weighted average, is too high.

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Annex

Occupational exposure limits for benzenethiol 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	2	8 h	administrative		SZW03
Germany						
- AGS	-	2	8 h			TRG00
- DFG MAK-Kommission	-	-				DFG03
Great-Britain						
- HSE	0.5	2.3	8 h	OES		HSE02
Sweden	-	-				Swe00
Denmark	0.5	2.3	8 h	OEL		Arb02
USA						
- ACGIH	0.5[c]	-	8 h	TLV		ACG03b
- OSHA	-	-				ACG03a
- NIOSH	0.1	0.5	15 min; ceiling	REL		ACG03a
European Union						
- SCOEL	-	-				EC04

[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] Intended to be changed for 2003 to 0.1 ppm, with a skin notation.