Perchloromethyl mercaptan

(CAS reg no: 594-42-3)

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 perchloromethyl mercaptan 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 H Stouten, M.Sc. (TNO Nutrition and Food Research, Zeist, the Netherlands).

The evaluation of the toxicity of perchloromethyl mercaptan has been based on the review by the American Conference of Governmental Industrial Hygienists (ACG99). Where relevant, the original publications were reviewed and evaluated as will be indicated in the text. In addition, literature was retrieved from the online data bases Medline, Toxline, Chemical Abstracts, and NIOSHtic covering the period 1966 to 26 April 1999 (19990426/UP), 1965 to 29 January 1999 (19990129/ED), 1967 to 24 April 1999 (19990424/ED; vol 130, iss 18), and 1973 to 16 July 1998 (19980716/ED), respectively, and using the following key words: perchloromethyl mercaptan, trichloromethyl sulfenyl chloride, perchloromethanethiol, trichloromethanesulfenyl chloride, trichloromethanesulphenyl chloride, trichloromethanethiol, trichloromethyl mercaptan, CSCl4, 594-42-3, 75-70-7, and 20434-91-7. HSDB and RTECS, data bases available from CD-ROM, were consulted as well (NIO99, NLM99). The final literature search has been carried out in April 1999.

In July 2001, the President of the Health Council released a draft of the document for public review. The committee received no comments.

2 Identity

name	:	perchloromethyl mercaptan
synonyms	:	methane sulfenyl chloride; perchloromethanethiol; trichloromethylsulfenyl chloride; trichloromethylsulphenyl chloride; trichloromethanesulfenyl chloride; trichloromethanesulphenyl chloride; thiocarbonyltetrachloride
molecular formula	:	CCl_4S
structural formula	:	Cl_3-C-S-Cl
CAS reg no	:	594-42-3

Data from ACG99, NLM99.

3 Physical and chemical properties

molecular weight	:	185.87
boiling point	:	147-148°C (decomposes)
melting point	:	-
flash point	:	-
vapour pressure	:	at 20°C: 0.4 kPa
solubility in water	:	insoluble
Log $P_{octanol/water}$	:	3.47 (estimated)
conversion factors	:	1 ppm = 7.7 mg/m^3
(20°C, 101.3 kPa)	:	1 mg/m^3 = 0.13 ppm

Data from ACG99, Env80, NLM99, http://esc.syres.com.

Perchloromethyl mercaptan is an oily, yellow liquid with a disagreeable, acrid odour. It is not flammable. Upon heating or in a fire, it gives off toxic and corrosive gases. With water, it reacts in a rate-limiting first step to trichlorosulphenic acid (Cl_3C-S-OH) and then to thiophosgene-*S*-oxide (Cl_2C=S=O). Both steps yield hydrochloric acid (HCl) (ACG99, Env80, NLM99).

A human odour threshold of 0.0075 mg/m^3 (0.001 ppm) has been reported (Rut86).

4 Uses

Perchloromethyl mercaptan is used as an intermediate for the synthesis of dyes and fungicides (ACG99).

5 Biotransformation and kinetics

The commitee did not find experimental data on the absorption, distribution, biotransformation, and excretion of perchloromethyl mercaptan.

However, perchloromethyl mercaptan is thought to be able to react readily with nucleophilic groups such as hydroxyl groups (water) or amino and thiol groups (peptides, *e.g.*, glutathione). Its metabolism may therefore be similar to the fate of the trichloromethylthio moiety of captan (1,2,3,6-tetrahydro-*N*-(trichloromethylthio)-phthalimide) (see Figure 1). Reactions with amino or thiol groups yield via a number of steps the very reactive

thiophosgene. This compound can be detoxified in at least three ways: 1) condensation with either free or protein-bound cysteine to, ultimately, TTCA (thiazolidine-2-thione-4-carboxylic acid), 2) hydrolysis and/or oxidation to CO_2 and H_2S, and 3) reaction with sulphite to a sulphonic acid and its monoxide derivative (see metabolism scheme Annex II) (Env80, Hea98).

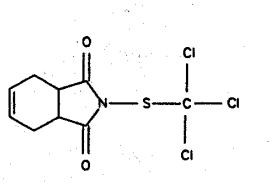

Figure 1 Captan.

6 Effects and mechanism of action

Human data

Inhalation of unspecified, but low concentrations of perchloromethyl mercaptan were stated to have resulted in strong eye, throat, and chest irritation. Exposure may induce nausea and vomiting as well (Flu31).

A few cases of poisoning due to accidental exposure have been reported. Due to accidental dermal (face) exposure, a man experienced conjunctival and mucosal respiratory tract irritation instantly and, amongst others, extensive dispersed toxic bronchopneumonia with global respiratory insufficiency and heavy hypoxaemia within 20 hours, upon medical treatment completely healing within 14 days (Spá71). In its criteria document, the German DFG presents 3 cases (reported in an inaugural dissertation) in which dermal and inhalation exposure caused, among others, blepharospasms and almost complete corneal erosion, pulmonary oedema, coughing, dyspnea, and cyanosis. One of the cases was fatal, and tracheal necrosis, (haemorrhagic) oedema of the lungs, brain, and heart, marked renal nephrosis, and vacuolization of hepatic centrilobular cells were seen at autopsy (Gre98; see also Alt73).

From a NIOSH health hazard evaluation report, it was cited that at production plants with levels below 0.1 ppm (0.8 mg/m^3; 8-hour time-weighted average), no reports of illness had been filed (ACG99).

Animal data

Irritation

Perchloromethyl mercaptan was cited to be severely irritating to the skin of rabbits (ACG99, NIO99). When amounts of 0.5 to 5 mL/kg of undiluted perchloromethyl mercaptan were used to moisten a gauze pad and held in contact with the depilated skin of guinea pigs (n=3) for 24 hours, severe skin irritation (gross oedema, entire area necrotic surrounded by erythema or haemorrhages; eschar; scarring) was observed during the 2-week observation period (Eas61). When 0.5 mL of neat test substance was applied to the intact and abraded clipped skin of rabbits (n=3/sex/group) under occlusion for 24 hours and then washed off, perchloromethyl mercaptan was found to be corrosive yielding maximum scores for erythema and oedema at all time points (*i.e.*, at 24 and 72 hours) (Draize score: 8.0) (Say71).

Perchloromethyl mercaptan was cited to be severely irritating to the eyes of rabbits (ACG99, NIO99). When instilled into the eyes of rabbits, perchloromethyl mercaptan was highly corrosive causing complete destruction of the eyes. Three out of the 6 animals died 7 to 10 days after treatment (Say71).

Single exposure

An LC_{50} of *ca*. 13 ppm (*ca*. 100 mg/m^3) has been estimated when groups of rats (n=5/sex/group) were exposed to concentrations of 9 to 2314 ppm (69-17,818 mg/m^3), for 1 hour (observation time: 14 days). At all levels tested, eye and mucosal irritation as well as dyspnoea, gasping, and acute depression were seen. All animals survived exposure to 9 ppm (69 mg/m^3). At autopsy of the animals that died due to exposure to higher levels, pulmonary oedema, congestion of heart and liver, and inflammation of the pericardial and peritoneal membranes and of the upper gastrointestinal tract were observed. There was inflammation of mouth and nasal mucosa in all cases. At levels of 122 ppm (940 mg/m^3) and higher, animals showed total corneal opacity (Say71). In a separate paper, 1-hour LC_{50}s of 11 and 16 ppm (85 and 123 mg/m^3) were reported in male and female rats, respectively (Ver77). All rats (number not reported) died due to a 4-hour exposure to 34 ppm (262 mg/m^3) (Izm82). All 4 rats died following a 1-hour exposure to 100 ppm (770 mg/m^3) and 3/4 following a 6-hour exposure to 10 ppm (77 mg/m^3). Animals showed lethargy and respiratory difficulties and lung oedema upon autopsy (Gag70). For mice, a 2-hour LC_{50} of 38 ppm (293 mg/m^3)

has been listed (Izm82), while in another paper, a 3-hour LC_{50} of 9 ppm (69 mg/m^3) was cited (Alt73). Both mice and cats (numbers not indicated) died from lung oedema within 1 to 2 days following a 15-minute exposure to 45 ppm (347 mg/m^3) (Flu31).

In rabbits, dermal LD_{50}s of 1410 and 1780 mg/kg bw have been reported (Say71, Ver77). No signs of toxicity or mortality were observed in animals (n=4) treated under occlusion with 464 or 1000 mg/kg bw. Slight depresssion was seen after treatment with 2150 mg/kg bw, and 3/4 rabbits died within 3 to 7 days. Upon autopsy, these latter animals showed severe haemorrhages of the gastrointestinal tract and moderate haemorrhages of the lungs (Say71). In a skin irritation study, guinea pigs died within 2 days after application of doses of 2.5 mL/kg bw (*i.e.*, *ca*. 4250 mg/kg) and higher (Eas61).

An oral LD_{50} in rats of 83 mg/kg bw has been cited (ACG99, NIO99). Following administration of single oral doses of 215-2150 mg/kg bw to male rats (Sprague-Dawley; n=5/group), the LD_{50} was calculated to be 909 mg/kg bw. No mortality, signs of toxicity, or gross pathology were seen at 215 and 464 mg/kg bw while doses of 1000 and 2150 mg/kg resulted in severe depression, diarrhea, excessive urination and mortality (in 4/5 of each group). In the animals that died, slight and severe haemorrhages were noted in lungs and adrenal glands and in liver and kidneys, respectively (Say71). Given oral doses of 50-800 mg/kg to rats (undiluted and 10% solution) and mice (10 and 1% solution), the LD_{50} was between 400-800 mg/kg bw in both species. Symptoms included weakness, darkening of the eyes, cyanosis, laboured respiration, diarrhea, tremors, prostration, and signs of irritation. In rats given a single oral dose of 200 mg/kg bw, no methaemoglobin was found (Eas61).

An iv LD_{50} in mice of 56 mg/kg bw has been reported (Gre98). Following single ip injections, LD_{50}s in rats and mice were 25 and 10-25 mg/kg bw, respectively (Eas61).

Repeated exposure

In a poorly documented paper (summarising single and repeated exposure studies of over 100 chemicals), 20 6-hour exposures to 2 ppm (15 mg/m^3) were stated to have induced initial respiratory difficulties and congested lungs in male rats (n=4) while no toxic signs and organ pathology were seen following 20 6-hour exposures to 0.5 ppm (4 mg/m^3) (n=4, both males and females tested) (Gag70).

No treatment-related mortality was observed in rats (Sprague-Dawley; n=15/sex/group) exposed to 0 and *ca*. 0.02, 0.1, and 1.1 ppm (0.13, 1.0, 8.7 mg/m^3), 6 hours/day, 5 days/week, for 2 weeks. At the highest dose level, clinical signs including haircoat stains, laboured breathing, tremors, and decreased body weight gain were seen. Necropsy observations were restricted to the lungs showing oedema, increased weights, and increased mucus secretion. Upon microscopic examination, only effects on the respiratory tract (alveolitis, interstitial hyperplasia, perivascular oedema, mild nasal epithelial changes) were seen. In the mid-concentration group, only mild nasal epithelial changes were reported while there were no effects in the animals exposed to 0.02 ppm (study reported in an abstract only) (Kna87b).

When rats (Sprague-Dawley CD; n=18/sex/group) were exposed to 0 and *ca*. 0.01, 0.08, and 0.6 ppm (0.11, 0.6, 4.4 mg/m^3), 6 hours/day, 5 days/week, for 14 weeks (70-72 exposures), survival rates were not affected. Statistically significant body weight (gain) decreases were found in the animals of the high-concentration group only: in females, throughout the study; in males, at weeks 2 and 3. There were no effects on food consumption. Apart from a slight increase in the incidence of salivation in the male animals of the high-concentration group and of sneezing in the female animals of the mid-concentration group and in the male and female animals of the high-concentration group, in-life observations did not show consistent treatment-related clinical signs of toxicity. Except for a decrease in median urine specific gravity in high-concentration females at study termination, no treatment-related, biologically significant effects were found upon interim and termination clinical chemistry analyses (haematology, blood chemistry, urinalysis). Treatment caused an increase in the absolute (males only) and relative total lung weights (both males and females) in the high-concentration group, increases in accessory lobe dry weights in the male animals of the low- and high-concentration group, and decreases in the wet:dry weight ratios of the accessory lobes in the male and female animals of these latter exposure groups. Furthermore, there were changes in the relative kidney (increases) and absolute brain (decreases) weights in all female exposure groups, but these changes did not show a dose-response relationship. In addition, relative heart weights were increased in the female animals of the low- and high-concentration groups. At necropsy, the only treatment-related gross finding was the finding of mucus within the tracheas of 2 female and 4 male animals of the high-concentration group. Microscopic changes were limited to the respiratory tract, especially the nasal cavities of the animals exposed to 0.6 ppm (4.4 mg/m^3). These included

residues of purulent exudates in 16/18 males and 12/18 females, acute or subacute respiratory epithelial inflammation in 13/18 males (mostly of slight severity) and 8/18 females (mostly of minimal severity), acute inflammation of stratified squamous nasal epithelium ("minimal" and "slight") in 3/18 males, and respiratory epithelial hypertrophy and/or hyperplasia in 7/18 males (all of slight severity) and 2/18 females ("slight" and "moderate" or more), and respiratory epithelial squamous metaplasia in 2/18 males ("slight" and "moderate" or more). In some of the animals (5 males, 1 female), there was mostly minimal interstitial pneumonia. At 0.08 ppm (0.6 mg/m^3), one female animal showed purulent exudate, stratified squamous nasal epithelial inflammation, and squamous respiratory epithelial metaplasia, and one male animal purulent exudate. In the animals exposed to 0.01 ppm (0.11 mg/m^3), no microscopic changes were seen. Apart from one isolated tumour, *i.e.*, a mammary gland adenocarcinoma in a female animal of the mid-concentration, no neoplastic lesions were observed (Kna87a).

The committee feels it difficult to assess the significance of the changes in brain, kidney, and heart weights in the exposed females. In view of the lack of a clear dose-response, the absence of these effects in the male animals, and the feeling that this reactive compound will induce local effects before systemic effects, the committee considers these changes as probably not treatment related. Based on the histological effects on the respiratory tract epithelium found in 2/36 animals exposed to 0.08 ppm (0.6 mg/m^3), the committee places the NOAEL in this study at 0.01 ppm (0.11 mg/m^3).

When rats (n=7), guinea pigs (n=7), and dogs (n=2) were exposed to 1 ppm (7.7 mg/m^3) perchloromethyl mercaptan, 8 hours/day, 5 days/week, for 3 months, 6/7 guinea pigs died within 3 weeks while all other animals survived. In-life and *postmortem* macro- and microscopic observation showed irritation (conjunctiva of the eyes, respiratory tract mucous membranes) to be the principle effect. This irritation caused secondary infections in, especially, guinea pigs (pneumonia) and dogs (bronchiolitis, foci of bronchopneumonia) (Hor52).

Mutagenicity and genotoxicity

In vitro, in bacteria, perchloromethyl mercaptan was mutagenic in *S. typhimurium* strains TA1535, TA1537, TA1538, TA98, TA100 (both with and without metabolic activation) (Maj82a) as well as in DNA-polymerase-deficient *E. coli* (pol A_1^- assay) (tested without metabolic activation only (Ros80). In

mammalian cells, there were positive results in the mouse lymphoma L5178Y $TK^{+/-}$ forward mutation assay both with and without induced rat-liver metabolic activation (Maj83a). Testing in Chinese hamster ovary cells both with and without metabolic activation at sufficiently high doses did not induce significant increases in the incidences of chromosomal aberrations and SCEs. However, the occurrence of elevated aberration frequencies and complex chromosome rearrangement figures were concluded to indicate a weak potential clastogenic activity (Maj83b). Perchloromethyl mercaptan inhibited concentration dependently the DNA polymerase activity in isolated bovine liver nuclei (Dil80). In the morphological transformation assay in BALB/3T3 cells, a statistically significant increase (almost a doubling of control values) in the numbers of transformed foci was found at a single dose of 0.0075 µL/mL. The next two higher concentrations did not induce significant responses but decreases in cell survival (from *ca*. 90 % to < 60%) may have masked a weak positive response (Maj82b).

In vivo, no significant increases in micronuclei were found in the bone marrow of mice (CDl; n=5/sex/group) exposed by inhalation to 1.6 and 4.2 ppm (12, 32 mg/m^3), for 6 hours, and sacrificed after 24, 48, or 72 hours. Concentrations were selected from a preceding range finding in which 6-hour exposures to 2.7 and 5.7 ppm (21, 44 mg/m^3) were said to cause reduced activity and mortality (no details presented). No reduction in PCE frequency was seen in the bone marrow of these animals when harvested 72 hours after ending exposure. The authors did not present data on possible toxic effects observed during the micronucleus test; due to the great variation and the lack of consistency in the PCE frequency determined at the various time points, the bone marrow toxicity could not be assessed (Maj84).

The committee did not find data on the potential carcinogenicity or reproduction toxicity of perchloromethyl mercaptan.

7 Existing guidelines

The current administrative occupational exposure limit (MAC) for perchloromethyl mercaptan in the Netherlands is 0.8 mg/m^3 (0.1 ppm), 8-hour TWA.

Existing occupational exposure limits for perchloromethyl mercaptan in some European countries and in the USA are summarised in Annex I.

8 Assessment of health hazard

Although no data were found on the kinetics of perchloromethyl mercaptan *per se*, the compound is thought to be metabolised to the very reactive thiophosgene which can readily be detoxified by condensation with free or protein-bound cysteine, hydrolysis and/or oxidation, or reaction with sulphite.

Perchloromethyl mercaptan is corrosive to the eyes and the skin of experimental animals. From 1-hour LC_{50} values in rats of 85-123 mg/m^3 (11-16 ppm), the committee concludes that perchloromethyl mercaptan is very toxic by inhalation. From dermal and oral LD_{50} values of 1410 and 1780 (both in rabbits) and *ca*. 400-900 (rats) mg/kg bw, respectively, the committee concludes that the compound is harmful in contact with skin and if swallowed.

Data from acute and repeated inhalation studies showed that irritation of the eyes and the respiratory tract is the critical effect. In a well-performed 14-week study using rats (Kna87a), exposure to 4.4 mg/m^3 (0.6 ppm) caused increased lung weights and histological changes in the noses of the majority of the animals. After exposure to 0.6 mg/m^3 (0.08 ppm), one out of 18 female animals showed, stratified squamous nasal epithelial inflammation, and squamous respiratory epithelial metaplasia and 1/18 male animals purulent exudate. No effects were observed at 0.11 mg/m^3 (0.01 ppm).

In *in vitro* mutagenicity/genotoxicity testing, perchloromethyl mercaptan was mutagenic in bacteria and in a mammalian cell system. It showed weak responses in a clastogenicity and a transformation assay. *In vivo*, it did not induce micronuclei in the bone marrow of mice after a single 6-hour exposure up to 32 mg/m^3 (4.2 ppm), but bone marrow toxicity was not clearly assessed.

The committee did not find data on the potential carcinogenicity or reproduction toxicity.

The *in vitro* mutagenicity of perchloromethyl mercaptan is reason for concern, and the compound may, therefore, be considered as a suspect carcinogen. On the other hand, a negative result was obtained in an *in vivo* bone marrow micronucleus assay in mice, although it is not clear whether or not the test substance had reached the bone marrow. The committee considers perchloromethyl mercaptan to be a very reactive compound which will be detoxified rapidly and will not pose a carcinogenic risk at concentrations low enough to prevent effects on the respiratory tract as described above. This is supported by the data on captan, a pesticide rapidly decomposing into, amongst others, perchloromethyl mercaptan, as evaluated by the Dutch Expert Committee

on Occupational Standards (DECOS) (Hea98). Following oral administration (the only route tested), captan was carcinogenic in mice, but not in rats, inducing intestinal tumours at high oral doses. DECOS concluded that captan was genotoxic/mutagenic *in vitro*, but not *in vivo*, based on the majority of negative results in *in vivo* tests, especially those of the DNA binding test and of the nuclear aberration test both performed in the target organ (*i.e.*, the murine small intestine), and that the tumour formation in the mouse was due to overwhelming of detoxification mechanisms. DECOS took a LOAEL of 0.13 mg/m^3 from a 13-week inhalation study, in which minimal to mild hyperplasia of laryngeal squamous epithelium was found, as a starting point for standard setting for captan.

Therefore, the committee is of the opinion that the NOAEL of 0.11 mg/m^3 (0.01 ppm) from the 14-week inhalation rat study (Kna87b) can be taken as a starting point in deriving a health-based recommended occupational exposure limit (HBROEL). For the extrapolation to a HBROEL, an overall assessment factor of 8 is established. This factor covers the following aspects: intra- and interspecies variation, differences between experimental conditions and the exposure pattern of the worker, and the type of critical effect. Thus, applying this factor of 8 and the preferred value approach, a health-based occupational exposure limit of 0.01 mg/m^3 is recommended for perchloromethyl mercaptan.

The committee recommends a health-based occupational exposure limit for perchloromethyl mercaptan of 0.01 mg/m^3, as an 8-hour time-weighted average (TWA).

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Annex I

Occupational exposure limits for perchloromethyl mercaptan in various countries.

country organisation	occupational exposure limit		time -weighted average	type of exposure limit	note[a]	lit ref[b]
	ppm	mg/m^3				
The Netherlands						
- Ministry of Social Affairs and Employment	0.1	0.8	8 h	administrative		SZW01
Germany						
- AGS	-	0.8	8 h			TRG00
- DFG MAK-Kommission	-[c]	-				DFG01
Great Britain						
- HSE	-	-				HSE01
Sweden	-	-				Arb00b
Denmark	0.1	-	8 h			Arb00a
USA						
- ACGIH	0.1	0.76	8 h	TLV		ACG01
- OSHA	0.1	0.8	8 h	PEL		ACG00
- NIOSH	0.1	0.8	10 h	REL		ACG00
European Union						
- SCOEL	-	-				CEC00

[a] S = skin notation; which means 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] Listed among substances for which studies of the effects in man or experimental animals have yielded insufficient information for the establishment of MAK values

Annex II

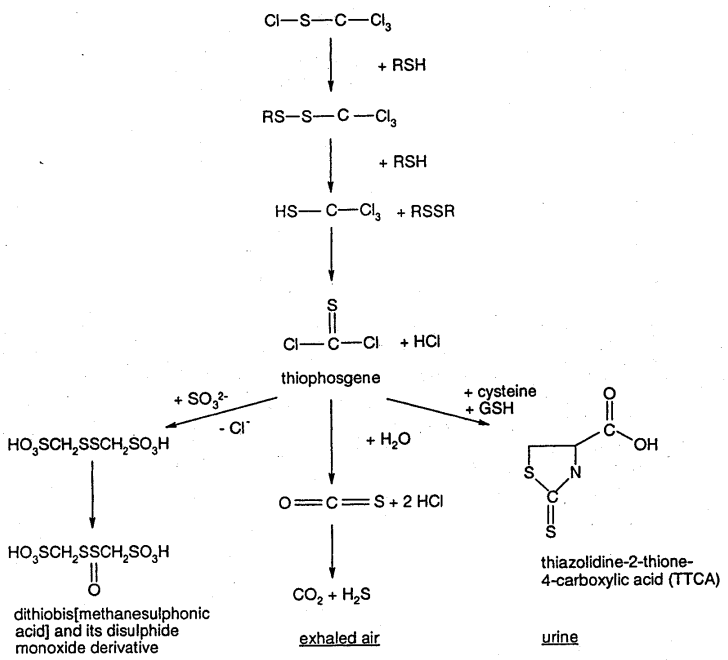

Figure2 Biotransformation scheme of perchloromethyl mercaptan (adapted from Env80 and Hea98).