Carbon tetrabromide

(CAS No: 558-13-4)

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 carbon tetrabromide 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 MA Maclaine Pont, M.Sc. (Wageningen University and Research Centre, Wageningen, the Netherlands).

The evaluation of the toxicity of carbon tetrabromide has been based on the review by the American Conference of Governmental Industrial Hygienists (ACG98). Where relevant, the original publications were reviewed and evaluated as will be indicated in the text. In addition, in December 1999, literature was searched in the databases Toxline, Medline, and Chemical Abstracts, starting from 1981, 1961, and 1937, respectively, and using the following key words: carbon tetrabromide, tetrabromomethane, and 558-13-4.

In February 2001, the President of the Health Council released a draft of the document for public review. No comments were received.

An additional search in Toxline and Medline in January 2004 did not result in information changing the committee's conclusions.

2 Identity

name	:	carbon tetrabromide
synonyms	:	tetrabromomethane; methane tetrabromide; carbon bromide
molecular formula	:	CBr_4
CAS number	:	558-13-4

3 Physical and chemical properties

molecular weight	:	331.63
boiling point	:	189.5°C (slight decomposition)
melting point	:	ß-form: 90.1°C; α-form: 48.4°C (slight decomposition)
flash point	:	not available
vapour pressure	:	at 25°C: 96 Pa
solubility in water	:	not soluble (at 30°C: 24 mg/100 mL)
log $P_{octanol/water}$	:	3.42 (experimental); 2.80 (estimated)
conversion factors	:	at 20°C, 101.3 kPa: 1 mg/m^3 = 0.07 ppm 1 ppm = 13.8 mg/m^3

Data from NLM04, Tor94, http://esc.syrres.com.

At room temperature, pure carbon tetrabromide is a colourless, non-flammable solid. However, samples are generally yellow-brown in colour (ACG98).

All 8 human volunteers were able to detect carbon tetrabromide at a concentration of ca. 5 ppm (ca. 69 mg/m^3), while none of them was able to detect the compound at concentrations of 0.3-0.5 ppm (ca. 4-7 mg/m^3) (Wuj62).

4 Uses

Not widely used, carbon tetrabromide finds some employment in organic synthesis (ACG98).

Carbon tetrabromide occurs naturally in small amounts in the alga *Asparagopsis taxiformis* (Bur76).

5 Biotransformation and kinetics

The committee did not find adequate data on the biotransformation and kinetics of carbon tetrabromide.

Data from skin testing suggested that carbon tetrabromide was not absorbed by the skin in amounts resulting in overt toxic signs (Wuj62).

Torkelson stated that either hydrolysis or metabolism might produce some bromide ion but that carbon tetrabromide would not be expected to produce physiologically significant quantities of bromide ion in the blood at levels of exposure considered acceptable by inhalation (Tor94).

Wolf et al. reported that *in vitro* incubation of carbon tetrabromide with induced rat liver microsomal preparations resulted in cytochrome P450 complex formation and in metabolic formation of carbon monoxide (Wol77).

6 Effects and mechanism of action

Human data

The committee did not find data on effects on humans following (occupational) exposure to carbon tetrabromide.

Animal data

Instillation of unknown amounts of the solid compound into the eyes of rabbits caused severe conjunctival irritation, oedema with moderate pain, and permanent

corneal damage. Instillation for 15 seconds followed by washing with water resulted in pain, conjunctival irritation, and temporary corneal damage (Wuj62).

Occluded application of unknown amounts of carbon tetrabromide to the shaven skin of rabbits caused severe hyperaemia, oedema, and moderate necrosis. Repeated application of a 10% solution of carbon tetrabromide in Dowanol 50B resulted in very slight scaliness after 10 applications to the ear and moderate to severe hyperaemia, oedema, and slight necrosis to the shaven abdomen of rabbits. Very faint hyperaemia to the ear and slight to moderate hyperaemia and scaliness of the abdomen were observed following application of a 1% solution (Wuj62).

Exposure to a saturated atmosphere at 25°C* for 1.3 or 0.5 hours was lethal to all rats, the rats exposed for 0.5 hours dying within 1-2 days after exposure. All rats survived exposure to a saturated atmosphere at 26°C for 0.2 hours, showing eye and nasal irritation and retarded weight gain subsequent to exposure (Wuj62).

The oral LD_{50} in rats was 1800 mg/kg bw (5.4 mmol/kg bw) (Wuj62), compared with 2350 mg/kg bw (15.3 mmol/kg bw) for carbon tetrachloride (NIO04b).

The subcutaneous LD_{50} in mice was estimated to be 298 mg/kg bw (0.9 mmol/kg bw), compared with 30,768 mg/kg bw (200 mmol/kg bw) for carbon tetrachloride (Kut62a).

An intravenous LD_{50} of 56 mg/kg bw has been listed for mice (NIO04a).

Single intraperitoneal injections did not cause changes in hepatic function or serum enzymes in rats in one study at doses up to 125 µL/kg bw (Aga83), but in another study, it increased the relative liver weight of rats at 10 µL/kg bw (Kli81).

After a single subcutaneous injection into mice, liver function damage was observed 24 hours later in the form of a decreased plasma clearance of bromosulphalein in 1 out of 10 mice at 0.05 mmol/kg bw (16.6 mg/kg). At 0.3 mmol/kg bw (100 mg/kg bw), 40% of the animals had liver function damage and 2 out of 5 animals had histological changes in the liver. The type of changes was not described (Kut62b).

After exposure to a concentration of 4-8 ppm (ca. 55-110 mg/m^3) for 1 or 2 weeks, rats showed mild eye and nasal irritation. Gross pathology yielded slight

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* The (theoretic) concentration in saturated air can be calculated using the formula: (vapour pressure in Pa x 10^6 ppm)/10^5 Pa. Using a vapour pressure at 25°C of 96 Pa, the committee estimates that these animals could have been exposed to 960 ppm or 1325 mg/m^3.

lung, liver, and kidney damage. Microscopic examination showed mild to advanced degenerative changes in the liver of all female rats and most of the male rats. Further, cloudy swelling, necrosis, and fatty changes were observed in the livers. The kidney damage was not further described (Wuj62).

Groups of 5 male and 5 female rats, 4 male guinea pigs, and 1 female rabbit were exposed to 0.3-0.5 ppm CBr_4 (ca. 4-7 mg/m^3), 7 hours/day, 5 days/week, for 5 weeks. The concentration was determined by combustion and analysed for bromide. The authors estimated the actual concentration to have been 1 ppm (13.8 mg/m^3) when compared with results of a polarographic analysis that gave a 30% higher concentration. Only the tissues of the male rats were examined microscopically. No effects were observed in the lungs, spleen, pancreas, adrenal gland, testicle, and heart. In the livers, there was dilation of the sinusoids, cloudy swelling of the cells, and usually small areas of necrosis. Degenerative changes were observed in the renal epithelium of the kidneys characterised by necrosis of the convoluted tubules, glomerular degeneration, and sometimes shrinkage of the glomerular tufts and proliferation of the interstitial tissue (Wuj62).

Groups of 10 male and 10 female rats, 5 male and 5 female guinea pigs, and 2 male and 2 female rabbits were exposed to 0.3-0.5 ppm CBr_4 (ca. 4-7 mg/m^3), presumably 7 hours/day, 5 days/week, for 6 months. The concentration was measured by a polarographic method. Control groups of rats and guinea pigs were either not exposed, or sham exposed. Growth, general appearance, and mortality records showed no evidence of adverse effects in the rats or female guinea pigs. The final body weight of the male guinea pigs was depressed, but not statistically significant ($p>0.05$). All organ weights and clinical values were within normal limits. No adverse effects were observed either grossly or microscopically in the various species and sexes (Wuj62). The committee concludes that under the circumstances of the study, intermittent exposure to carbon tetrabromide concentrations of 4-7 mg/m^3 (0.3-0.5 ppm) was a NOAEL for rats, guinea pigs, and rabbits.

Exposure of rats to 10-1000 mg/m^3 of CBr_4 fumes, 4 hours/day for 4 months, was reported to cause metabolic changes in the livers. Even the lowest concentration caused irritation of the eyes and respiratory tract (Pau69).

Mutagenicity and genotoxicity

Carbon tetrabromide was positive in a forward mutation assay to resistance to L-arabinose in *S. typhimurium* strain BA13; without rat liver metabolic activation, the number of mutants was much higher than with metabolic activation (Rol93).

Carbon tetrabromide was negative in a test for chromosomal malsegregation in the mould *A. nidulans* (Cre95).

The committee did not find data from carcinogenicity and reproduction toxicity studies on carbon tetrabromide.

7 Existing guidelines

The current administrative occupational exposure limit (MAC) for carbon tetrabromide in the Netherlands is 1.4 mg/m^3 (0.1 ppm), 8-hour TWA.

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

8 Assessment of health hazard

In rabbits, carbon tetrabromide exerted local effects like severe irritation and permanent corneal damage to the eyes and slight irritation, hyperaemia, and oedema to the skin of rabbits.

After inhalation exposure, the target organ of toxicity is the liver. Mild to advanced degenerative changes, cloudy swelling, necrosis, and fatty changes have been observed in the livers of rats after exposure to 55-110 mg/m^3 (4-8 ppm). Also, after exposure to 13.8 mg/m^3 (1 ppm), degenerative changes were observed in the livers and kidneys of rats. In a 6-month study with rats, guinea pigs, and rabbits, intermittent exposure to 4-7 mg/m^3 (0.3-0.5 ppm) did not induce any effect, and was, therefore, an NOAEL. Given the poor documentation of the study and the difficulties in measuring the concentration, the committee considers the study insufficient as a starting point to establish a health-based occupational exposure limit.

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

The committee concludes that there is insufficient information to comment on the level of the present MAC-value.

References

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Annex

Occupational exposure limits for carbon tetrabromide 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	0.1	1.4	8 h	administrative		SZW04
Germany						
- AGS	-	1.4	8 h			TRG03
- DFG MAK-Kommission	-	-				DFG03
Great Britain						
- HSE	0.1	1.4	8 h	OES		HSE02
	0.3	4.1	15 min			
Sweden	-	-				Swe00
Denmark	0.1	1.4	8 h			Arb02
USA						
- ACGIH	0.1	-	8 h	TLV		ACG04
	0.3	-	15 min	STEL		
- OSHA	-	-				ACG03
- NIOSH	0.1	1.4	10 h	REL		ACG03
	0.3	4	15 min	STEL		
European Union						
- SCOEL	-	-				EC04

[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.