Tetramethyl orthosilicate

(CAS No: 681-84-5)

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 tetramethyl orthosilicate 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 KJ van den Berg, Ph.D. and H Stouten, M.Sc. (TNO Nutrition and Food Research, Zeist, the Netherlands).

The evaluation of the toxicity of tetramethyl orthosilicate has been based on the review by the American Conference of Governmental Industrial Hygienists (ACGIH) (ACG98). Where relevant, the original publications were reviewed and evaluated as will be indicated in the text. In addition, in April 1999, literature was searched in the on-line databases Medline, Toxline, and Chemical Abstracts, starting from 1966, 1965, and 1967, respectively, and using the following key words: 681-84-5, tetramethoxysilane, methyl orthosilicate, methyl silicate, silicon methoxide, silicon tetramethoxide, tetramethyl orthosilicate, and tetramethyl silicate.

In July 2000, 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 November 2003 did not result in information changing the committee's conclusions.

2 Identity

name	:	tetramethyl orthosilicate
synonyms	:	methyl silicate; tetramethoxysilane; tetramethyl silicate; *o*-silicic acid, tetramethyl ester; silicic ester, tetramethyl ester; methyl orthosilicate; silicon methoxide
molecular formula	:	$C_4H_{12}O_4Si$
structural formula	:	$Si(O\text{-}CH_3)_4$
CAS number		681-84-5

3 Physical and chemical properties

molecular weight	:	152.22
boiling point	:	121-122°C
melting point	:	-2°C
flash point	:	45°C
vapour pressure	:	at 25°C: 1.3 kPa
solubility in water	:	decomposes
log $P_{octanol/water}$	:	-1.93 (estimated)
conversion factors	:	at 20°C, 101.3 kPa : 1 ppm = 6.3 mg/m^3 1 mg/m^3 = 0.16 ppm

Data from ACG98, NLM03, http://esc.syrres.com.

Tetramethyl orthosilicate is a colourless liquid.

4 Uses

Tetramethyl orthosilicate is used in coating the screens of television picture tubes. In addition, it may be employed in mould binders, in corrosion-resistant coatings, in catalyst preparation, and as a silicone intermediate (ACG98).

5 Biotransformation and kinetics

The committee did not find data on the kinetics of tetramethyl orthosilicate.

6 Effects and mechanism of action

Human data

The occupational experience in general with tetramethyl orthosilicate indicates a severe ocular hazard, ranging from eye pain to blindness and eye loss. Human exposure to 200-300 ppm (1260-1900 mg/m^3) tetramethyl orthosilicate for 15 minutes has been reported to induce minimal ocular lesions, while exposure to 1000 ppm (6300 mg/m^3) was found to produce corneal injury requiring hospitalisation. When exposure is moderate, recovery can be complete after 1 week if medical treatment is instituted promptly (ACG98).

Animal data

Irritation and sensitisation

When instilled into the eyes of rabbits, tetramethyl orthosilicate scored an injury grade of 9 (i.e., 5 µL and 5% solution give injury scores of over 5.0 points; 1% solution not over 5.0) on a scale of 1 to 10 (Car46, Smy51). In an unpublished report, it was stated that introduction of 1 µL liquid tetramethyl orthosilicate into a rabbit's eye produced a chemical burn. The characteristics of a burn were described as inflamed eyelids, oedema of the mucous membrane, resulting in the lids swollen but shut, dull or opaque cornea, and revealing a sharply defined central area of necrosis over the iris upon staining with fluorescein solution. Within 5-12 days, the cornea returned to a normal appearance without evident opacities remaining. Tetramethyl orthosilicate, diluted with an equal amount of water and applied within one minute into the eye in amounts equivalent to 0.01 mL of the undiluted test compound, did not cause eye burning (Smy37).

In the aforementioned unpublished report, effects of exposure to tetramethyl orthosilicate vapours were described as well. Exposure to a saturated mixture of droplet-free vapour in air (about 0.6% v/v, i.e., 6000 ppm) produced a typical eye burn being less severe than that produced by 0.01 mL of liquid tetramethyl orthosilicate. Exposure for 10 to 30 minutes caused a very severe eye burn. A 30-minute exposure to air saturated with tetramethyl orthosilicate and with water vapour produced eye injury less severe than that from exposure at normal humidity (Smy37).

In another unpublished report, it was stated that a 3- or 5-minute exposure to 10,000 ppm (63,000 mg/m^3) resulted in immediate eye injury in rabbits. Exposure to 750-1000 ppm (4725-6300 mg/m^3) caused delayed burns, while no such effects were observed at 500 ppm (3150 mg/m^3). Injury was scored 'immediately', after 3 hours, and after 1, 2, and 7 days (Ano47).

In guinea-pigs exposed daily for 5-15 minutes to approximately 800-2400 ppm (5000-15,000 mg/m^3), severe eye damage was reported from exposure day 3 onwards (Bad52). No eye injury was found in guinea pigs exposed to 170 ppm (1070 mg/m^3) for 15 minutes, 100 ppm (630 mg/m^3) for 1 hour, 20 ppm (130 mg/m^3) for 8 hours, or 25 ppm (160 mg/m^3), 8 hours/day, for 5 days. Brief exposure to high concentrations produced greater injury than did exposure to low concentrations for much longer periods. The latent period of ophthalmological changes was 16-48 hours. Histologically, the lesion was characterised as keratitis. The opacification was fully reversible while the microscopic changes

(keratitis) were almost completely reversible after the recovery period (probably 7 days) (Ver69).

Data on skin irritation are limited to the statement that tetramethyl orthosilicate did not materially injure unbroken (clippped) skin of rabbits during 0.5 hour of contact, although slightly reddening was observed (Smy37).

Acute toxicity

Using 3 groups of rats exposed to concentrations ranging from 31 to 88 ppm (195-555 mg/m^3), a 4-hour LC_{50} of 53 ppm (335 mg/m^3) was determined. The major signs observed during the post-exposure period were coughing and loss of body weight. Most of the animals with these symptoms did not recover and died within the first week of the post-exposure period. Upon necropsy, the principle finding was lung damage, ranging from small, discrete foci to areas covering the entire lobes of the lung (Kol82). Rats could tolerate exposure to a saturated* concentration of tetramethyl orthosilicate without mortality occurring for a maximum of 5 minutes. Six out of 6 rats survived a 4-hour exposure to 125 ppm (790 mg/m^3) while exposure to 250 ppm (1575 mg/m^3) was lethal to 6/6 (Smy51). In guinea pigs, the 1-hour, 4-hour, and 8-hour LC_{50} values were 320 ppm (2015 mg/m^3), 100 ppm (630 mg/m^3), and 30 ppm (190 mg/m^3), respectively. Effects observed were corneal opacification, lung oedema, and histological abnormalities in eyes and lungs (Ver69). A toxic pneumonia was seen in rabbits after a 10- to 30-minute exposure to a saturated mixture of droplet-free tetramethyl orthosilicate vapour (about 0.6% v/v, i.e., 6000 ppm). The lungs of the exposed animals were haemorrhagic and oedematous in large areas (Ano47).

The dermal LD_{50} in rabbits was 17 mL/kg bw (ca. 17.4 g/kg bw) (observation period: 14 days) (Smy51).

An oral dose of 700 mg/kg bw was lethal to rats and caused kidney damage (BIB88).

The intraperitoneal LD_{50} in mice was 250 mg/kg bw (BIB88, Ric94). When mice were given a single intraperitoneal administration of 1000 mg/kg bw, all animals died within 12 hours of administration. Histological examination revealed acute tubular necrosis, cytolysis in the white and red pulp of the spleen, congestion and oedema of the lung, and hepatic congestion. The cytolysis of the spleen was characterised by lympholysis and phagocytosis of the debris by

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* Theoretically (at 25°C), the concentration in saturated atmosphere can amount to 13,000 ppm or 80,860 mg/m^3 (calculated from: vapour pressure in Pa/10^5 Pa x 10^6 ppm).

infiltrating macrophages in the white pulp. In the red pulp, cytolysis of erythroblasts and/or granulopoietic cells and phagocytosis by macrophages were observed (Nak93).

Kidney damage, pulmonary oedema, and death were seen in rabbits after an intravenous dose of 90 mg/kg bw (BIB88).

Repeated-dose toxicity

In guinea pigs daily exposed to approximately 800 to 2400 ppm (ca. 5000-15,000 mg/m^3), for 5-15 minutes, mortality was observed from day 7 onwards. Other effects included ophthalmic lesions, lung haemorrhaging and pulmonary oedema, liver and kidney damage, and increased white blood cell levels. In some cases, the weight of the adrenals was increased. No effects on the brain were reported (Bad52).

In a range-finding study (for a 28-day study), rats (n=10/sex/group) were exposed to 5, 12, or 20 ppm (32, 76, 126 mg/m^3), 6 hours/day, for 5 days. No deaths and/or behavioural changes were seen. Exposure did not affect body weight gain. In the high-concentration group, there was a slight reduction in food consumption. Apart from lung haemorrhages in the animals exposed to 12 or 20 ppm, no gross pathology was seen in any of the exposure groups. In the high-concentration group, they were moderate and severe in 8/20 and 2/20 animals, respectively. In the animals of the mid-concentration group, minor and moderate haemorrhage was observed in 14/20 and 2/20, respectively. According to Kolesar and Siddiqui, these results suggested that a concentration of 10 ppm (63 mg/m^3) should be the maximum level in a 28-day study (Kol85).

In the subsequent 28-day study, rats (Sprague-Dawley; n=10/sex/group) were exposed to 1, 5, or 10 ppm (6, 32, and 63 mg/m^3). Study parameters included animal observations, body and organ weights, food consumption, haematology, clinical chemistry, urinalysis, and gross and histological examination. No treatment-related effects were seen in any treatment group. Therefore, a follow-up experiment using a similar protocol was performed with exposure concentrations of 15, 30, or 45 ppm (95, 190, 285 mg/m^3), 6 hours/day, 5 days/week. In the 45-ppm group, all animals died or were sacrificed moribund during the exposure period. Clinical signs such as lethargy, rough coat, dyspnoea, eye squinting, and nasal discharge were observed. In addition, mean body weights and food consumption were reduced. With respect to relative and/or absolute organ weights, there were no consistent, treatment-related changes. Because of untimely death, no haematology, clinical chemistry, or urinalysis parameters were evaluated. No treatment-related changes were found

in the bone marrow smears. Gross necropsy revealed nasal irritation and discharge. Lung and intestinal congestion or haemorrhage observed as well were considered agonal rather than directly treatment related. Upon microscopic examination, lesions were found in the respiratory tract tissues and the eyes. These lesions were most severe and had the greatest incidence in the nasal area and were of decreasing severity and incidence in the lower parts of the respiratory tract (pharynx, larynx, trachea, lungs); no lesions were found below the level of the tertiary bronchioles. In the nasal cavity, the respiratory epithelium was most severely affected. The principal types of lesions observed were epithelial ulceration, inflammation, and necrosis. The treatment-related ocular changes were confined to the cornea, consisted of desquamation of the central corneal epithelium, and were accompanied by acute or chronic keratitis. Other organs affected were the kidneys (tubule dilation), the liver (vacuolation and hyaline droplet formation in parenchymal cells), the spleen (lymphoid necrosis and hypoplasia), and the thymus (haemorrhage, necrosis, and hypoplasia). In the animals exposed to 30 ppm, there was no mortality. Clinical signs included lethargy, rough coat, dyspnoea, eye squinting, and nasal discharge. Furthermore, mean body weights and food consumption were reduced; there were no treatment-related effects on organ weights. Haematology or urinalysis parameters were not affected while decreases were found in total serum protein, serum LDH, and serum albumin levels. No treatment-related changes were found in the bone marrow smears. There were no macroscopic lesions. Histological lesions found were limited to those in the respiratory tract and eyes. The respiratory tract lesions were similar but less severe than those seen in the 45-ppm group. In the 15-ppm group, effects observed were clinical signs (lethargy, rough coat, eye squinting), decreased food consumption, and decreased total protein. Body weights were not affected. There were no macroscopic changes. Only minimal (as to severity and incidence) histological lesions were observed in the respiratory tract and eyes (Kol89).

These studies showed a steep dose-response curve with severe effects and lethality at 45 ppm (285 mg/m^3), moderate to severe effects at 30 ppm (190 mg/m^3), minimal effects at 15 ppm (95 mg/m^3), and no observable effects (NOAEL) at 10 ppm (63 mg/m^3).

In guinea-pigs orally dosed with 40-240 mg/kg bw/day for 30 days, toxic effects observed were kidney damage and increased white blood cell levels (BIB88).

The committee did not find data from mutagenicity, genotoxicity, carcinogenicity, or reproduction toxicity studies on tetramethyl orthosilicate.

7 Existing guidelines

The current administrative occupational exposure limit (MAC) for tetramethyl orthosilicate in the Netherlands is 1 ppm (6 mg/m^3), 8-hour TWA.

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

8 Assessment of health hazard

Human exposure to tetramethyl orthosilicate at concentrations of 6300 mg/m^3 (1000 ppm) has been found to produce corneal injury, while concentrations of 1260-1900 mg/m^3 (200-300 ppm) for 15 minutes induced minimal ocular lesions.

Experimental animal studies showed liquid and vapourous tetramethyl orthosilicate to be eye irritating. Based on acute lethal toxicity data (4-hour LC_{50} rats: 335 mg/m^3 or 53 ppm), the committee considers tetramethyl orthosilicate as toxic following inhalation. The toxicity following dermal exposure is low (LD_{50} rabbit: 17.4 mg/kg bw).

Following repeated inhalation exposure, the respiratory tract and the eyes appeared to be the target organs.

The committee did not find data from mutagenicity, genotoxicity, carcinogenicity, or reproduction toxicity studies on tetramethyl orthosilicate.

In the absence of a study with longer exposure duration, the committee takes the 28-day inhalation studies in rats as a basis for deriving a health-based recommended occupational exposure limit (HBROEL). These studies showed a steep dose-response curve. Exposure to 285 mg/m^3 (45 ppm), 6 hours/day, 5 days/week, caused the death of all animals while no mortality was observed in the 190-mg/m^3 (30 ppm) group (the next lower exposure group). Effects on the respiratory tract and the eyes were most prominent and, generally, severity and incidence decreased with decreasing exposure concentration from severe at 285 mg/m^3 (45 ppm) to severe to moderate and to minimal at 190 and 90 mg/m^3 (30, 15 ppm), respectively. No effects were observed at concentrations up to 63 mg/m^3 (10 ppm). The committee takes this NOAEL of 63 mg/m^3 (10 ppm) as a starting point. For the extrapolation to a HBROEL, the committee establishes an overall assessment factor of 18. This factor covers the following aspects: intra- and interspecies variation and the duration of the study. Thus, applying this factor and the preferred-value approach, a health-based occupational exposure limit of 2 mg/m^3 (0.3 ppm) is recommended for tetramethyl orthosilicate.

The committee recommends a health-based occupational exposure limit for tetramethyl orthosilicate of 2 mg/m^3 (0.3 ppm), as an 8-hour time-weighted average (TWA).

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Annex

Occupational exposure limits for tetramethyl orthosilicate 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	1	6	8 h	administrative		SZW04
Germany						
- AGS	0.16	1	8 h			TRG03
	0.16	1	15 min			
- DFG MAK-Kommission	-	-				DFG03
Great Britain						
- HSE	1	6.3	8 h	OES		HSE02
	5	32	15 min			
Sweden	-	-				Swe00
Denmark	1	6	ceiling			Arb02
USA						
- ACGIH	1	-	8 h	TLV		ACG04
- OSHA	-	-				ACG03
- NIOSH	1	6	10 h	REL		ACG03
European Union						
- SCOEL	-	-				EC04

[a] = 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.