Tetraethyl orthosilicate

(CAS No: 78-10-4)

Health-based Reassessment of Administrative Occupational Exposure Limits

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

No. 2000/15OSH/131, The Hague, June 8, 2004

Preferred citation:
Health Council of the Netherlands: Committee on Updating of Occupational Exposure Limits. Tetraethyl orthosilicate; Health-based Reassessment of Administrative Occupational Exposure Limits. The Hague: Health Council of the Netherlands, 2004; 2000/15OSH/131.

1 Introduction

The present document contains the assessment of the health hazard of tetraethyl 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 H Stouten, M.Sc. (TNO Nutrition and Food Research, Zeist, the Netherlands).

The evaluation of the toxicity of tetraethyl 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, Chemical Abstracts, and NIOSHTIC, starting from 1966, 1965, 1967, and 1973, respectively, and using the following key words: 78-10-4, tetraethoxysilane, ethyl silicate, tetraethyl orthosilicate, ethyl orthosilicate, silicon ethoxide, silicon tetraethoxide, tetraethoxysilicon, and tetraethyl 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	:	tetraethyl orthosilicate
synonyms	:	ethyl silicate; tetraethoxysilane; tetraethoxysilicon; tetraethyl silicate; *o*-silicic acid, tetraethyl ester; silicic acid, teraethyl ester; ethyl orthosilicate; silicon ethoxide; silicon tetraethoxide
molecular formula	:	$C_8H_{20}O_4Si$
structural formula	:	$Si(O\text{-}CH_2\text{-}CH_3)_4$
CAS number		78-10-4

3 Physical and chemical properties

molecular weight	:	208.3
boiling point	:	168°C
melting point	:	-82.5°C
flash point	:	37.2°C (closed cup); 51.7°C (open cup)
vapour pressure	:	at 20°C: 0.3 kPa
solubility in water	:	practically insoluble (slow hydrolysis into ethyl alcohol)
log $P_{octanol/water}$	:	0.04 (estimated)
conversion factors	:	at 20°C, 101.3 kPa: 1 ppm = 8.7 mg/m^3 1 mg/m^3 = 0.12 ppm

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

Tetraethyl orthosilicate is a colourless, flammable liquid with a faint odour. Odour thresholds of ca. 31 to 61 mg/m^3 (ca. 4-7 ppm) (Rut86) and of ca. 150 mg/m^3 (17 ppm) (Amo83) have been reported.

In view of the known slow reaction of tetraethyl orthosilicate with water (to form ethanol and silicic acid), partial hydrolysis of the vapour may occur by atmospheric humidity (Smy40).

4 Uses

Tetraethyl orthosilicate is used to weatherproof and acidproof mortar and cements, in heat- and chemical-resistant paints, and in other coatings (ACG98).

5 Biotransformation and kinetics

The committee did not find data on the biotransformation and kinetics of tetraethyl orthosilicate.

6 Effects and mechanism of action

Human data

Collaborators in experimental animal studies complained of slight eye and nose irritation at (probably) short-term exposures to 250 ppm (ca. 2175 mg/m^3). Severeness of these effects increased with increasing concentrations (up to ca. 26,000 mg/m^3 or 3000 ppm). A concentration of 85 ppm (740 mg/m^3) could be detected by odour, but was obviously not irritating (Smy40).

Animal data

Irritation and sensitisation

When instilled into the eyes of rabbits, tetraethyl orthosilicate scored an injury grade of 1 (i.e., 0.5 mL of undiluted test compound gives injury scores of 0 to 1.0 points) on a scale of 1 to 10 (Car46, Smy49). In a separate test, immediate marked irritation was reported when 0.2 mL of tetraethyl orthosilicate was instilled into the eyes of rabbits; eyes were normal 24 hours after instillation (Row48).

A 'drying' effect, but no 'appreciable' irritation was seen following application of 0.2 mL to the ear or abdomen of rabbits. Intradermal injection of 0.1 mL into the clipped dorsal rabbit skin caused erythema, oedema, and slight necrosis at the injection site, but treated areas were hardly detectable after 5 days while little, if any, immediate irritation was reported following a subcutaneous injection (Row48).

The committee did not find data on the potential sensitising properties of tetraethyl orthosilicate.

Acute toxicity

A 4-hour exposure to 2500 ppm (21,750 mg/m^3) caused the death of 4 out of 6 rats (observation period: 14 days) (Smy49). A 4-hour exposure to 4000 ppm (34,800 mg/m^3) killed all 5 rats. Exposure to 1837 ppm (15,980 mg/m^3) for 2, 3, 4, 6, or 8 hours induced mortality in 0/5, 1/5, 3/5, 9/10, and 5/5 animals, respectively. At an 8-hour exposure to 949 ppm (8255 mg/m^3), 4/5 rats died. Symptoms observed included eye and nose irritation, unsteadiness, tremors, salivation, respiratory difficulty, and unconsciousness. In 2 rats immediately killed after a 7-hour exposure to 949 ppm, weight loss and kidney damage (increased weight, microscopic lesions) were observed. Pulmonary damage was reported as well but it is not clear whether this was seen in these animals or only in the animals receiving 7-hour exposures for 2 or 3 days, which were part of this study as well (see Section 'Repeated-dose toxicity') (Row48). Other studies showed that 4-hour exposures to 1080-2400 ppm (ca. 9000-20,000 mg/m^3) were lethal to rats within 5 days and that exposure to 1115 ppm (9700 mg/m^3) for 2, 4, or 8 hours killed 1/6, 5/6, and 6/6 rats, respectively (Kas37, Smy40).

When male mice (ICR; n=10/group) were exposed to 1000 ppm (8700 mg/m^3), for 1, 2, 4, or 8 hours, mortality was observed during the 14-day post-exposure

observation period in 1/10, 1/10, and 6/10 animals exposed for 2, 4, and 8 hours, respectively. Body weights of animals exposed for 2 to 8 hours decreased up to 4 days post-exposure and did not reach the levels of the control animals during the observation period. In all dead animals exposed for 4 and 8 hours (2-hour exposed animal not examined because of autolysis), acute tubular necrosis, acute splenic atrophy, and olfactory epithelial necrosis were observed. Furthermore, pulmonary congestion and oedema and hepatic congestion were seen. In the surviving animals, there was a high incidence in kidney atrophy, interstitial nephritis, and effects on the olfactory epithelium (Nak94b).

When tested in guinea pigs, no mortality or signs of toxicity (irritation, tremors, respiratory difficulties) were seen following exposure to 395 ppm (3440 mg/m^3) for 8 hours while exposure to 700 ppm (6090 mg/m^3) for 6 hours caused narcosis and death in 1/6 animals. Irritation, lachrymation, tremors, respiratory difficulties, narcosis, and death were observed at exposures levels of 1115 (for 8 hours), 1970 (for 6 hours), and 2530 (for 4 hours) ppm (9700, 17,140, and 22,010 mg/m^3). Apart from eye and nose irritation and lachrymation, no effects were seen at exposure to 3070 ppm (26,710 mg/m^3) for 30 minutes. Some limited experiments with tetraethyl orthosilicate vapours in air of zero relative humidity resulted in somewhat more severe effects than experiments with similar concentrations in air of 70% relative humidity suggesting that atmospheric humidity may reduce acute toxicity by partly hydrolysing tetraethyl orthosilicate (Smy40).

In rabbits, a dermal LD_{50} of 5880 mg/kg bw has been reported (Smy49).

An oral LD_{50} of 6270 mg/kg bw has been reported in rats (Smy49). All 5 rats survived a single dose of 600 mg/kg bw, while doses of 1000 and 1400 mg/kg bw caused the death of 1/5 animals at each dose. At doses of 2000, 3000, and 5000 mg/kg bw, mortality was 2/3, 4/5, and 5/5 animals, respectively (Row48). No rats (F344; n=5/sex/group) died following single doses of 111, 223, or 333 mg/kg bw (observation time: 1 day), but dose dependent decreases in body weight and increases in silica-containing urinary crystals were observed. Post-mortem examinations showed microscopic changes in the kidneys, renal pelvis, bladder, stomach glands, muscle layers of the forestomach, and glandular stomach. The incidence and severity of these lesions was dose dependent (Oka92).

A single intravenous injection of ca. 190 mg/kg bw induced mortality in rabbits within one hour. When administered intraperitoneally, the minimum lethal dose in rats was ca. 560 mg/kg bw (Kas37). In mice (male; ICR), an intraperitoneal LD_{50} of ca. 500 mg/kg bw was reported (Nak94a). Single intraperitoneal injections of 250-1670 mg/kg bw into male mice (ICR) induced

mortality and effects on the kidney such as increased absolute kidney weights, acute tubular necrosis, tubular dilatation, and tubular interstitial nephritis (Nak93, Nak94a, Yam92).

Repeated-dose toxicity

In male rats (Wistar; n=2-10) exposed to 128 ppm (1115 mg/m^3), 7 hours/day, 5 days/week, for 5 to 30 days, only slight to moderate kidney damage and increased relative kidney and liver weights were seen. The kidney damage did not increase with increased exposure duration while the relative organ weights returned to control levels at the end of the study. Exposure to 250 ppm (2235 mg/m^3), 7 hours/day, 5 days/week, for 4, 8, or 10 days (n=2/group), induced body weight loss and kidney and lung lesions. There were no effects on the eyes or other organs (upper respiratory tract not examined). When animals exposed for 10 days were allowed to recover for 7 or 14 days, kidney lesions were still present at microscopic examination. Rats exposed to 470 ppm (4090 mg/m^3), 7 hours/day, for 3 or 5 days (n=2 and 5, respectively), lost weight and died or were killed. At post-mortem examination, pronounced kidney changes, slight lung irritation, and, occasionally, very slight parenchymal changes in the liver were observed. Weight loss, mortality, definite kidney and lung damage, and slight liver changes were induced by 2 and 3 7-hour exposures to 949 ppm (8255 mg/m^3) (n=2/group) (Row48).

In an experiment preceding a 90-day study, significant mortality (in 11/30) and decreased body weight gains and kidney, liver, and lung effects were found in albino Sherman rats (n=15/sex) exposed to 400 ppm (3480 mg/m^3), 7 hours/day, for 30 days (Poz68).

In male mice (ICR; n=10/group), no mortality occurred at exposure to 200 ppm (1740 mg/m^3), 6 hours/day, 5 days/week, for 2 or 4 weeks. During exposure, body weights were depressed and returned to control levels in mice exposed for 2 weeks, but not in those exposed for 4 weeks, during a 2-week post-exposure observation period. At post-mortem examinations, persistent tubulointerstitial nephritis was seen; incidences were 4/5 and 5/5 animals sacrificed one day after the 2- and 4-week exposure, respectively, and 4/5 and 4/5 in both recovery groups. Furthermore, persistent nasal irritation was observed in all animals, manifesting in the form of exudate containing inflammatory cells and necrotic epithelial cells (in 4/5 and 3/5, respectively), submucosal infiltration with polymorphonuclear neutrophils (in all), and hyaline droplets in and around the nasal mucosa (in all). In all animals of the recovery groups, the hyaline droplets were still present while there was still submucosal

infiltration in the 4-week-exposure recovery group (in 3/5). No effects were observed on organ weights or on the other organs examined (i.e., liver, lungs, spleen, pancreas). Blood biochemical and haematological parameters were only sporadically and transiently affected. Among these, there were decreases in the concentrations of blood urea nitrogen (not statistically significant in the 4-week group) and in haemoglobin and lymphocytes (in the 4-week group) (Nak94b).

In order to define a no-effect level for the kidney and nasal effects described above, a follow-up study was conducted in which male mice (ICR; n=10/group) were exposed to 0, 50, and 100 ppm (0, 435, and 870 mg/m^3), 6 hours/day, 5 days/week, for 2 or 4 weeks. Animals were observed daily for behavioural and external appearance; body weights were recorded 3 times a week. After sacrifice 2 days following the final exposure, organs were grossly examined and the cornea, nasal cavity, respiratory tract, lungs, liver, kidneys, spleen, pancreas, thymus, thyroid, and bone marrow were selected for microscopic evaluation. Blood and urine were analysed as well. Treatment did not cause mortality or effects on body weight gain. Immediately after ending exposure, most mice showed some behavioural changes (face-washing movements, licking lower abdomen). Post-mortem, no statistically significant changes were found in absolute organ weights (no data on relative weights presented) although the mean kidney weights were dose-dependently decreased in all exposure groups. No histological changes were seen in the liver, lungs, respiratory tract, spleen, pancreas, thymus, thyroid, and cornea. As to the kidneys, tubular interstitial nephritis was not observed in any of the animals exposed to 50 ppm (435 mg/m^3), but incidences in the high-concentration group were 2/10 and 2/10 animals exposed for 2 and 4 weeks, respectively. Inflammation of the nasal mucosa (nasal cavity: exudates containing inflammatory cells and necrotic epithelial cells; submucosal tissue: inflammatory cell infiltration; olfactory epithelium: eosinophilic hyaline droplets) was found in almost all exposed animals with a dose-dependent increase in severity. In the bone marrow of the femoral bone, there were increases in the M:E ratio. Haematological examinations showed decreases in red blood cell counts and packed cell volume in all exposure groups reaching statistically significance in the animals exposed to 50 ppm (435 mg/m^3) or to 100 ppm (870 mg/m^3) for 2 weeks only and in haemoglobin (estimated for animals exposed for 4 weeks only) while in the animals exposed for 2 weeks, the proportion of neutrophils and lymphocytes were significantly higher and lower, respectively. There were no changes upon biochemical and urinary examinations (Oma95).

In guinea pigs daily exposed to ca. 960-3000 ppm (ca. 8000-25,000 mg/m^3), 20-30 minutes/day, for about one month, no mortality occurred. Exposure

induced kidney and lung lesions and an increased urinary excretion of albumin and white and red blood cells. There were no effects on the eyes or the liver (Bad52).

When albino Sherman rats (n=15/sex/group), albino mice (n=13 males/group, 10 females/group), and guinea pigs (n=12/sex/group) were exposed to 0, 23, 50, and 88 ppm (0, 200, 435, and 765 mg/m^3), 7 hours/day, 5 days/week, for 90 days, no effects were seen at in-life and post-mortem examinations (liver and kidney weights; microscopic examination of heart, lung, liver, kidney, spleen, pancreas, adrenal glands, testes) other than a decrease in relative kidney weight in the mice of the high-exposure group (no dose-response relationship) (Poz68).

When rats (F344; n=5/sex/group) were given daily oral doses of 0 and ca. 1300, 2800, or 4300 mg/kg bw, for 2 or 4 days, all animals of the low-dose group survived treatment. Only one male and one female of the mid-dose group survived before sacrifice on day 4 while all animals of the high-dose group were dead by day 4 (day of first administration is day 0). Treatment induced histological changes in the kidneys (acute tubular necrosis, silicate accumulation, superficial necrotising papillitis), in the renal pelvis and bladder (urothelial simple hyperplasia, focal erosion of the mucosa, oedema, inflammation), and in the stomach glands, muscle layers of the forestomach, and glandular stomach (silicate accumulation). The incidence and severity of these lesions was time and dose dependent (Oka92). In male rats (Sprague-Dawley; n=7-37/group), fed daily doses of 0.5-2.0% tetraethyl orthosilicate (i.e., roughly 400-1600 mg/kg bw/day*) in the diet for up to 8 weeks, no silica urinary calculi or kidney effects were observed in the animals of the lowest dose group. Doses of 1.0 and 1.5% caused calculi in 1/7 animals of both groups, and kidney damage in 0/7 and 1/7, respectively. Examined in 3 separate experiments, doses of 2.0% induced body weight decreases of ca. 9%, calculi in 6/7, 19/37, and 7/20 rats, respectively, and kidney damage in 2/7 and 6/37 animals (not examined in third experiment) (Eme84, Gre97, Sch86).

The committee did not find data from carcinogenicity or reproduction toxicity studies on tetraethyl orthosilicate.

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* Assuming a body weight of 285 g and a daily food intake of 23 g; see Pau98.

Mutagenicity and genotoxicity

Tetraethyl orthosilicate did not cause a statistically significant increase in the frequency of mutations or a consistent dose-related increase in the frequency of SCE when tested *in vitro* in Chinese hamster ovary cells both in the presence and absence of an S9 metabolic activation system. When tested in rat hepatocytes, tetraethyl orthosilicate produced DNA damage as was indicated by highly positive results in a UDS test (Sle81). The committee did not find data on *in vivo* genotoxicity testing.

7 Existing guidelines

The current administrative occupational exposure limit (MAC) for tetraethyl orthosilicate in the Netherlands is 85 mg/m^3 (10 ppm), 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 data are limited to reports by collaborators in experimental animal inhalation studies who experienced (probably short-time) exposure to 2175 mg/m^3 (250 ppm) to be slightly irritating to eyes and nose, while a concentration of 740 mg/m^3 (85 ppm) could be detected by odour but was obviously not irritating.

Based on acute lethal toxicity data - mortality in 4/6, 3/5, and 5/6 rats at 4-hour exposures to 21,750 (2500 ppm), 15,980 (1837 ppm), and 9700 mg/m^3 (1115 ppm), respectively - , the committee considers tetraethyl orthosilicate as harmful following inhalation. Acute oral rat data varied considerably: an oral LD_{50} of 6270 mg/kg bw and mortality in 2/3 animals at a dose of 2000 mg/kg bw were reported. Following dermal exposure (LD_{50} rabbit: 5880 mg/kg bw), the committee considers the compound of low toxicity.

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

From repeated inhalation experiments, the mouse is concluded to be the most sensitive species, the nose and the kidneys being the target organs. The committee takes the 28-day inhalation study in mice (Oma95) as a basis for deriving a health-based recommended occupational exposure limit (HBROEL). In this study, irritation of nasal tissues was the critical effect, observed in all

animals exposed to 435 mg/m^3 (50 ppm), the lowest level tested. At the next higher level of 870 mg/m^3 (100 ppm), there were also effects on the kidneys (tubular interstitial nephritis) in 2/10 animals. The level of 435 mg/m^3 (50 ppm) is concluded to be the LOAEL for local effects (target organ: the nose) and the NOAEL for systemic effects (target organ: the kidneys), and taken as a starting point. For the extrapolation to a HBROEL, the committee establishes an overall assessment factor of 36. This factor covers the following aspects: the absence of an NOAEL for local effects, intra- and interspecies variation, and differences between experimental conditions and the exposure pattern of the worker. Thus, applying this factor and the preferred-value approach, a health-based occupational exposure limit of 10 mg/m^3 (1.2 ppm) is recommended for tetraethyl orthosilicate.

The committee recommends a health-based occupational exposure limit for tetraethyl orthosilicate of 10 mg/m^3 (1.2 ppm), as an 8-hour time-weighted average (TWA).

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Annex

Occupational exposure limits for tetraethyl orthosilicate in various countries.

country - organisation	occupational exposure limit ppm	occupational exposure limit mg/m^3	time-weighted average	type of exposure limit	note[a]	reference[b]
the Netherlands						
- Ministry of Social Affairs and Employment	10	85	8 h	administrative		SZW04
Germany						
- AGS	20	170	8 h			TRG03
	20	170	15 min			
- DFG MAK-Kommission	10	86	8 h		[d]	DFG03
	10	86	15 min[c]			
Great-Britain						
- HSE	10	87	8 h	OES		HSE03
	30	260	15 min			
Sweden	-	-				Swe00
Denmark	10	85	8 h			Arb02
USA						
- ACGIH	10	-	8 h	TLV		ACG04
- OSHA	100	850	8 h	PEL		ACG03
- NIOSH	10	85	10 h	REL		ACG03
European Union						
- SCOEL	10	87	8 h	[e]		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] Maximum number per shift: 4, with a minimum interval between peaks of 1 hour.

[d] Listed among compounds with MAK values but no pregnancy risk group classification.

[e] Listed among compounds for which OELs are agreed to be included in next Commission Directive