
Tetramethyl succinonitrile

(CAS reg no: 3333-52-6)

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/041, The Hague, 7 March 2002

Preferred citation:

Health Council of the Netherlands: Committee on Updating of Occupational Exposure Limits. Tetramethyl succinonitrile; Health-based Reassessment of Administrative Occupational Exposure Limits. The Hague: Health Council of the Netherlands, 2002; 2000/15OSH/041.

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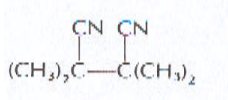
1 Introduction

The present document contains the assessment of the health hazard of tetramethyl succinonitrile 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 of the Academic Medical Centre, Amsterdam, the Netherlands).

Literature was retrieved from the data bases: Medline, Embase and Chemical Abstracts, starting from 1966, 1988 and 1970, respectively. Also Current contents and CD-ROM data bases from HSEline, Cisdoc, Mhidas and NIOSHTic, which cover the period up to and including 1997, were consulted. Another CD-ROM data base, from Poltox (Toxline, Cambridge Scient. Abstr. and FSTA), contained information on the period up to and including 1994. The following key words were used: tetramethyl succinonitrile, TMSN, and 333-52-6. The final literature search was carried out in May 1998.

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

2 Identity

name	:	tetramethyl succinonitrile
synonyms	:	tetramethyl succinyl acid dinitrile; tetramethyl butanedinitrile
molecular formula	:	$C_8H_{12}N_2$
structural formula	:	
CAS reg no	:	3333-52-6

3 Physical and chemical properties

molecular weight	:	136.2
boiling point	:	-
melting point	:	170°C (sublimes)
vapour pressure	:	-
solubility in water	:	insoluble
log P _{octanol/water}	:	1.11 (estimated)
conversion factors (20°C, 101.3 kPa)	:	1 mg/m ³ = 0.18 ppm 1 ppm = 5.68 mg/m ³

Data from ACG99, <http://esc.syres.com>.

Tetramethyl succinonitrile (TMSN) is an odourless and colourless crystalline solid material.

4 Uses

TMSN and nitrogen are released when the blowing agent, azo-bisisobutyronitrile, is heated and decomposes during the production of vinyl foam. TMSN is also the by-product of a polymerisation catalyst in photocopier toner (ACG99).

5 Biotransformation and kinetics

Hathaway *et al.* (Hat91) reported that uptake occurs after inhalation and through the skin, but no quantitative data are available. There is no specific information on the metabolism and excretion of this compound. Since tetramethyl succinonitrile belongs to the group of organic compounds that contain a cyanogroup as the characteristic functional group, it can be surmised that the compound will undergo biotransformation to cyanide, which is further metabolised to thiocyanate.

6 Effects and mechanism of action

Human data

Reinl (Rei57) reported five cases of acute accidental occupational exposure to tetramethyl succinonitrile. All cases showed about the same symptoms. After inhalation they got unconscious with convulsions. Further investigations on workers employed at the same factory displayed that some symptoms were prominent in the group: frequent headaches, excessive salivation and sense of taste, nausea, and vomiting. No exposure levels were reported.

Animal data

Harger and Hulpieu (Har49, abstract only), reported that experimental animals poisoned with tetramethyl succinonitrile exhibited violent convulsions, with asphyxial death between 1 minute and 5 hours after the first convulsion. The subcutaneous LD₅₀ was 30 mg/kg bw in rats and 23 mg/kg bw in guinea pigs. The intravenous LD₅₀ was 20 mg/kg bw in rabbits. A dose of 2.5 mg/kg bw caused convulsions. In rats, inhalation of 60 ppm (341 mg/m³) of tetramethyl succinonitrile was fatal in 2 to 3 hours, and a concentration of 6 ppm (34 mg/m³) was fatal in about 30 hours.

Reinl (Rei57) studied ten rats injected intraperitoneally with 5 mg/kg bw/day tetramethyl succinonitrile during 14 successive days. During the experiment and postexperimental observation the animals did not show any effects. However, the authors did not describe the clinical parameters they used in their experiment. They only reported that the body weights were even increased. No control group was used in this experiment.

Johannsen and Levinskas (Joh86) performed well conducted subchronic toxicity studies in rats and dogs. First, they performed a pilot study in which they found a single oral rat LD₅₀ of TMSN of 38.9 (31.5 - 46.1) mg/kg bw. Next, they performed three subchronic gavage studies in rats. In the first study, groups of 15 male and 15 female rats were administered 0, 1, 3 or 10 mg/kg bw/day TMSN during 90 days. Clinical chemistry as well as pathological examinations of all organs of the exposed and control groups were performed. The authors found treatment-related morphological changes in the kidney of male, but not female rats at all dosage levels. These changes mainly consisted of degeneration of the proximal convoluted tubules, also some of the distal

convoluted tubules were affected. Hyaline droplet formation was observed in the cytoplasm of epithelial cells lining the tubules. Treatment-related liver changes were also seen in both male and female rats given 10 mg/kg bw/day TMSN. Microscopic changes consisted of enlarged hepatocytes in the centrilobular and midzonal regions of the liver. Absolute and relative liver weights were significantly increased in rats exposed to doses of 3 mg/kg bw/day TMSN or higher.

In the second study, groups of 15 male rats were administered 0, 0.1, 0.3 or 1.0 mg/kg bw/day TMSN for 90 days. Similar effects on the kidneys as in the first study were found. The renal changes were consistent with the definition of renal nephrosis. Again, numerous hyaline droplets were observed in the cytoplasm of epithelial cells of the tubules. No other toxicological effects were found.

The third gavage subchronic study was performed to determine the no-adverse effect level of renal tubular nephrosis in male rats. Groups of 15 male rats were administered 0, 0.001, 0.01 or 0.1 mg/kg bw/day TMSN during 90 days. At doses of 0.001 and 0.01, no microscopic changes were observed in the kidneys. The authors concluded that the no-observed-adverse-effect level (NOAEL) for effects on the kidney of male rats was 0.01 mg/kg bw/day TMSN.

A study on male rats using a dose of 0.3 mg/kg bw/day during 90 days and an observation period of 7 days showed that the effects on the kidney were reversible. The kidney as target organ in male rats was also found when TMSN was administered via drinking water.

The authors also performed a similar experiment in dogs (4 groups of 4 males and 4 females). TMSN was administered via gelatin capsules for 90 days. The doses were equivalent to 0, 0.3, 1.0 and 3.0 mg/kg bw/day. In the female dogs body weight gain was slightly suppressed. In 4 out of 8 dogs (3 female, one male) of the highest dose group relative liver weights were significantly increased at necropsy. No (microscopic) histological effects related to the treatment in either liver or kidney were found. Blood cyanide concentrations among the treated animals were comparable to the untreated controls, as well as haematological and urine analyses.

There is no data available on long-term exposure, carcinogenicity, mutagenicity, genotoxicity and reproduction toxicity.

7 Existing guidelines

The current administrative occupational exposure limit (MAC) for tetramethyl succinonitrile in the Netherlands is 3 mg/m³ (0.5 ppm), 8-hour TWA, with a skin notation.

Existing occupational exposure limits for tetramethyl succinonitrile in various countries are summarized in the annex.

8 Assessment of health hazard

Accidental exposure of workers to tetramethyl succinonitrile caused acute systemic toxicity, with convulsions as the most prominent symptom. No data on exposure concentrations are available.

The committee considers the subchronic gavage experiment performed by Johanson and Levinkas (Joh86) as the key study. In this study, a no-observed-adverse-effect level (NOAEL) of 0.01 mg/kg bw per day TMSN was found for effects on the kidneys of male rats only (not in female rats, nor in male or female dogs). However, the committee considers the kidney effects, among which hyaline droplet formation, as not relevant to man because it is thought to be induced by the accumulation of the male rat-specific protein α -2u-globulin.

The committee considers the liver to be the target organ. Liver effects were found in male and female rats (increased relative liver weight and microscopic cellular changes) and dogs (increased relative liver weight) (Joh86). These effects were observed in rats at doses of 3 and 10 mg/kg bw/day, resp., and in dogs at 3 mg/kg bw/day. This means that the NOAEL for liver effects in both species is 1 mg/kg bw/day TMSN administered during 90 days.

The committee uses the NOAEL of 1 mg/kg bw/day in rats as a starting point for the assessment of a health-based recommended occupational exposure limit (HBROEL). Since workers are exposed for 5 days a week this NOAEL from a continuous feeding study (*i.e.*, 7 days/week) is adjusted by multiplying with a factor of 7/5, resulting in a no-adverse-effect level (NAEL) of 1.4 mg/kg bw/day. For differences in caloric demand between rats and humans the committee applies a scaling factor of 4. To account for inter- and intraspecies variation and the duration of exposure, the committee considers an overall assessment factor of 12 to be appropriate for the extrapolation of the subchronic oral NAEL in rats to a working lifetime exposed worker. A lower factor for interspecies variation is justified because the effects on the liver were found in two species and the effect

levels were comparable. After applying the overall factor and assuming 100% absorption, an average body weight of a worker of 70 kg and a breathing volume of 10 m³ per working day*, the committee recommends a preferred value of 0.2 mg/m³, 8-hour TWA.

The committee recommends a health-based occupational exposure limit for tetramethyl succinonitrile of 0.2 mg/m³ (0.036 ppm), as an 8-hour time-weighted average (TWA).

References

- ACG99 American Conference of Governmental Industrial Hygienists (ACGIH). Tetramethyl succinonitrile. In: TLVs[®] and other occupational exposure values -1999. [CD-ROM]. Cincinnati OH, USA; ACGIH[®], 1999.
- ACG00 American Conference of Governmental Industrial Hygienists (ACGIH). Guide to occupational exposure values - 2000. Cincinnati OH, USA: ACGIH[®], Inc, 2000: 118.
- ACG01 American Conference of Governmental Industrial Hygienists (ACGIH). 2001 TLVs[®] and BEIs[®]. Threshold Limit Values for chemical substances and physical agents. Biological Exposure Indices. Cincinnati OH, USA: ACGIH[®], Inc, 2001: 56.
- Arb00a Arbejdstilsynet. Grænseværdier for stoffer og materialer. Copenhagen, Denmark: Arbejdstilsynet, 2000; (At-vejledning C.0.1).
- Arb00b Arbetarskyddstyrelsen. Hygieniska gränsvärden och åtgärder mot luftföroreningar. Solna, Sweden: National Board of Occupational Safety and Health, 2000; (Ordinance AFS 2000/3).
- CEC00 Commission of the European Communities (CEC). Commission Directive 2000/39/EC of 8 June 2000 establishing a first list of indicative occupational exposure limit values in implementation of Council Directive 98/24/EC on the protection of the health and safety of workers from the risks related to chemical agents at work. Official Journal of the European Communities 2000; L142 (16/06/2000): 47-50.
- DFG01 Deutsche Forschungsgemeinschaft (DFG): Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area. List of MAK and BAT values 2001. Maximum concentrations and biological tolerance values at the workplace. Weinheim, FRG: Wiley-VCH, 2001: 101; (rep no 37).
- HSE01 Health and Safety Executive (HSE). EH40/2001. Occupational exposure limits 2001. Sudbury (Suffolk), England: HSE Books, 2001: 26.
- Har49 Harger RN, Hulpieu HR. Toxicity of tetramethyl succinonitrile and the antidotal effects of thiosulfate, nitrite and barbiturates. Fed Proc 1949; 8: 205 (abstr.).

* (1.4 mg/kg : (4 x 12)) x (70 kg : 10 m³)

- Hat91 Hathaway GJ, Proctor NH, Hughes JP, *et al.*, eds. Tetramethylsuccinonitrile. In: Proctor and Hughes' Chemical hazards of the workplace. New York, USA: Van Nostrand Reinhold, 1991: 539-40.
- Joh86 Johannson FR, Levinkas GJ. Subchronic toxicity of tetramethylsuccinonitrile. *Fundam Appl Toxicol* 1986; 7: 41-8.
- NIO78 National Institute for Occupational Safety and Health (NIOSH). Criteria for a recommended standard. Occupational exposure to nitriles. Washington DC, USA: NIOSH, 1978.
- Rei57 Reinl W. Erkrankungen durch Tetramethylbernsteinsäuredinitril bei der Schaumstoffherstellung. *Arch Toxikol* 1957; 16: 367-80.
- SZW01 Ministerie van Sociale Zaken en Werkgelegenheid (SZW). Nationale MAC-lijst 2001. The Hague, the Netherlands: Sdu, Servicecentrum Uitgevers, 2001: 41.
- TRG00 TRGS 900. Grenzwerte in der Luft am Arbeitsplatz; Technische Regeln für Gefahrstoffe. B ArbB1 2000; 2.

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Annex

Occupational exposure limits for tetramethyl succinonitrile 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	0.5	3	8 h	administrative	S	SZW01
Germany -AGS	0.5	3	8 h		S	TRG00
-DFG MAK-Kommission	2	12	15 min		S	DFG01
	-	- ^c			S	
Great-Britain -HSE	0.5	2.8	8 h	OES	S	HSE01
	2	11	15 min			
Sweden	-	-				Arb00b
Denmark	0.5	3	8 h		S	Arb00a
USA -ACGIH	0.5	-	8 h	TLV	S	ACG01
-OSHA	0.5	3	8 h	PEL	S	
-NIOSH	0.5	3	10 h	REL	S	
European Union -SCOEL	-	-				CEC00

^a S = skin notation; skin uptake can contribute substantially to the 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 in experimental animals have yielded insufficient information for the establishment of a MAK value