Tricarbonyl(*eta*-cyclopentadienyl)-manganese

(CAS reg no: 12079-65-1)

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/042, The Hague, 7 March 2002

Preferred citation:
Health Council of the Netherlands: Committee on Updating of Occupational Exposure Limits. Tricarbonyl(eta-cyclopentadienyl)manganese; Health-based Reassessment of Administrative Occupational Exposure Limits. The Hague: Health Council of the Netherlands, 2002; 2000/15OSH/042.

1 Introduction

The present document contains the assessment of the health hazard of tricarbonyl(*eta*-cyclopentadienyl)manganese 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 RN Hooftman, M.Sc. and H Stouten, M.Sc. (TNO Nutrition and Food Research, Zeist, the Netherlands).

The evaluation of the toxicity of tricarbonyl(*eta*-cyclopentadienyl)manganese has been based on the review by ACGIH (ACG91). Where relevant, the original publications were reviewed and evaluated as will be indicated in the text. In addition, literature was retrieved from the on-line data bases Medline, Toxline, and Chemical Abstracts covering the period 1966 to 24 October, 1997 (19971024/UP), 1965 to 20 October 1997 (19971020/ED), and 1967 to 28 October, 1997 (971028/ED); vol 127 iss 18), respectively, and using the following key words: manganese cyclopentadienyltricarbonyl (excluding manganese methylcyclopentadienyl tricarbonyl with CAS Registry Number 12108-13-3) and 12079-65-1. HSDB (no record) and RTECS, data bases available from CD-ROM, were consulted as well (NIO98, NLM98). The final literature search has been carried out in October 1997, followed by an additional search in May 2001.

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	:	tricarbonyl(*eta*-cyclopentadienyl)manganese (TCM)
synonyms	:	tricarbonyl (η^{5}-2,4-cyclopentadien-1-yl)-manganese tricarbonyl-pi-cyclopentadienylmanganese tricarbonyl-π-cyclopentadienylmanganese cyclopentadienyl manganese tricarbonyl manganese cyclopentadienyl tricarbony manganese, tricarbonyl-pi-cyclopentadienyl
molecular formula	:	$C_8H_5MnO_3$
structure	:	
CAS reg no	:	12079-65-1

Data from ACG91, Ric94.

3 Physical and chemical properties

molecular weight	:	204,1
boiling point	:	232 - 233^{0}C
melting point	:	75 - 77^{0}C (sublimes)
flash point	:	-
vapour pressure	:	-
solubility in water	:	sparingly soluble
Log $P_{octanol/water}$	:	-0.57 (estimated)
conversion factors (20^{0}C, 101.3 kPa)	:	not applicable

Data from ACG91, Ric94.

TCM is a bright yellow crystalline substance with camphoraceous odour (ACG91).

4 Uses

TCM is used as an octane enhancement additive for unleaded gasoline (ACG91).

5 Biotransformation and kinetics

There is only some limited information on the toxicokinetics of TCM available.

Twenty-four hours after a single subcutaneous administration of 0.5-2.5 mg Mn/kg bw as TCM to male rats, there was a significant increase in the amount of manganese in the lungs. Since this manganese was in a nonlipid soluble form, metabolites rather than parent compound may have been accumulated. Treatment did not affect blood and hepatic nonprotein sulphydryl levels measured in animals sacrificed at 1.5, 6, or 24 hours after administration. Pulmonary levels were statistically significantly increased (twofold) over control levels, but at t=24 h only. Pretreatment with piperonyl butoxide partially prevented this increase after a dose of 0.5 mg Mn/kg (as TCM), but had no effect on a dose of 1.0 mg Mn/kg. Since TCM treatment did not alter pulmonary levels of thiobarbituric acid reactive materials, it was concluded that there were no indications for detectable lipid peroxidation (Cla89).

When given a single oral (gavage) dose of 50 mg/kg bw to rats after a 3-day pretreatment with phenobarbital, a decrease in urine volume and a sharp rise in urinary manganese excretion was found on day 1 and 2 after TCM administration, amounting to approximately 16% of the dose administered. The majority of the urinary manganese was concluded to be in the organometallic form. Although metabolites were not identified, the authors considered it conceivable that TCM may have undergone ring hydroxylation followed by conjugation and excretion of at least some of the hydroxylated material. Toxicity studies in which phenobarbital was shown to prevent the occurrence of toxic effects (convulsions, oedema) in rats (see also next section) suggested (enhancement of) biotransformation to more polar and less toxic metabolites (Pen85).

The *in vitro* metabolism of TCM has been studied using nasal, pulmonary, and hepatic microsomes isolated from rats sacrificed 2, 12, or 24 hours after a intraperitoneal injection of 0.5 or 1.0 mg *m*-xylene/kg bw. Pretreatment with *m*-xylene (known to differently alter cytochrome P450 activation in rodent pulmonary *vs* hepatic tissues) inhibited nasal and pulmonary, but not hepatic microsomal metabolism of TCM at all time points. Comparison with the results of concomitantly performed experiments suggested the involvement of the pulmonary cytochrome P450 IIB1 isozyme (Bla94).

Further *in vitro* studies showed that TCM was metabolis ed by rat lung and liver homogenates or microsomes, but not by the cytosol. For TCM, the apparent

K_m was estimated to be 1.0 and 20 µg/mL, the V_{max} to be 4.8 and 89 µg/min/g, in lung and liver tissue, respectively. Thus, the intrinsic pulmonary and hepatic clearance of TCM as calculated from the *in vitro* V_{max}/K_m ratio (4.5 mL/min) were similar. In the experiments, no metabolites were detected in the incubation medium by HPLC analysis, but gas chromatographic analysis of headspace air showed the presence of an unidentified, volatile metabolite with a low boiling point. This metabolite was cytochrome P450 mediated. Phenobarbital pretreatment induced hepatic, but not pulmonary TCM metabolism, while both 3-methylindole and *m*-xylene pretreatment inhibited pulmonary but not hepatic metabolism. In microsomes of freshly prepared alveolar type II cells, no TCM-metabolising capacity could be detected. From these *in vitro* data together with the results of toxicity studies both with and without adding metabolism-interfering compounds, the authors summarised that *in situ* activation of TCM within the lungs is necessary to induce its alveolar toxicity. However, since the alveolar type II cells did not exhibit metabolically activating capacity, it was suggested that a volatile, active metabolite was produced in the bronchiolar Clara cells and from there transported to the alveolar region (Bla96).

6 Effects and mechanism of action

Human data

There were no data on workers occupationally exposed to TCM.

Animal data

TCM was stated to cause a certain degree of irritation (not further specified) when applied as an oil emulsion to selected areas of the skin of rabbits (Ark65). When the tails of mice (n=10/group) were exposed to a solution of 1 g TCM/100 mL gasoline, 2 hours/day, for 5 days, first petechial and then confluent haemorrhages were seen after 4 to 5 applications. The greater part of the tail was subsequently lost by necrosis. Since similar effects were observed to the gasoline-alone exposed controls, these effects were attributed to gasoline rather than to TCM (Ark65).

Eighty percent of the rats exposed to 120 mg/m^3, for 2 hours, died, while there was no mortality following a 2-hour exposure to 20 or 40 mg/m^3. The authors stated that they did not succeed in obtaining a concentration that killed all animals. Although guinea pigs and rabbits were involved in the experiments as

well, no data regarding these species were presented. Acute effects reported to be observed following inhalation exposure were vascular changes (increased permeability of vessels, oedema, haemorrhages, decreased blood pressure), effects on the nervous system (atrophic changes in the nerve cells), and haematological changes (erythrocytosis, decreased osmotic pressure of the erythrocytes) (Ark65).

Following immersing of the tails of mice (n=10/group) in a solution of 1 g TCM/100 mL gasoline, 2 hours/day, for 5 days, no differences were seen in effects found in animals exposed to gasoline with and without TCM. Inhalation was prevented by placing the animals at the edge of a fume cupboard with their muzzles towards its door. However, tetrahydrofuran solutions of TCM were found to be more toxic than solutions in oil. All animals whose tails had been immersed in tetrahydrofuran solutions died within 1 hour, while no mortality occurred in the group exposed to tetrahydrofuran alone (Ark65).

When injecting single subcutaneous doses of 0, 0.5, 1.0, and 2.5 mg Mn/kg bw as TCM (vehicle: propylene glycol) to male rats, 5/9 animals of the high-dose group died within 24 hours most likely due to pulmonary oedema and/or inflammation. There were no changes in plasma lactate dehydrogenase, sorbitol dehydrogenase, and blood urea nitrogen levels (measured at t=24 h) in any of the treatment groups suggesting the absence of marked hepatic or renal damage. Lung lavages (performed only in the animals surviving for 24 hours) showed dose-dependent lung damage (small increase in the LDH level, large increase in albumin and protein content). Piperonyl butoxide diminished pneumotoxicity suggesting that this effect may be caused by the formation of mono-oxygenase metabolites (Cla89).

In a follow-up study, 3.76 mg TCM/kg bw was administered subcutaneously to male rats. At histological examination of the lungs and trachea, pulmonary lesions were observed in all animals sacrificed 48 or 96 hours after injection, but in none of the animals killed after 24 hours. The lesions were found in the alveolar region only and consisted of areas of thickened alveolar septa containing mononuclear cells, distended perivascular lymphatics, and alveolar haemorrhage; there were neither overt signs of necrosis nor infiltration of neutrophils. In additional experiments, the pulmonary toxicity of TCM was quantified by bronchoalveolar lavage fluid protein, albumin, and lactate dehydrogenase levels in rats treated with TCM alone or with TCM following pretreatment with *m*-xylene, 3-methylindole, and phenobarbital. Pretreatment with each of these compounds considerably or completely reduced pneumotoxicity as estimated by the lavage parameters (Bla96).

Following oral administration, LD_{50} values of 22 (95% C.I.: 19-26 mg/kg) and 80 mg/kg bw in rats and of 150 mg/kg bw in mice have been reported (Ark63, Pen85). Furthermore, there was an intraperitoneal LD_{50} of 14 mg/kg bw (95% C.I.: 10 - 20 mg/kg) in rats (Pen85) and there were intravenous LD_{50}s of 0.7 (NIO98) and 3.2 mg/kg bw (Str64) in mice.

Single oral or intraperitoneal administration of 15.9-40 and 8.0-31.7 mg/kg bw, respectively, to male rats (n=4/group) produced convulsions, pulmonary oedema, and increased relative lung weights. The ED_{50}s for convulsion were 32 (95% C.I.: 24-42 mg/kg) and 20 mg/kg (95% C.I.: 15-26 mg/kg) following oral and intraperitoneal administration, respectively. Lethal effects were not directly related to convulsions: some animals died without ever showing convulsions. Phenobarbital pretreatment prevented the occurrence of both convulsions and oedema, presumably by enhancing the biotransformation of TCM to more polar and less toxic metabolites. After pretreatment with relatively small intraperitoneal doses of 5 mg TCM/kg bw, for 3 days, a single oral dose of 34 mg TCM/kg bw induced convulsions (in 4/7 *vs* 10/10 in not pretreated animals) but no mortality (pneumotoxicity) (0/7 *vs* 10/10); a preceding 3-day fasting period had similar effects (convulsions in 1/5, mortality in 1/5) (Pen85).

Single intraperitoneal doses of 10 and 30 mg/kg bw induced moderate necrosis of the nonciliated bronchiolar (Clara) cells in rat and mouse, respectively (time of sacrifice: at 24 h) (Has82).

Rabbits, guinea pigs, and rats (number unknown) were exposed to an average concentration of 1 mg/m^3, 4 hours/day, for 11 months. In rats, there were no visible signs of toxicity, but some effect on the nervous system (*i.e.*, an increase in the threshold level of neuromuscular excitability measured by electric stimuli) occurred in the course of the experiment. Exposure induced effects on the kidneys as was indicated by decreased diuresis and proteinuria (no data presented). Especially in guinea pigs and rabbits, there was a decrease in resistance to infection. Although it was stated that animals were examined histologically, results were not presented (Ark65). The significance of the result reported in this study are difficult to assess. No quantitative data or statistical analyses were presented. The results of the neuromuscular excitability threshold were presented by a graph, but there were some discrepancies between this graph and the text. In addition, no standard deviations were included.

There were no data available from genotoxicity, carcinogenicity, and reproduction toxicity studies.

7 Existing guidelines

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

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

8 Assesment of health hazard

No human data and only limited data from single dose inhalation, oral, subcutaneous, or intraperitoneal experiments in animals are available.

Limitedly reported acute inhalation data (80% mortality in rats exposed to 120 mg/m^3 for 2 hours) suggest that TCM should be considered as very toxic by inhalation.

From acute oral mortality studies (LD_{50} rat: 22 mg/kg bw), the committee considers TCM to be very toxic if swallowed.

Following single oral, intraperitoneal, or subcutaneous exposure of rats, the lung is the target organ, although convulsions have been observed as well.

The committee considers the toxicological data base on tricarbonyl(*eta*-cyclopentadienyl)manganese 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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ACG00 American Conference of Governmental Industrial Hygienists (ACGIH). Guide to occupational exposure values - 2000. Cincinnati OH, USA: ACGIH®, Inc, 2000: 73.

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: 38.

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).

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Cla89 Clay RJ, Morris JB. Copmparitive pneumotoxicity of cyclopentadienyl manganese tricarbonyl and methylcyclopentadienyl manganese tricarbonyl. Toxicol Appl Pharmacol 1989; 98: 434-43.

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Str64 Strohmeier W. Toxizität von Cyclopentadienylmangantricarbonyl- und Chromhexacarbonyl-Derivaten. Z Naturforsch 1964; 19: 540.

SZW01 Ministerie van Sociale Zaken en Werkgelegenheid (SZW). Nationale MAC-lijst 2001. The Hague, the Netherlands: Sdu, Servicecentrum Uitgevers, 2001: 42.

TRG00 TRGS 900: Grenzwerte in der Luft am Arbeitsplatz; Technische Regeln für Gefahrstoffe. BArbBl 2000; 2.

Annex

Occupational exposure limits for tricarbonyl(*eta*-cyclopentadienyl) manganese in various countries.

country -organisation	occupational exposure limit		time-weighted average	type of exposure limit	note[a]	lit ref[b]
	ppm	mg/m^3 [c]				
the Netherlands						
-Ministry of Social Affairs	-	0.1	8 h	administrative	S	SZW01
and Employment	-	0.3	15 min			
Germany						
-AGS	-	0.1	8 h		S	TRG00
-DFG MAK-Kommission	-	-				DFG01
Great-Britain						
-HSE	-	0.1	8 h	OES	S	HSE01
	-	0.3	15 min			
Sweden	-	-				Arb00b
Denmark	-	0,1	8 h		S	Arb00a
USA						
-ACGIH	-	0.1	8 h	TLV	S	ACG01
-OSHA	-	0.1	8 h	PEL	S	ACG00
-NIOSH	-	0.1	10 h	REL	S	ACG00
European Union						
-SCOEL	-	-				CEC00

[a] S = skin notation; this 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] In all cases, exposures are measured as manganese