Gezondheidsraad **Voorzitter**
Health Council of the Netherlands

Aan de Staatssecretaris van Sociale Zaken en Werkgelegenheid

Onderwerp : Aanbieding adviezen herevaluatie bestuurlijke MAC-waarden
Uw kenmerk : ARBO/AMIL/97/00648
Ons kenmerk : U 2706/CB/MP/563-O3
Bijlagen : 18
Datum : 14 december 2000

Mijnheer de staatssecretaris,

Op verzoek van uw ambtsvoorganger bied ik u hierbij de eerste adviezen aan van een reeks over de gezondheidskundige basis van uit het buitenland overgenomen grenswaarden voor beroepsmatige blootstelling aan stoffen. Het verzoek om deze adviezen is in algemene zin vervat in brief nr ARBO/AMIL/97/00648 en in latere stadia door uw departement toegespitst op afzonderlijke stoffen. De adviezen zijn opgesteld door een daartoe door mij geformeerde internationale commissie van de Gezondheidsraad en beoordeeld door de Beraadsgroep Gezondheid en Omgeving.

De beoogde reeks van in het Engels gestelde adviezen zal losbladig worden gepubliceerd onder ons publicatienummer 2000/15OSH en, conform de aan de Gezondheidsraad voorgelegde toespitsingen van de adviesaanvraag, betrekking hebben op 168 stoffen. Het u thans aangeboden eerste pakket bestaat uit een Algemene Inleiding (publicatienummer 2000/15OSH/000) en uit de adviezen genummerd 2000/15OSH/001 tot en met 2000/15OSH/017, respectievelijk betrekking hebbend op:
cesiumhydroxide, cyclopentaan, diboraan, dimethoxymethaan, dipropylketon, fenylfosfine, germaniumtetrahydride, hexachloornaftaleen, methaanthiol, methylcyclohexanol, methylisopropylketon, mica, natriumhydroxide, octachloornaftaleen, silaan, tetrachloornaftaleen, en yttrium en yttriumverbindingen.

Bij afronding van de werkzaamheden van de hierboven bedoelde commissie ontvangt u een Nederlandstalige samenvatting van de in de gehele reeks van adviezen neergelegde bevindingen.

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Gezondheidsraad
Health Council of the Netherlands

Onderwerp : Herevaluatie uit het buitenland overgenomen grenswaarden
Ons kenmerk : U
Pagina : 2
Datum : 14 december 2000

De u thans aangeboden adviezen heb ik vandaag ter informatie doen toekomen aan de Minister van Volksgezondheid, Welzijn en Sport en aan de Minister van Volkshuisvesting, Ruimtelijke Ordening en Milieubeheer.

Hoogachtend,

prof. dr JJ Sixma

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Methyl isopropyl ketone

(CAS reg. nr: 563-80-4)

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/009, The Hague, 14 December 2000

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1 Introduction

The present document contains the assessment of the health hazard of methyl isopropyl ketone (MIPK) 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, Current Contents, Embase and Chemical Abstracts, starting from 1966, 1970, 1988 and 1970, respectively, and using the following key words: methyl isopropyl ketone, isopropylmethylketone, methylbutanone, MIPK or 563-80-4. Also CD-roms Poltox (from 1994 backwards), HSEline, Cisdoc, Mhidas and NIOSHtic (from 1997 backwards) were consulted. Data considered to be critical were evaluated by reviewing the original publications. The final literature search has been carried out in January 1998.

In March 2000, the President of the Health Council released a draft of the document for public review. Comments were received by the following individuals and organizations: A Aalto (Ministry of Social Affairs and Health, Tampere, Finland), dr P Wardenbach (Bundesanstalt für Arbeitsschutz und Arbeitsmedizin, Dortmund, Germany). These comments were taken into account in deciding on the final version of the document.

2 Identity

name	:	methyl isopropyl ketone
synonyms	:	2-acetyl propane isoprpopylmethylketone 3-methyl-2-butanone 3-methyl butane-2-one MIPK
molecular formula	:	$C_5H_{10}O$
structural formula	:	$CH_3COCH(CH_3)_2$
CAS reg nr	:	563-80-4

3 Physical and chemical properties

molecular weight	:	86.14
boiling point	:	94.5^0C
melting point	:	?
vapour pressure	:	8.3^0C: 1.33 kPa
log $P_{oct/water}$	:	not known
solubility in water	:	slight
conversion factors (20^oC, 101.3 kPa)	:	1 mg/m^3 = 0.28 ppm 1 ppm = 3.58 mg/m^3

Data from ACG96.

MIPK is a colourless, flammable liquid with an acetone-like odour. The odour threshold of this compound lies between 1.9 and 3.1 ppm (6.8 and 11 mg/m^3) (Amo83, ACG96).

4 Uses

MIPK is used as a solvent for nitro-cellulose lacquers (ACG96).

5 Biotransformation and kinetics

There is no information on routes of intake. MIPK may be absorbed through inhalation of its vapour or aerosol, and by ingestion.

Ketones are not readily metabolized in the body (Ano78). With most of the lower ketones as much as 50% of the dose may be eliminated unchanged from the body, mainly in the exhaled air and to a small extent in the urine. The major metabolic pathway of ketones is reduction to the corresponding secondary alcohols, which are usually eliminated as glucuronic acids. In rats, 38-54% of a dose of 1000 mg/kg bw MIPK was eliminated unchanged in about 25-35 hours, mainly in the expired air. Administration of this ketone to rabbits increased the glucuronic acid output. It has been suggested that MIPK is a normal constituent of human urine.

6 Effects and mechanism of action

Human data

A maximization test performed on 25 human volunteers using a 10% MIPK solution in petrolatum produced no sensitization reaction (Ano78). No other human data on (occupational) exposure to MIPK have been found.

Animal data

A 4 hour inhalation exposure to 20,406 mg/m^3 (5700 ppm) MIPK was fatal to one out of six rats (Car74). The single oral LD_{50} for rats was 5.66 ml/kg bw (4528 mg/kg bw). The single skin penetration LD_{50} for rabbits was 6.35 ml/kg bw (5080 mg/kg bw). This range finding test result indicated an acute toxicity somewhat greater than that of diethyl ketone, but less than that of di-n-propyl ketone or methyl-n-propyl ketone (Car74). No other animal data have been found. According to Topping *et al*. (Top94) MIPK appears to be biologically active primarily through its irritant properties and by induction of narcosis.

Mutagenicity and genotoxicity

Zimmermann *et al*. (Zim85) studied the induction of mitotic chromosomal malsegregation, mitotic recombination and point mutation of various ketones and some other agents, using a diploid yeast *Saccharomyces cerevisiae* strain D61.M. They found that MIPK induced only recombination and point mutation but not aneuploidy.

No data on long-term exposure, carcinogenicity and reproduction toxicity of MIPK have been found.

7 Existing guidelines

The current administrative occupational exposure limit (MAC) of MIPK in the Netherlands is 705 mg/m^3 (200 ppm), 8 h TWA.

Existing occupational exposure limits for MIPK in some European countries and the USA are summarized in the annex.

8 Assessment of health hazard

There are hardly any toxicological data available on MIPK. The critical effects probably are irritation and depression of the central nervous system. In humans a 10% MIPK solution caused no sensitization of the skin. In acute animal studies MIPK was found to be slightly more toxic than diethyl ketone, but less toxic than di-n-propyl ketone or methyl-n-propyl ketone (Car74). In *in vitro* mutagenicity tests MIPK induced recombination and point mutations but no aneuploidy.

No data on long-term exposure, carcinogenicity and reproduction toxicity of MIPK have been found.

The committee considers the toxicological data base on MIPK 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

ACG96 American Conference of Governmental Industrial Hygienists (ACGIH). TLVs and other occupational exposure values - 1996 (CD ROM, version 1.7-s4 02/01/95). Cincinnati OH, USA: ACGIH 1996.

ACG00 American Conference of Governmental Industrial Hygienists (ACGIH). 2000 TLVs and BEIs. Threshold limit values for chemical and physical agents. Biological Exposure Indices. Cincinnati OH, USA: ACGIH, 2000.

Arb96 Arbejdstilsynet. Exposure limit values for substances and materials. Copenhagen, Denmark: The Working Environment Service: Instruction no. 3.1.0.2. 1996.

Amo83 Amoore JF, Hautala E. Odor as an aid to chemical safety: odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. J Appl Toxicol 1983; 3: 272-90.

Ano78 Anonymus. Methyl isopropyl ketone. Food Cosmetic Toxicol 1978; 16: 819-20.

Car74 Carpenter CP, Weil CS, Smyth Jr HF. Range-finding toxicity data: List VIII. Toxicol Appl Toxicol 1974; 28: 313-9.

DFG99 Deutsche Forschungsgemeinschaft (DFG): Senatskommission zur Prüfung gesundheitsschädlicher Arbeitsstoffe. MAK- und BAT-Werte-Liste 1999. Maximale Arbeitsplatzkonzentrationen und biologische Arbeitsstofftoleran zwerte. Weinheim, FRG: VCH Verlagsgesellschaft MBH, 1999 (Mitteilung 35).

HSE99 Health and Safety Executive (HSE). EH40/99 Occupational exposure limits 1999. Sudbury (Suffolk), England: HSE Books, 1999.

NBO96 National Board for Occupational Safety and Health. Occupational exposure limit values. Solna, Sweden: NBOSH, 1996; Ordinance AFS1996/2.

SZW00 Ministerie van Sociale Zaken en Werkgelegenheid (SZW). Nationale MAC-lijst 2000. The Hague, the Netherlands: Servicecentrum Sdu Uitgevers, 2000.

Top94 Topping DC, Morgott DA, David RM, O'Donoghue L. Ketones. In: Patty's industrial hygiene and toxicology, fourth edition, Vol II, Part C, Clayton GD, Clayton FE, editors, New York: John Wiley & Sons Inc., 1994: 1776.

TRG00 TRG 900: Grenzwerte in der Luft am Arbeitsplatz; Technische Regeln für Gefahrstoffe; B Arb Bl 2000; 2.

Zim85 Zimmermann FK, Mayer VW, Scheel I, Resnick MA. Acetone, methyl ethyl ketone, ethyl acetate, acetonitrile and other polar aprotic solvents are strong inducers of aneuploidy in Saccharomyces cerevisiae. Mutat Res 1985; 149: 339-51.

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Annex

Occupational exposure limits for methyl isopropyl ketone 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	200	705	8 h	administrative		SZW00
Germany						
-AGS	-	705	8 h			TRG00
-DFG MAK-Kom.	-	-				DFG99
Great-Britain						
-HSE	-	-				HSE99
Sweden	-	-				NBO96
Denmark	-	-				Arb96
USA						
-ACGIH	200	705	8 h	TLV		ACG00
-OSHA	-	-				
-NIOSH	200	705	10 h	REL		
European Union						
-SCOEL						

[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