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
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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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Dipropyl ketone

(CAS reg. nr: 123-19-3)

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/005, The Hague, 14 December 2000

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1 Introduction

The present document contains the assessment of the health hazard of dipropyl ketone 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: dipropyl ketone, propyl ketone, heptanone, butyrone, or 123-19-3. 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 December 1997.

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	:	dipropyl ketone
synonyms	:	propyl ketone 4-heptanone butyrone heptan-4-one
molecular formula	:	$C_7H_{14}O$
structural formula	:	$CH_3CH_2CH_2COCH_2CH_2CH_3$
CAS reg nr	:	123 - 19 - 3

3 Physical and chemical properties

molecular weight	:	114.2
boiling point	:	143.7^{0}C
melting point	:	-32.6^{0}C
vapour pressure	:	0.73 kPa
solubility in water	:	insoluble
log $P_{oct/water}$	:	not known
conversion factors (20^oC, 101.3 kPa)	:	1 mg/m^3 = 0.21 ppm 1 ppm = 4.66 mg/m^3

Data from Top94, CKB00, Wea86.

Dipropyl ketone is a stable, colourless liquid with a pleasant but penetrating odour and a burning taste. The odour threshold is not known.

4 Uses

Dipropyl ketone is used as a solvent for nitro-cellulose, oils, resins and polymers, and in flavourings (ACG96).

5 Biotransformation and kinetics

No data on biotransformation and kinetics of dipropyl ketone have been found. The compound may be absorbed via inhalation, ingestion and through the skin (Car74, Hat91).

6 Effects and mechanism of action

Human data

No data on human (occupational) exposure to dipropyl ketone have been found.

Animal data

Single applications of dipropyl ketone to the skin of guinea pigs or rabbits produced slight irritation. Repeated skin applications of 0.5 ml for a 10-day

period produced slight erythema (Top94). When dipropyl ketone was applied to the eyes of rabbits, only slight irritation was observed (Top94). There is no information whether the compound causes skin sensitization.

The single oral LD_{50} in rats was 3047 mg/kg bw and the single skin application LD_{50} in rabbits 4624 mg/kg bw (Car74). An LD_{100} of 271 mg/kg bw after intravenous injection was reported for mice (Jep75).

From six rats none died after 4 h inhalation exposure to 9320 mg/m^3 (2000 ppm) dipropyl ketone (Car74). The LC_{50} of a single 6 h exposure of rats was 12,535 mg/m^3 (2690 ppm) (Top94).

Panson and Winek (Pan80) studied the aspiration hazard of dipropyl ketone on SD albino rats. The dosis used was 1 ml/kg bw. They found that six of seven animals died within the next 24 hours. The lungs showed from 25 to 50% congestion with only a very small amount of focal hemorrhage in the lobes. Two out of seven animals had blood clots at the base of their hearts.

Dipropyl ketone administered by gavage to eight rats at a dose of 2000 mg/kg bw, 5 days/week produced severe central nervous system (CNS) depression and reduced weight gain (it is not mentioned how many weeks this effect lasted) (unpublished data, cited in Top94). One rat died after 1 week of treatment due to cardiorespiratory failure. Lowering the dose to 1000 mg/kg bw resulted in restored weight gain and the absence of deleterious clinical effects over a 12-week period. Haematological determinations and serum clinical chemistry were unaffected, except for a reduction in glucose level. Relative liver and kidney weights were increased, and histological examination of the liver revealed hypertrophy of the hepatocytes. Repeated contact with the stomach resulted in hyperkeratosis and evidence of chronic irritation of the nonglandular gastric epithelium. Inhalation exposure to a concentration of 1864 mg/m^3 (400 ppm) dipropyl ketone decreased respiration and 3845 mg/m^3 (825 ppm) produced CNS depression. Narcosis occurred after exposure to 7456 mg/m^3 (1600 ppm), exposure to 14,912 mg/m^3 (3200 ppm) killed three out of four rats. The duration of exposure was not reported (Top94).

Six-hour exposure to 5592 mg/m^3 (1200 ppm) dipropyl ketone, 5 days/week, for 2 weeks resulted in a slightly decreased response to stimulation during exposure (unpublished data, cited in Top94). The species and number of animals used in the experiment were not reported. In this study, marginal liver enlargement, but no change in haematology, clinical chemistry or pathology were seen at the end of the 2-week exposure period.

No data on long-term exposure, mutagenicity, genotoxicity, carcinogenicity and reproduction toxicity of dipropyl ketone have been found.

7 Existing guidelines

The current administrative occupational exposure limit (MAC) of dipropyl ketone in the Netherlands is 235 mg/m^3 (50 ppm), 8 h TWA.

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

8 Assessment of health hazard

There are no human data on exposure to dipropyl ketone. In experimental animals dipropyl ketone was found to be slightly irritating to the eyes and the skin. No information on skin sensitization has been found. Besides some acute animal data only unpublished data from repeated dose studies were available. Since the original data were not available to the committee, they can not be used to establish a health-based occupational exposure limit for dipropyl ketone. The committee considers depression of the central nervous system to be the critical effect of dipropyl ketone.

The committee considers the toxicological data base on dipropyl ketone 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). 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.

CKB00 Chemiekaarten. Gegevens voor veilig werken met chemiecalien. 15^e editie. 2000. TNO Arbeid. p. 480.

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

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

Hat91 Hathaway GJ, Proctor NH, Hughes JP, Fischman ML, editors. n-Butane, In: Proctor and Hughes' Chemical hazards of the workplace, third edition, New York: Van Nostrand Reinhold 1991: 122.

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

Jep75 Jeppsson R. Parabolic relationship between lipophilicity and biological activity of aliphatic hydrocarbons, ethers and ketones after intravenous injections of emulsion formulations into mice. Acta Pharmacol Toxicol 1975; 37: 56-64.

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

Pan80 Panson RD, Winek CL. Aspiration toxicity of ketones. Clin Toxicol 1980; 17: 271-317.

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 JL. Ketones. In: Patty's industrial hygiene and toxicology, fourth ed., Vol II, Part C, Toxicology, Clayton GD and Clayton FE (eds), Wiley-Interscience Pub, New York, 1994, p.1808-1809.

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

Wea86 Weast RC, editor. In: CRC Handbook of chemistry and physics. 66th edition, Boca Raton: CRC Press Inc., 1986: 299.

Annex

Occupational exposure limits for dipropyl 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	50	235	8 h	administrative		SZW00
Germany						
-AGS	-	238	8 h			TRG00
-DFG MAK-Kom.	-	-				DFG99
Great-Britain						
-HSE	-	-				HSE99
Sweden	-	-				NBO96
Denmark	-	-				Arb96
USA						
-ACGIH	50	233	8 h	TLV		ACG00
-OSHA	-	-				
-NIOSH	50	235	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