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Ministry of Social Affairs
and Employment

Health-based recommended occupational exposure limit for methyl isobutyl ketone

Dutch expert committee for occupational standards
(Met Nederlandstalige samenvatting)

RA 4/91

Labour Inspectorate

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This is a report of the Dutch Expert Committee for occupational standards (DEC). The draft-document has been prepared by M.A. Maclaine Pont

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NEDERLANDSTALIGE SAMENVATTING

METHYL ISOBUTYL KETON

1. FYSISCHE EN CHEMISCHE EIGENSCHAPPEN

Methyl isobutyl keton (MIBK) is een kleurloze vloeistof met een zoete, zwak ketonachtige geur. De stof is uitermate geschikt als oplosmiddel, met name voor coatings.

Molecuulformule: $C_6H_{12}O$

Voor fysisch-chemische eigenschappen, zie tabel in hoofdstuk 1.

2. MONITORING

Voor wat betreft omgevingsmonitoring wordt verwezen naar de methode van NIOSH (1984). Deze analyse verloopt via een gaschromatografische methode.

Voor biologische monitoring is geen gevalideerde methode voorhanden.

3. GRENSWAARDEN

De hoogste grenswaarde wordt in Duitsland gehanteerd: 400 mg/m³. Zweden, Engeland en de Verenigde Staten hanteren een grenswaarde van 200 mg/m³, tgg 8 uur, met een excursielimiet van 300 mg/m³. Alleen Engeland heeft een huid-notatie.

4. TOXICOKINETIEK

Er is een beperkt aantal gegevens.

Na opname verdeelt MIBK zich snel in het menselijk lichaam, met een hogere concentratie in de lever.

Na intraperitoneale injectie in cavia's is de halfwaardetijd van MIBK 66 min en de klaring 6 uur. De belangrijkste metaboliet is 4-hydroxy-4-methyl-2-pentanon; deze heeft een klaringstijd van 16 uur.

In de mens is deze metaboliet niet aangetoond, evenmin de metaboliet 4-methyl-2-pentanol, ook niet na 2 uur blootstelling aan 200 mg/m³. Van de opgenomen hoeveelheid wordt 0,04 % onveranderd uitgescheiden in de urine.

5. EFFEKTEN

Bij laboratoriumdieren heeft MIBK een geringe irriterende werking op ogen en huid. Systemische effekten zijn niet gevonden na dermale blootstelling.

De acute toxiciteit van een eenmalige inhalatoire blootstelling is laag (rat, muis).

Een geen-nadelig-effekt-niveau van 1043 mg/m³ (250 ppm) is gevonden bij ratten en muizen na blootstelling 6 uur/dag, 5 d/week gedurende 90 dagen. Bij blootstelling aan 4170 mg/m³ was het absolute en relatieve levergewicht bij mannelijke ratten en muizen verhoogd. Daarnaast was in toenemende mate de vorming van hyaline-druppeltjes waarneembaar in de nieren van mannelijke ratten. Dit effekt kan worden beschouwd als niet relevant voor de mens.

Bij de mens induceert 417 mg/m³ in de ene groep werknemers hoofdpijn en misselijkheid, in een andere groep slechts irritatie van de luchtwegen. In een derde groep werd deze concentratie aanvaardbaar geacht voor 8 uur blootstelling.

In een studie met vrijwilligers kon geen dosis-effekt-relatie vastgesteld worden met blootstellingsniveau's tot 200 mg/m³.

6. EVALUATIE EN ADVIES

De WGD gaat uit van een geen-nadelig-effekt-niveau van 1043 mg/m³ (ratten en muizen, 90 dagen). Teneinde systemische effekten te voorkomen in de beroepsbevolking wordt een onzekerheidsfaktor van 10 geïntroduceerd.

Derhalve wordt de gezondheidkundige advieswaarde 104 mg MIBK/m³ (= 25 ppm) tgg 8 uur. Om irritatie van de luchtwegen te voorkomen wordt een STEL van 208 mg/m³ (= 50 ppm) over 10 min. geadviseerd.

(Datum afronding advies: juli 1991)

1. IDENTITY, PHYSICAL AND CHEMICAL PROPERTIES

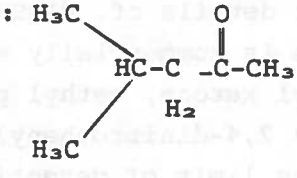
1.1 IDENTITY

Methyl isobutyl ketone (MIBK) is a colourless liquid with a sweet, acrid, faint ketonic and camphor odour.

Chemical substance prime name	: 4-methyl-2-pentanone
Synonyms	: hexanone; hexone; methyl isobutyl ketone; isobutyl methyl ketone; isopropyl acetone; 4-methyl-pentan-2-one; 2-methyl-4-pentanone
CAS reg. nr.	: 108-10-1
Abbreviation	: MIBK
Odour threshold, detection	: 0.7-32 mg/m³ air
recognition	: 0.6-64 mg/m³ air
unknown	: 0.41-193 mg/m³ air (Ruth 1986)
Conversion factors (100 kPa, 20°C)	: 1 ppm = 4.17 mg/m³ 1 mg/m³ = 0.24 ppm

1.2 PHYSICAL AND CHEMICAL PROPERTIES

(RTECS 1988, Weast 1985, Windholz 1976, Van Gemert and Nettenbreijer 1977 and 1984, Verschueren 1983, Ecetoc 1987, Kirk-Othmer 1981, Ullmann 1977, Dräger 1986).

Molecular formula	: $C_6H_{12}O$
Structural formula	: 
Molecular weight	: 100.16
Boiling point (100 kPa)	: 116.8 °C
Melting point (100 kPa)	: -84.7 °C
Vapour pressure (100 kPa, 20 °C)	: 2.6 kPa (Rathbun and Thai 1987)
Relative density of the saturated vapour in air (air=1; 100 kPa, 20 °C)	: 1.06
Percentage of the vapour in saturated air (100 kPa, 20 °C)	: 2.6%

Flash point: closed and open cup	:	23 °C (Kirk-Othmer, Windholz)
closed cup	:	14 °C (Ullmann, Ecetoc)
Explosion limit	:	1.3 - 7.9 vol %
Density (20 °C/4 °C)	:	0.8017
Solubility (100 kPa, 20 °C)	:	1.7-1.9 g/100 ml water, soluble in ethanol, diethylether, acetone, benzene and chloroform
Azeotrope with water	:	76% MIBK (b.p. 87.9 °C)
$\log P_{oct}$	:	1.31 (Tanii et al 1986)

Condensation of MIBK with another methyl ketone can produce ketones containing 9-15 carbons. Hydrogenation gives methyl isobutyl carbinol.

1.3 ANALYTICAL METHODS

1.3.1 Environmental monitoring

MIBK can be monitored by means of a NIOSH method (1984) apt for several ketones.

1-25 l of air is drawn through a solid sorbent tube (coconut shell charcoal), desorbed with CS_2 and analyzed with a GLC, equipped with an FID. For MIBK a detection range is not given. For diisobutyl ketone the range was 145 to 582 mg/m³ (or 1.8 to 7.0 mg per sample). There are reported to be no interferences. For further details cf. NIOSH (1984).

A test tube is commercially available, which can measure acetone, methyl ethyl ketone, methyl propyl ketone and MIBK. The ketone reacts with 2,4-dinitrophenylhydrazine resulting in a yellow product. The limit of detection is 100 ppm, but with MIBK it can have an underestimation of 20% (Dräger, 1986).

Levin and Carleborg (1987) evaluated several solid sorbents for the sampling of ketones in workroom air. Ambersorb XE-348 showed good capacity for most of the ketones and decomposition was insignificant.

1.3.2 Biological monitoring

No validated data available. See section 5.5.

2 SOURCES OF EXPOSURE

2.1 NATURAL OCCURRENCE

No data available.

2.2 MAN-MADE SOURCES

2.2.1 Production

MIBK is produced commercially in three steps from acetone: liquid phase condensation, acid-catalyzed dehydration and selective hydrogenation.

Owing to recent catalyst developments, a long-known one-step hydrogenation of acetone has become commercially feasible:

$$2CH_3COCH_3 + H_2 \xrightarrow{\text{catalyst}} (CH_3)_2CHCH_2COCH_3 + H_2O$$

In spite of the good selectivities obtained with the newly developed catalysts, formation of various by-products continues to be a problem. By-product diisobutyl ketone is usually marketed. A typical product specification is given in table 1.

Table 1. A product specification of MIBK (Kirk-Othmer 1981)

compound	mol %
isopropanol	0.08
2-methyl pentane	0.45
2-methyl-2-pentene	0.01
MIBK	96.50
mesityl oxide	0.01
methyl isobutyl carbinol	0.03
diisobutyl ketone	2.20
4,4-dimethylheptanone	0.55
residue	0.17

The production capacity in the USA in 1977 was 107.10^3 ton/yr. Generally, facilities manufacturing MIBK also make other acetone derivatives.

MIBK is the most important product derived from acetone. As solventless coating systems are developed to meet future pollution requirements, the demand for MIBK is expected to stabilize at about 91,000 t/yr (Kirk-Othmer 1981).

The production in the Western Countries in 1972 was estimated to be 160,000 t (Ullmann 1977).

2.2.2 Uses

MIBK is highly compatible with a variety of organic reagents and is a good solvent for a wide range of industrial materials. Its principal uses are in coating solvents (70%) and for rare-metal extraction (5%); export from the USA (11%) and miscellaneous solvent and denaturant uses (14%) account for the remaining production (Kirk-Othmer 1981).

3 ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

3.1 ENVIRONMENTAL LEVELS

3.1.1 Water

No data available.

3.1.2 Food

type of food	quantity of MIBK present	reference
papaya (Carica papaya L.)	8 µg/kg	Schreier et al 1985
mushroom (Marasmius oreades)	0.34% of the volatile fraction	Vidal et al 1986
chinese quince (Pseudocydonia sinensis Schneid)	20 µg/kg peel	Mihara et al 1987

3.1.3 Air

MIBK has been identified in forest air. No quantitative data are given (Jüttner 1986).

3.2 HUMAN EXPOSURE

3.2.1 General population

No data available.

3.2.2 Occupational population

MIBK is found in several production facilities, as part of a mixture of solvents. Only the quantitative data of MIBK are shown.

type of plant (n=number of workers exposed)	main other solvents	concentration MIBK mean (range) mg/m³	sampling time (n=number of meas.)	reference
printing ink manufacture (n=3)	ethanol	96 (4-246)	8 hr	Winchester 1985
painting line in plywood production plant	butyl acetate, xylene	(8-117)	not given (n=12)	Kauppinen 1986
filler and varnish production plant (n=55)	n-hexane dichloromethane	median:109 (25-124)	8 hr? (n=54)	Franco et al 1986
finishing in a leather tannery	toluene, xylene, respirable dust	27.1 (1.3-213)	not given (n=83)	Stern et al 1987
painting sheet metal	benzene	(7-10)	not given	Souza and Puig 1987

4. GUIDELINES AND STANDARDS

4.1 GENERAL POPULATION

No data available.

4.2 OCCUPATIONAL POPULATION

country	concentration mg/m³	concentration ppm	interpretation	reference
The Netherlands	205 H	50 H	MAC-TGG 8 hr	Arbeids-inspectie 1989
West Germany	400	100	MAC-TWA 8 hr	DFG 1989
USA	205	50	TLV-TWA 8 hr	ACGIH 1989
	308	75	STEL 15 min	
Sweden	200	50	MAC-TWA 8 hr	SBOSH 1987
	300	75	STEL 15 min	
UK	205	50	MAC-TWA 8 hr	HSE 1989
	300	75 skin	STEL 10 min	
USSR	5		ceiling	IRPTC 1984

H = skin absorption is possible

5 TOXICOKINETICS

5.1 ABSORPTION

Due to the high vapour pressure of MIBK inhalatory exposure is possible.
Pulmonary absorption by volunteers was circa 60% (Wigaeus Hjelm et al 1989). See section 5.2.

5.2 DISTRIBUTION

After the death of two individuals who had been exposed to several volatile organic solvents while spray painting the interior of a water storage tank MIBK was assayed in several body tissues and fluids. One person died traumatically as a result of a fall within the tank (case 1); the other was removed from the exposure and lived some nine hours prior to death due to cerebral oedema (case 2). No measurements were performed in the tank. In table 2 the data are presented.

Table 2. MIBK found in several human tissues and body fluids after exposure to several organic solvents and subsequent death (mg/100 g; Bellanca et al 1982).

	brain	liver	lung	vitreous body	kidney	blood	
case 1	0.25	0.49	0.43	0.52	0.24	0.14	a)
case 2	0.06	0.22	0.11	0.02	0.08	0.04	b)

a) femoral blood
b) heart blood

In both cases the liver contained a high amount of MIBK.
Case 2 showed lower levels than case 1, but when the ratio blood/liver is compared very little change has taken place. MIBK is distributed over the organs in the same manner as the other solvents assayed in the bodies (Bellanca et al 1982).

MIBK can cross the placenta, which was established in maternal and umbilical cord blood samples from eleven pregnant women. No quantitative data are available (Dowty et al 1976).
Wigaeus Hjelm et al (1990) measured the kinetics of MIBK in volunteers. Eight male subjects were exposed to 10, 100 and 200 mg/m^3 for 2 hr during light physical exercise (50 W on a bicycle

ergometer). Measurements were performed on exhaled air, capillary blood and urine, before, during and up tot 3 hr after exposure. The relative pulmonary uptake of MIBK was about 60% and the total uptake increased linearly with the increasing exposure concentration. At the two highest exposures the concentration of MIBK in blood rose rapidly after the onset of exposure and no plateau level was reached during exposure. No tendency for saturation kinetics could be observed within the dose interval and the apparent blood clearance was 1.6 1/hr/kg at all exposure levels (see Figure 1).

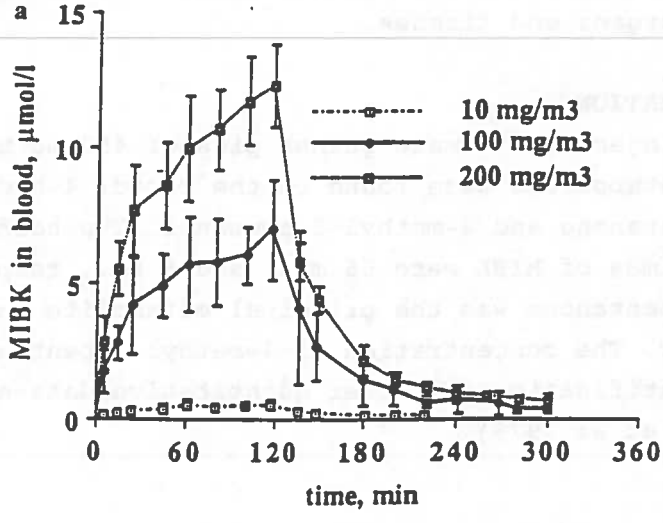


Figure 1. MIBK concentration in capillary blood during and after 2 hr of exposure at three different exposure levels. Mean values and standard deviations of eight persons are given (Wigaeus Hjelm et al 1990).

It can be concluded that the 2 hr exposure is not representative for the 8 hr occupational exposure. However, the body seems to be able to metabolize MIBK completely at dose levels between 10 and 100 mg/m³.
The data on urinary excretion will be described in section 5.4.
The data on effects will be described in section 6.2.2.

Partition coefficients

Imbriani et al (1985) measured partition coefficients of MIBK in urine/air and blood/air. The blood and urine samples came from

healthy non-exposed volunteers. The coefficient for urine/air was 73, and for blood/air it was 96.
Sato and Nakajima (1979) measured a blood/air partition coefficient of 90. Blood was purchased from a blood bank. The water/air partition coefficient was 79. These data are in accordance with the former study.
The latter study also measured the partition coefficient between olive oil and air: this was 926. Whether olive oil is representative for human body fat is not clear. However, it seems that MIBK has a high affinity for fat and therefore will accumulate in fat-containing organs and tissues.

5.3 BIOTRANSFORMATION

After i.p. injection to male guinea pigs of 450 mg MIBK/kg the following metabolites were found in the blood: 4-hydroxy-4-methyl-2-pentanone and 4-methyl-2-pentanol. The halflife and clearance times of MIBK were 66 min. and 6 hr., resp.. 4-Hydroxy-4-methyl-2-pentanone was the principal metabolite and was cleared within 16 hr. The concentration of 4-methyl-2-pentanol was too low for quantification. No other quantitative data are given. (DiVincenzo et al 1976).

5.4 ELIMINATION

Zlatkis et al (1973) assayed MIBK in the urine of healthy individuals (n=150) and in subjects with diabetes mellitus (n=40). No quantitative data are given.
In guinea pigs the urinary excretion of the main metabolite 4-hydroxy-4-methyl-2-pentanone can be expected; DiVincenzo et al (1976) do not mention possible excretion of MIBK as such.
Urinary excretion by volunteers, as described by Wigaeus Hjelm et al (1990) (see section 5.2), of unchanged MIBK, was proportional with the total uptake. Only 0.04% of the total MIBK dose was eliminated unchanged via the kidneys within 3 hr post exposure. The concentrations of the metabolites 4-hydroxy-4-methyl-2-pentanone and 4-methyl-2-pentanol were below the detection limit (5 nmol/l). The calculated half-life times were 11 and 13 min. resp. for the faster elimination phase (0-30 min after exposure to 100 and 200 mg/m^3) and 59 and 74 min for the slower phase (60-180 min after exposure). Again it can be concluded that the body

seems to be able to excrete MIBK completely at dose levels between 10 and 100 mg/m³.

5.5 BIOLOGICAL MONITORING

MIBK has been found in the urine of healthy non-exposed individuals. The exposure to MIBK, in the occupational setting, can be monitored in the urine, although a base concentration range must be established in non-exposed individuals. A meal with papaya and chinese quince will undoubtedly increase the urinary MIBK excretion. Because of lack of data no validated method for monitoring MIBK can be given.

5.6 SUMMARY

Very limited data are available with respect to the toxicokinetics of MIBK.
From two fatal cases it was learned that in humans MIBK is rapidly distributed throughout the body, with the highest concentration found in the liver.
In vitro studies show that MIBK has low partition coefficients in human tissues except for fat.
In experimental animals (guinea pigs) the half-life and clearance time of MIBK were resp. 66 min. and 6 hr after i.p. injection.
4-Hydroxy-4-methyl-2-pentanone was the main metabolite (found in blood) and its clearance time was 16 hr.
In humans urinary excretion is proportional to the uptake.
Inhalatory exposures between 10 and 100 mg/m³ for 2 hr can be metabolized and excreted completely. The expected metabolites 4-hydroxy-4-methyl-2-pentanone and 4-methyl-2-pentanol were not detected in the urine, not even after exposure to 200 mg/m³ for 2 hr (limit of detection: 5 nmol/l). Only 0.04% MIBK was excreted unchanged.

6 EFFECTS

6.1 ANIMAL EXPERIMENTS

6.1.1 Irritation and sensitization

De Ceaurriz et al (1981) determined an RD 50 in mice (50% decrease in respiratory rate), after exposure during 5 min. to MIBK. At least 4 exposure levels and 6 animals per group were used. The RD50 was calculated to be 13.3 g MIBK/m^3. This is a relatively high concentration.

Skin

McOmie and Anderson (1949): a single dermal exposure of undiluted MIBK, either by flooding the clipped skin or by applying a soaked cotton pad, induced in rabbits (n=2) moderate erythema which persisted for 24 hr (exposure time: 10 hr). During an observation period of 10 days there was no evidence of systemic effects in these rabbits.

After seven daily applications of 3 ml/kg (equals 2.4 g/kg) over 100 cm^2 area MIBK induced in rabbits (n=2) drying of the skin with some exfoliation. No systemic effects were noted (McOmie and Anderson, 1949).

Undiluted MIBK (5 and 10 ml) held in contact with the depilated skin of guinea pigs under an occlusive wrap for 24 hr produced slight irritation with no clinical evidence of absorption. Other studies showed that 500 mg MIBK produced moderate irritation of rabbit skin after 24 hr. MIBK, with or without DMSO, when applied on the backs of guinea pigs in amounts up to 2 ml twice daily for 31 weeks, produced only desquamation with no clinical or histological evidence of toxic neuropathy (Patty, 1982, from unpublished data; no further data are given).

Eye

McOmie and Anderson (1949): After instillation of MIBK (unknown quantity) in rabbit eye (n=1) some conjunctivitis was observed with some oedema and corneal injury. However, light accommodation seemed unaffected, nor was there any pupillary damage. Seven days after the instillation the eye was grossly normal again, indicating that there was no irreversible damage.

Patty (1982): Undiluted MIBK (0.1 ml) produced some irritation within 10 min. when instilled in the rabbit eye. Inflammation and swelling occurred within 8 hr, and inflammation, swelling and exudate were present at 24 hr.

6.1.2 Acute toxicity

species	route of exposure	lethal dose	reference
male ddY mice	oral	LD50 2,670 mg/kg	Tanii et al 1986
mouse	oral	LD50 1,200 mg/kg	McOmie and Anderson 1949
mouse	oral	LD50 1,900-2,850 mg/kg	Ecetoc 1987
Sprague Dawley rat	oral	LD50 2,080 mg/kg	Panson and Winek 1980
rat	oral	LD50 4,600 mg/kg	Ecetoc 1987
Sprague Dawley rat	inhalatory (aspiration)	1 mg/kg 6/6 died	Panson and Winek 1980
rat	inhalatory (6 hr)	lowest lethal concentration: 16,700 mg/m³	Patty 1982
rat	inhalatory (4 hr)	LC50 > 8,340 mg/m³ and < 16,700 mg/m³	Ecetoc 1987
mouse	inhalatory (2 hr)	± 20,900 mg/m³	Ecetoc 1987
mouse	inhalatory (0.5 hr) (0.5 hr) (1.25 hr (1 hr) (0.25 hr	81,300 mg/m³ 0/10 died 83,400 mg/m³ 18/23 died 83,400 mg/m³ 5/10 died 89,200 mg/m³ 21/22 died 101,800 mg/m³ 0/10 died	Anderson and McOmie 1945
male quinea pig	i.p.	1000 mg/kg: 1 of 4 animals died	DiVincenzo and Krasavage 1974

Some older data (from 1933 and 1940) are reviewed by Ecetoc (1987). Inhalatory exposure to guinea pigs showed that 4170 mg MIBK/m³ during 24 hr caused little or no ocular or nasal irritation. 70,000 mg MIBK/m³ caused immediate signs of eye and nose irritation, followed by salivation, lacrimation, ataxia, progressive narcosis and death.

Nine of 10 guinea pigs died during the first 6 hr of exposure. Complete recovery could be effected by removal from exposure at any but the terminal stages. 117,000 mg MIBK/m³ killed 50% of the animals within 45 min. and only a few animals survived 60 min. of exposure.

6.1.3 Short-term toxicity

When a group of 10 mice was exposed to 74,000 - 98,000 mg/m³ 20 min/day for 15 days six animals died in the course of the experiment (resp. on day nr. 1, 6, 9, 9, 9 and 10).
The toxic effect before death was profound depression. MIBK is a poorer anaesthetic and frequently caused death before loss of rigthing reflex in mice than other organic solvents tested (McOmie and Anderson 1949).
Geller et al (1979) used a match-to-sample task in baboons to measure behavioral changes during and after exposure to MIBK. Four baboons were exposed to 209 mg/m³ during 7 days, 24 hr/day. The test was performed before, during and after exposure, so each animal served as its own control; moreover other animals were sham-exposed to clean air, and served as a control group. Animals were consecutively exposed to 300 mg butanone-2/m³, 209 mg MIBK/m³, 1187 mg acetone/m³ and a combination of 300 mg butanone-2/m³ and 209 mg MIBK/m³. At least one month elapsed between each of the above exposures. MIBK produced no significant effect upon the accuracy of performance of the task, but it slowed the response time and the response during delay. The authors conclude that this might be an early manifestation of incoordination and narcosis.
When exposed to different concentrations of MIBK mice showed behavioral changes in a dose-related way. Groups of 10 male Swiss OF1 mice were exposed during 4 hr to 2761, 3157, 3365 or 3720 mg MIBK/m³. At the end of the exposure period each animal was immersed in water and the total duration of immobility observed during the first 3 min. was measured. The duration of immobility was significantly reduced in the three highest dosages ($p<0.05$) compared to control; the percentage was resp. 25, 38, 46 and 70%. From these data an ID50 of 3349 mg MIBK/m³, associated with a 50% decrease in the total duration of immobility, was calculated (De Ceaurriz et al 1984).

Some behavioural changes were found in rats after 3 hr exposure to 104 mg/m³, however, the discriminatory behaviour and memory of baboons was not impaired by exposures of 83 to 167 mg/m³ (Ecetoc 1987).

6.1.4 Subchronic toxicity

In a 14 wk inhalation study Phillips et al (1987) exposed 14 male and 14 female F344 rats and B6C3F1 mice to 0, 209, 1043 or 4170 mg MIBK/m³, 6 hr/day, 5 d/wk. Animals were sacrificed after at least 3 consecutive days of exposure in the 14th week of exposure. Complete gross pathological examination was performed on all animals.

Haematologic and serum chemistry tests were performed on all rats and haematological analyses were performed on all mice. Sections of many tissues were examined histologically. There was no adverse effect on the clinical health or growth of rats or mice. Male rats and male mice exposed to 4170 mg MIBK/m³ had a slight but statistically significant increase in liver weight and the liver weight/body weight ratio. At 1043 mg/m³ the absolute liver weight of male mice and the absolute kidney weight of female rats were increased, however, the relative weights of the organs were not increased. No gross or microscopic hepatic lesions related to MIBK exposure were observed. Furthermore, the only microscopic change observed was an increase in the incidence and extent of hyalin droplets within proximal tubular cells of the kidneys of male rats exposed to 1043 or 4170 mg/m³. It is common opinion that the kidney effect observed in male rats are male rat specific and therefore, not an appropriate model for man. From this study a NAEL for rats and mice can be concluded of 1043 mg/m³ (14 wk intermittend exposure); at 4170 mg/m³ slight liver effects were observed.

MacEwen et al (1971) exposed rats, dogs and monkeys continuously for 90 days to 410 mg MIBK/m³. The study was performed at hypobaric pressure, 260 mm Hg, with 68% O_2 and 32% N_2. The authors state clearly that the concentration of MIBK is 410 mg/m³ (= 100 mM/25 m³). This does not equal 100 ppm. The control and exposed group consisted each of 100 male Wistar rats, 8 male Beagle dogs and two male macaca mulatta. Several interim kills were provided for as well as removal from exposure with necropsy

later on to determine the reversibility of the kidney lesion observed in the preliminary experiments. After necropsy several clinical and histopathological parameters and organ weights were measured. No adverse effects were observed except in the rats. Hyaline droplet tubular nephrosis developed but did not result in debilitation or death. The lesions developed within 2 weeks of exposure and were reversible upon removal from the MIBK environment, even after 90-day exposure.

Abou-Donia et al (1985) exposed groups of 5 hens continuously to 0 and 4170 mg MIBK/m^3 during 90 days. Subsequently the birds were kept for a 30-day observation period. During exposure the hens weighed 90.5% of their initial weight when they developed leg weakness (probably an effect on the CNS). By the end of the 90-day exposure period the hens regained most of the lost weight (97.9%) and continued to gain weight during the 30-day observation period (110.0%). Leg weakness disappeared when exposure was discontinued. At termination all tissues were grossly examined; no differences were observed in size, shape and colour. Further, MIBK did not induce any histopathological changes in the spinal cord or peripheral nerves. It is concluded that MIBK is not neurotoxic. We conclude that MIBK is not a peripheral neurotoxicant.

In table 3 several studies, reviewed by Ecetoc (1987), are presented.

Table 3. Neurotoxicity studies cited by Ecetoc (1987)

Species	route of administration	dose regimen MIBK	results	cited from
rat	i.p.	10, 30 and 100 mg/kg 5 d/wk, for 2 wk; 20, 60 and 200 mg/kg 5 d/wk, for 33 wk	transient narcosis during the first month in the 200 mg/kg animals; no toxic neuropathy	Krasavage et al 1982 a)
dog	s.c.	300 mg/kg daily for 11 mo	no neurotoxicity	Krasavage et al 1982 a)
male rat	inhalatory	6255 mg/m³ for 5 mo	minimal distal axonal changes which might be caused by 3% MnBK b) present in the MIBK, or, more likely, to a compression neuropathy caused by the design of cages used. Slight narcosis, no clinical signs of neurological dysfunction	Spencer et al 1975; Spencer and Schaumburg 1976

a) unpublished study quoted by
b) MnBK = methyl n-butyl ketone

Groups of cats were s.c. injected twice daily with 150 mg MIBK/kg (n=4) or saline (n=4), 5 days a week during 8.5 months. Narcosis and excessive salivation commonly commenced shortly after injection. Abscess formation and skin ulceration was seen in several animals. Further, MIBK was tolerated well. No peripheral neurotoxicological signs were observed (Spencer and Schaumburg 1976).

Administration of MIBK in the drinking water of female Wistar rats (1 g/kg/day) for 120 days did not produce neurotoxic effects (Homan and Maronpot 1978).

From the abovementioned studies it is concluded that MIBK is not a peripheral neurotoxic agent, but can act on the central nervous system.

No studies on carcinogenicity have been found.

6.1.5 Mutagenicity

In a study of 24 workers exposed to thinner (containing 1.5% MIBK) peripheral blood was scored for SCEs (sister chromatid exchanges). Air samples contained a.o. benzene, the only compound which was above TLV level (5.6-6 ppm, TLV 1 ppm). No significant differences in SCEs were found between the exposed and control group. Use of tobacco increased significantly the SCE frequencies among the exposed group, but not in the control group (Souza and Puig 1987). This study is not informative on MIBK as such.

In table 4 the mutagenicity data, as summarized by IPCS (1990) are presented.

Table 4 Mutagenicity data summarized by IPCS (1990)

type of test	species		dose	result	cited from
Ames	S. typhimurium TA98, TA100, TA1537, TA1538	RLiA a)	0.04-4 µg/plate	-	CMA b) 1984; O 'Donoghue et al 1988
Ames	S. typhimurium TA1535, TA1537, TA1538, TA98, TA100	RLiA	up to 8000 µg/ml	-	Brooks et al 1988
Trp +/- c)	E. coli WP2 and WP uvr A	RLiA	up to 8000 µg/ml	-	Brooks et al 1988
Mitotic gene conversion	S. cerevisiae	NA RLiA	up to 5 mg/ml	-	Brooks et al 1988
TK +/- d)	L5178Y mouse lymphoma	NA RLiA	0.001-100 µl/ml and 0.4-6 µl/ml	- -	CMA 1984; O 'Donoghue et al 1988
unscheduled DNA synthesis	primary rat hepatocytes		0.01-100 µl/ml	- -	CMA 1984; O 'Donoghue et al 1988
chromosomal aberrations	cultured rat liver cells		up to 1000 µg/ml	-	Brooks et al 1988
cell tranformation	Balb/3T3	NA RLiA	2-5 µl/ml 1-7 µl/ml	inconclusive	CMA 1984; O 'Donoghue et al 1988
micronucleus	male and female mice		0.73 ml/kg i.p. e)	-	CMA 1984; O'Donoghue et al 1988

a) RLiA = rat liver activated
NA = not activated
b) CMA = Chemical Manufactures Association
c) Trp +/- = backward mutation to tryptophan prototrophy
d) TK +/- = forward mutation at thymine kinase locus to resistance to thymidine analogues
e) maximum tolerated dose

It can be concluded that MIBK is not genotoxic in in vitro and in vivo short-term tests.

6.1.6 Reproduction toxicity and teratogenicity

Tyl et al (1987) exposed pregnant F344 rats and CD-1 mice to 0, 1251, 4170 or 12510 mg MIBK/m^3 on gestational day 6 through 15 during 6 hr/day. The number of dams was, resp. for the rats: 25,

26, 25 and 23 and for the mice 23, 22, 23 and 25. The animals were sacrificed on gestational day 21 (rats) or 18 (mice), and live foetuses were examined for external, visceral and skeletal alterations. In rats, exposure to 12510 mg/m³ resulted in maternal toxicity expressed as clinical signs (evidenced by loss of coordination, negative tail and/or toe pinch, paresis, muscular weakness in hindlimbs, piloerection, lacrimation and red perioral encrustation; all noted only during the exposure period), decreased body weight and body weight gain, increased relative kidney weight, and decreased food consumption, and in foetotoxicity expressed as reduced foetal body weight per liter and reductions in skeletal ossification. In mice, exposure to 12510 mg/m³ resulted in maternal toxicity expressed as exposure-related increases in deaths (12%, 3/25 dams), clinical signs (evidenced by irregular gait, paresis, hypoactivity, ataxia, negative toe pinch, unkempt fur and lacrimation; all noted only during the exposure period), and increased absolute and relative liver weight, and in foetotoxicity expressed as increased incidence of dead foetuses, reduced foetal body weight per litter and reductions in skeletal ossification. No treatment-related increases in embryotoxicity or foetal malformations were seen in either species at any exposure concentration tested. There was no evidence of treatment-related maternal, embryo or foetal toxicity (including malformations) at 4170 or 1251 mg/m³ in either species.

6.1.7 Other studies

Combined exposure

Several studies have been published on possible synergism or potentiation by MIBK in combination with other compounds. Data are presented in Table 5 and 6.

Table 5 Effects of MIBK in combination with other compounds

species	dose MIBK	dose other compound	effect	reference
cat	15 mg/kg s.c. injected twice daily, 5 d/wk, 8.5 mo	135 mg MEK/kg s.c. injected twice daily, 5 d/wk, 8.5 mo	no nervous damage in all cases	Spencer and Schaumburg 1976
baboon	209 mg/m³, 7 d, 24 hr/d	300 mg MEK/m³, 7 d, 24 hr/d	mixed exposure: behavioral changes much less than additive	Geller et al 1979
adult leghorn hen	417-4170 mg/m³, 90 d, continuously (four dose levels)	3600 mg-n-hexane/m³; 90 d continuously	mixed exposure: n-hexane neurotoxicity developed dose-related to MIBK; progression to paralysis, ataxia; (more than additive)	Abou-Donia et al 1985
male Sprague Dawley rat	376 and 751 mg/kg orally daily for 3 or 7 days	after MIBK: 5-25 mg sodium taurolitho-cholate/kg, one i.v. inj.	mixed exposure: decreased bile flow; minimally effective dosage: between 188 and 376 mg MIBK/kg	Plaa and Ayotte 1985
male Sprague Dawley rat	376-1502 mg/kg orally daily for 3 or 7 days	after MIBK: 4.5 or 6.0 mg Mn/kg as $MnSO_4$, one i.v. inj. or 4.5 or 6.0 mg Mn/kg as $MnSO_4$ + 15 mg bilirubin/kg, one i.v. inj.	mixed exposure: decreased bile flow	Vézina and Plaa 1987
male Sprague Dawley rat	30-2002 mg/kg orally daily for 8 days	after MIBK: 7.9-793 mg CCL_4/kg, one i.p. inj.	results not comparable, since single dose was different from combined exposure (effect observed: liver injury)	Pilon et al 1988
male CD-1 Mouse	250 and 500 mg/kg i.p. (once)	30 min. after MIBK: 4g ethanol/kg i.p.	after high dose: increased duration of loss of righting reflex	Cunningham et al 1989

NOTE: MEK = methyl ethyl ketone

Table 6. Effects of MIBK metabolites in combination with other compounds

species	dose metabolite	dose other compound	effect	reference
male Sprague Dawley rat	4-methyl-2-pentanol, 192-1533 mg/kg, orally daily for 1 or 3 days	after metabolite: 4.5 or 6.0 mg Mn as $MnSO_4$, one i.v. inj. or 4.5 or 6.0 mg Mn as $MnSO_4$ + 15 mg bilirubine/kg, one i.v. inj.	mixed exposure: decreased bile flow	Vézina and Plaa 1988
male Sprague Dawley rat	idem for 4-hydroxy-MIBK 218-1743 mg/kg	idem	idem, but higher concentrations were needed	Vézina and Plaa 1988

In summary it can be said that the only synergistic effect found was the combination MIBK + n-hexane for neurotoxic effects on the CNS. MIBK and two MIBK metabolites exerted a potentiator effect on the decrease in bile flow caused by taurolithocholate, Mn^{2+} or Mn^{2+}plus bilirubin. In one study (MIBK + MEK) behavioral changes were much less than additive and from the remaining two studies no conclusions can be drawn.

Enzyme activities

Franco et al (1986) found that serum bile acid (SBA) concentration was a specific and sensitive parameter for solvent exposure. Several serum liver enzyme activities were not significantly changed, in contrast to significantly elevated SBA concentrations, in a group of solvent exposed workers (n=30). In spite of the fact that this is a new possible technique, the scientific value for early health effect monitoring has not been validated.

6.2 OBSERVATIONS IN MAN

6.2.1 Acute toxicity (incidents)

A 16-yr male felt burning paresthaesia in his hands and feet after he had spray painted his motorcycle several times in a small, unventilated room. The symptoms first appeared after one week, and stayed 8 weeks. The combination of solvents (among them MIBK, acetone, dichloromethane, methyl ethyl ketone omd toluene) was considered the cause of the accident, especially the combina-

tion MIBK with methyl ethyl ketone (Au Buchon et al 1979). However, others (Tyrer 1979, Goldman 1979) questioned this conclusion.

4170 mg MIBK/m³ or more produced central nervous system depression and narcosis (Ecetoc 1987 cited from Krasavage et al 1982; from unknown source).

417 mg MIBK/m³ was a sensory response limit to humans. A majority of subjects found the odour objectionable at 834 mg/m³ and the vapour was irritant to the eyes.

When swallowed, MIBK may, because of its low viscosity, be aspirated into the lungs causing chemical pneumonitis (Ecetoc 1987).

6.2.2 Short-/long-term exposure (accidental, controlled)

Silverman et al (1946) exposed 12 volunteers of both sexes during 15 minutes. The majority estimated that 417 mg/m³ was acceptable for 8 hr exposure, but 834 mg/m³ was considered to have an objectionable odour and it irritated the majority of the subjects.

417 mg/m³ induced headache and nausea in a group of workers. Tolerance was said to be acquired during the working week, but was lost over the weekend. Another group exposed to a similar level complained only of respiratory irritation. Introduction of an exhaust system reduced the exposure to 83.4 mg/m³ and largely eliminated the complaints (Elkins,1959; no further data are given, without a reference).

Undiluted MIBK splashed in the eyes may cause painful irritation (Ecetoc 1987, cited from Shell 1957).

When exposed to 2000 mg/m³ for 20-30 min/d over half of the 19 workers complained of ill-defined and non-specific symptoms, e.g. weakness, loss of appetite, headache, etc. (Ecetoc 1987).

Wigaeus Hjelm et al (1990) exposed 8 male volunteers to 10, 100 and 200 mg/m³ for 2 hr. During the exposure the volunteers exerted light physical exercise (50 W on a bicycle ergometer). They were unaware of the sequence of the exposure conditions. Occurrence of irritative and CNS symptoms were recorded on nine occasions, with the first rating immediately before onset of exposure and the last rating almost 2 hr after the subject left the exposure chamber. Scoring of mood scale factors and two

performance tests were also executed. No effects were observed from exposure to MIBK to mood indices and performance tests. Acute symptoms were observed in a dose-related way as to irritation to eyes, nose and throat. CNS symptoms such as headache, nausea and vertigo were dose-related after quantitation and mathematical calculation. The symptoms disappeared gradually after discontinuation of the exposure. The rating increased over the 2 hr of exposure, however, the authors do not indicate what level of exposure is bearable as an occupational level. At 10 mg/m^3 not more than one person out of 8 complained, at 100 and 200 mg/m^3 not more than 3 out of 8 persons complained. Thus, there was no clear relationship between symptoms and exposure level using a questionnaire with yes/no alternatives. However, when using a 6 point rating scale there was a tendency of higher (subjective) rating of irritative symptoms with increasing exposure. Because of the lack of a clear dose-effect/response relationship and a lack of description of the severity of symptoms it is impossible to use these data to derive an occupational exposure limit.

6.2.3 Epidemiological studies

A retrospective mortality analysis was conducted in a cohort of 9365 individuals employed as of 1940 in two chrome leather tanneries in the United States and followed to the end of 1982. Mortality from all causes combined and from cancer of each site were lower than expected.

In the finishing department (with an unknown number of workers), the only department where MIBK was found, MIBK was found in low concentrations (mean: 27.1 mg/m^3), together with other organic solvents and respirable dust (70% without further specification). Also in this separate department no elevated SMR was found for any of the causes of death (Stern et al 1987). The relevance of this study for the effects of MIBK is questionable.

6.3 SUMMARY

Skin irritation and eye injury to rabbits is slight. Skin irritation to guinea pigs is also slight (occlusive method during 24 hr, and non-occlusive method during 31 weeks twice daily).

In de same studies no systemic effects were observed indicating that dermal absorption is negligible. After a single oral dose MIBK is slightly toxic (LD50; classification according to the EEC 1983).

After inhalatory exposure for 4 hr MIBK is slightly toxic (LC50; classification according to the EEC 1983).

The respiration rate in mice decreases 50% after exposure to 13.3 g MIBK/m^3 for 5 min.

70 g MIBK/m^3 to guinea pigs causes immediate signs of eye and nose irritation, followed by salivation, lacrimation, ataxia, progressive narcosis and death. The effects are reversible, except for the terminal stage. Nine of 10 guinea pigs died during the first 6 hr of exposure.

209 mg MIBK/m^3, 24 hr/d for 7 days induces some behavioral changes in baboons.

2761 mg MIBK/m^3 during 4 hr induces some behavioral changes in mice.

4170 mg MIBK/m^3, 6 hr/d, 5 d/wk for 14 weeks does not induce adverse effects in male and female rats and mice except with respect to male-rat-specific hyalin droplet formation in the kidneys. In this study the NAEL was 1043 mg/m^3 (rats and mice, 14 wk intermittent exposure); at 4170 mg/m^3 slight liver effects were observed.

Studies in hens (90 days), rats (35 weeks and 5 months), dogs (11 months) and cats (8.5 months) show that MIBK is not peripherally neurotoxic. However, MIBK exerted an effect on the CNS, as could be observed by

- the induction of leg weakness in hens when exposed to 4170 mg/m^3, 24 hr/d for 90 days, which disappeared when exposure was discontinued
- transient narcosis in rats when injected i.p. with 200 mg/kg, 5 d/wk or when inhalatory exposed to 6255 mg/m^3 for 5 mo
- narcosis and excessive salivation in cats when injected twice daily s.c. with 150 mg/kg, 5 d/wk for 8.5 mo.

MIBK is not genotoxic in several in vitro and in vivo short-term tests. In one cell transformation test in mammalian cells the out come was inconclusive.

MIBK is not teratogenic to mice and rats, tested at 1251 and 4170 and 12510 mg MIBK/m^3, (through gestational days 6-15, 6 hr/d).

At 12510 mg/m³ maternal and foetotoxicity was observed in both species.
Only synergistic effects were noted with the combination MIBK + n-hexane (neurotoxicity on the CNS); MIBK or two metabolites of MIBK exerted a potentiating effect on taurolithocholate, Mn^{2+} or Mn^{2+} + bilirubin (decreased bile flow).
417 mg/m³ induces headache and nausea in a group of workers, but in another group only respiratory irritation was observed. In a third group this value was considered acceptable for 8 hr exposure.
In a volunteer no dose-effect relationship could be established with exposure levels up to 200 mg/m³.

7 PREVIOUS EVALUATION BY (INTER)NATIONAL BODIES

No review is available from the German MAK Committee.

The AGGIH (1986) bases its TLV-value predominantly on human data (417 mg/m³ induces headache and nausea, Ecetoc 1987) and on animal data (increased kidney weights after 90 days continuous exposure on dogs, monkeys and rats). No quantitative data are presented in the evaluation. From these data a TLV is recommended of 50 ppm (205 mg/m³) and a STEL of 75 ppm (300 mg/m³), to protect workers from irritant effects and its potential effect on the kidney. The documentation contains 10 references, the most recent one from 1978.

Ecetoc (1987) reviews the toxicity data of MIBK, including the ecotoxicological data. MIBK has low mammalian and aquatic toxicity, indicating that environmental hazards of this substance are negligible.

The Technical and Medical Services of the INRS (Institut National de Recherche et de Sécurité) of France prepared a toxicological data sheet on MIBK (INRS 1988). After a short summary of the relevant toxicological data the MAC value (205 mg/m³) is set without any risk assessment. Regulations are given concerning transport and recommendations concerning storage and medical examination.

A criteria document for the Nordic countries was prepared by Hagberg (1988). The critical effect was concluded to be effects on the CNS and irritative effects. The effects have a reversible character. It is advised to study toxicokinetics, dose-response relationship and skin penetration in man.

8 EVALUATION OF HUMAN HEALTH RISKS

8.1 GROUPS AT RISK

No specific groups at risk could be determined.

8.2 ASSESSMENT OF HEALTH RISKS

MIBK is of low acute mammalian toxicity.
Skin irritation and eye injury is slight.
The longest study performed was a 14 wk inhalatory study with rats and mice (intermittent exposure). From this a NAEL could be concluded of 1043 mg/m³. At 4170 mg/m³ slight liver effects were observed and hyalin droplets were formed in the kidney of male rats.
In a 90 d study in rats, dogs and monkeys with inhalatory exposure to 410 mg/m³ (24 hr/d) at hypobaric pressure (260 mm Hg) the only adverse effect observed was hyalin droplet formation in the kidney of male rats, a reversible effect upon removal from MIBK exposure.
The relevance of this male-rat-specific effect to humans is questionable. The same opinion is found in several other studies, e.g.:

- after exposure of mice and rats during 22 hr/d, for 20, 28 or 35 days to several dosages of decalin the only effect found was hyalin droplet formation in the male rat. The authors suggest that this may be unique to the male rat. Hyaline droplets are not observed in non-diseased kidney sections from other mammalian species, including humans (Stone et al 1987).
- Oral dosing of d-limonene during 91 days to mice and rats induced only renal alterations in the male rat (Kanerva and Alden 1987).
- Since male rats are known to exhibit physiologic proteinuria, it is likely that these animals are unusually susceptible to chemical-induced nephropathy (Garg et al 1988, after oral dosing of gasoline to male rats).
- Also Kanerva et al (1987) argue that hyalin droplet formation is specific for the male rat. The formation is situated in the cytoplasm of proximal convoluted tubular (PCT) epithelial cells and men en women lack this specific PCT cell peculiarity.

The main effect of MIBK is exerted on the central nervous system. Narcosis was induced in rats (after i.p. injection with 200 mg/kg or inhalatory exposure to 6255 mg/m3) and cats (after s.c. injections with 150 mg/kg) and leg weakness was observed in hens (after inhalatory exposure to 4170 mg/m³). These effects were reversible after discontinuation of the exposure.
No peripheral neurotoxicity was observed.
Also in humans effects on the CNS can be observed after exposure to MIBK.
417 mg/m³ is a sensory response limit to humans. It induced headache and nausea in one group, but only respiratory irritation in another group. When exposure was reduced to 83.4 mg/m³ the complaints were largely eliminated.
However, these data lack adequate reporting.

As a starting point for the HBROEL the NAEL of 1043 mg/m³ is taken, found in a 14-week inhalatory study with rats and mice and with intermittent exposure. Since at the next highest dose, 4170 mg/m³, only slight liver effects were observed, the real NAEL lies between 1043 and 4170 mg/m³. Furthermore, long-term effects are not expected, therefore the subchronic NAEL is considered equivalent to the chronic NAEL. This animal NAEL is also considered a NAEL for humans. A safety factor of 10 is introduced in order to prevent systemic effects in occupationally exposed persons.
In rabbits and guinea pigs no systemic effects were observed after dermal exposure, indicating that this route of entry is negligible.

8.3 RECOMMENDED OCCUPATIONAL EXPOSURE LIMIT

An OEL of 104 mg MIBK/m³ TWA 8 hr (25 ppm) is advised. In order to avoid respiratory irritation a STEL 10 min of 208 mg MIBK/m³ is advised.

9 RECOMMENDATIONS FOR RESEARCH

A long-term inhalatory study on rats and mice is needed to corroborate the data found in the 14 wk study, especially that no other effect is found at 4170 mg/m³ besides male-rat-specific hyalin droplet formation in the kidneys.

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Literature survey was finished at September 30th 1990.

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gezondheidskundige adviezen van de werkgroep van deskundigen ter vaststelling van mac-waarden

Code		*Prijs*
RA 2/79	Koolmonoxyde	*f.* 23,=
RA 1/80	Fosfine	*f.* 12,=
RA 2/80	Anorganisch Lood	*f.* 18,=
RA 3/80	Carcinogene stoffen	*f.* 16,=
RA 4/80	Tolueen Diisocyanaat	*f.* 7,=
RA 5/80	Cadmium	*f.* 16,=
RA 6/80	Chloor	*f.* 13,=
RA 1/81	n-Heptaan	*f.* 11,=
RA 2/81	Pentaan	*f.* 9,=
RA 3/81	1,1,1-Trichloorethaan	*f.* 18,=
RA 4/81	Formaldehyde	*f.* 17,=
RA 5/81	Metallisch Kwik	*f.* 13,=
RA 1/82	Mangaan	*f.* 17,=
RA 2/82	Monochloorethaan	*f.* 11,=
RA 3/82	Anorganische Kwikzouten	*f.* 15,=
RA 4/82	Organische Kwikverbindingen *(Uitsluitend phenylkwik en alkoxyalkylverb.)*	*f.* 13,=
RA 5/82	Kwikalkylverbindingen - Korte keten *(Uitsluitend methylkwik en ethylkwik)*	*f.* 18,=
RA 1/83	Methyleenchloride	*f.* 17,=
RA 2/83	Triethylamine	*f.* 16,=
RA 3/83	Trichloorethyleen	*f.* 18,=
RA 1/84	Asbest	*f.* 28,=
RA 2/84	Anorganische Arseenverbindingen *(Exclusief Arseenwaterstof)*	*f.* 20,=
RA 4/84	Caprolactam	*f.* 17,=
RA 1/85	2-Nitropropaan	*f.* 12,=
RA 2/85	Lachgas	*f.* 21,=

Code		*Prijs*
RA 3/85	Nikkel en nikkelverbindingen	*f.* 21,=
RA 4/85	Zwaveloxide	*f.* 17,=
RA 5/85	Stikstofoxide	*f.* 15,=
RA 6/85	Chroom en chroomverbindingen	*f.* 20,=
RA 1/86	Epichloorhydrine	*f.* 19,=
RA 1/87	1,4-Dioxaan	*f.* 13,=
RA 2/87	Hydrazine, dimethylhydrazine, hydroxyethyl-hydrazine en fenylhydrazine	*f.* 21,=
RA 3/87	Formaldehyde *(Engelse uitgave)*	*f.* 22,=
RA 4/87	4,6-Dinitro-ortho-cresol	*f.* 13,=
RA 5/87	Dibroomethaan	*f.* 13,=
RA 6/87	Aflatoxine B1, B2, G1 en G2	*f.* 16,=
RA 7/87	Chloroform	*f.* 18,=
RA 8/87	1,1-Dichloorethaan	*f.* 9,=
RA 9/87	Trimethylamine	*f.* 13,=
RA 10/87	Vanadium metaal en anorganische verbindingen	*f.* 16,=
RA 11/87	n-Hexaan	*f.* 21,=
RA 12/87	2-Propoxyethanol, 2-Propoxyethylacetate, 2-Isopropoxyethanol *(Engelse uitgave)*	*f.* 9,=
RA 13/87	Acrilaten	*f.* 13,=
RA 14/87	Trichlorofluoromethane *(Engelse uitgave)*	*f.* 16,=
RA 15/87	Fluorcarbons(except FC11) *(Engelse uitgave)*	*f.* 21,=
RA 1/88	Para-Dichloorbenzeen	*f.* 15,=
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RA 2/88	Hexachlorobenzene	*f.* 24,=
RA 3/88	Carbonylfluoride and PTFE Pyrolysis products	*f.* 11,=
RA 4/88	Beryllium and Beryllium compounds	*f.* 22,=
RA 1/89	Fluorine, Hydrogenfluorine and Inorganic fluorine compounds	*f.* 22,=
RA 2/89	Aniline	*f.* 17,=

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RA 6/89	Ethyleenoxide *	*f.* 13,=
RA 7/89	Selenium en verbindingen *	*f.* 18,=
RA 8/89	Styreen *	*f.* 17,=
RA 9/89	Evaluatie van risico op kanker bij beroepshalve blootstelling aan asbest (aanvullend op RA 1/84) *	*f.* 12,=
RA 1/90	Methyl acrylate	*f.* 14,=
RA 2/90	2-Hexanone	*f.* 17,=
RA 3/90	Cyclohexanol	*f.* 16,=
RA 4/90	Amyl acetate	*f.* 11,=
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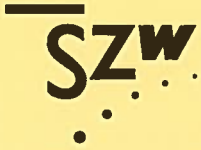

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