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DEC and NEG Basis for an Occupational Health Standard

7/8-Carbon Chain Aliphatic Monoketones

(2-Heptanone, 3-Heptanone, Ethylamylketone and Methylisoamylketone)

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PREFACE

An agreement has been signed by the Dutch Expert Committee for Occupational Standards (DEC) of the Dutch Directorate-General of Labour and the Nordic Expert Group for Documentation of Occupational Exposure Limits (NEG). The purpose of the agreement is to write joint scientific criteria documents which could be used by the national regulatory authorities in both the Netherlands and in the Nordic Countries.

This document on health effects of some aliphatic monoketones is a product of the agreement. The document was written by Dr. A. A. E. Wibowo from the Coronel laboratory in Amsterdam, The Netherlands, and was reviewed by the Dutch Expert Committee as well as by the Nordic Expert Group.

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Chairman
Dutch Expert Committee

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1. INTRODUCTION

A ketone is an organic compound containing a carbonyl group (C=0) attached to two carbon atoms. In this document special attention has been paid on four types of 7/8-carbon chain aliphatic mono-ketones:

- 2-Heptanone (MAK)
- 3-Heptanone (EBK)
- Ethylamylketone (EAK)
- Methylisoamylketone (MIAK)

Only a few data on the toxicology and epidemiology are available for these compounds. Nevertheless, an attempt is made to define the critical effect for occupational exposure.

For background material the following reports have been used:

- Krasavage, W.J., J.L. O'Donoghue and G.D. Divicenzo (1982). In: Patty's Industrial hygiene and toxicology. 3rd revised edition, pp. 4709-4800.
- NIOSH Criteria for a recommended standard ... Occupational exposure to ketones (1978). US Dept. Health, Education and Welfare. Washington DC.

2. IDENTITY, PHYSICAL AND CHEMICAL PROPERTIES; MONITORING

2.1. Identity

2-Heptanone (methylamylketone; MAK) is a liquid of low volatility with a penetrating fruity odour. It has an odour threshold of about 0.02 ppm (0.1 mg/m^3).

3-Heptanone (ethylbutylketone; EBK) is a clear liquid, with a strong fruity odour.

Ethylamylketone (5-methyl-3-heptanone; EAK) is a colourless liquid of low volatility. It has an agreeable penetrating odour which resembles the essence of apricots and peaches. The odour threshold concentration has been reported to be 6 ppm (32 mg/m^3) and less than 5 ppm (27 mg/m^3).

Methylisoamylketone (MIAK) is a clear, colourless liquid with a sharp but pleasant, sweet odour. The odour threshold level for MIAK is 0.01 ppm (0.06 mg/m^3). Its autoignition temperature is 425°C.

2.2. Physical and chemical properties

For physical and chemical properties see Table 1.

2.3. Analytical methods

2.3.1. Environmental monitoring

The NIOSH Manual of Analytical Methods (20) recommended the following procedures as validated for environmental monitoring of 2-heptanone, 3-heptanone and ethylamylketone. An analytical method for methylisoamylketone was not presented.

2-Heptanone

A known volume of air is drawn through a charcoal tube to trap the organic vapours present. The charcoal in the tube is transferred into a small, stoppered sample container and the analyte is desorbed with carbon disulfide containing 1% methanol. An aliquot of the desorbed sample is analysed by gas chromatograph. This

Table 1. Chemical and physical characteristics of 7/8-carbon chain aliphatic monoketones (21,28,29).

	2-Heptanone	3-Heptanone	Ethylamylketone	Methylisoamylketone
CAS numbers	110-43-0	106-35-4	541-85-5	110-12-3
Synonyms	Methylamylketone Amylmethylketone Methylpentylketone	Ethylbutylketone Butylethylketone Heptanone-3-one	Amylethylketone 5-Methyl-3-heptanone	Isoamylmethylketone 5-Methyl-2-hexanone Isopentylmethylketone
(Abreviations)	(MAK)	(EBK)	(EAK)	(MIAK)
Formula	$C_7H_{14}O$	$C_7H_{14}O$	$C_8H_{16}O$	$C_7H_{14}O$
Structural formula	CH_3 C=O $(CH_2)_4$ CH_3	C_2H_5 C=O $(CH_2)_3$ CH_3	C_2H_5 C=O CH_2 $HC-CH_3$ C_2H_5	CH_3 C=O $(CH_2)_2$ $HC-CH_3$ CH_3
Molecular weight	114.2	114.2	128.2	114.2
Boiling point (°C)	150.6	148.5	160.5	144
Melting point (°C)	-26.9	-39	-	-
Specific gravity	0.82 (15/4°C)	0.82 (20/4°C)	0.85 (0/4°C)	0.82 (17/4°C)
Refraction index (20°C)	1.4073	1.4057	-	1.4062
Vapour pressure (hPa, at 25°C)	2.08	1.82	2.60	1.95 (20°C)

	2-Heptanone	3-Heptanone	Ethylamylketone	Methylisoamylketone
Air saturation	0.21	-	0.26 (25°C)	-
Flash point (open cup) (F)	117	-	135	110
Solubility in water (g/l)	4.3	14.3	3	5.4
Conversion factor				
1 ppm=	4.66 mg/m³	4.66 mg/m³	5.33 mg/m³	4.66 mg/m³
1 mg/m³=	0.214 ppm	0.214 ppm	0.19 ppm	0.214 ppm

method is validated over the range of 200-925 mg/m³ at an atmospheric temperature and pressure of 25°C and 755 mm Hg, using a nominal 10 l sample.

The precision (CV_T) for the total analytical and sampling method in the range of 200 to 925 mg/m³ was 0.066.

3-Heptanone

The principle of the method is the same as that of 2-heptanone. For 3-heptanone, this method was validated over the range of 100-460 mg/m³ at an atmospheric temperature and pressure of 25°C and 758 mm Hg, using a nominal 10 l sample. The precision (CV_T) for the total analytical and sampling method in the range of 100 to 460 mg/m³ was 0.0864.

Ethylamylketone

The principle of the method is the same as that of 2-heptanone. For Ethylamylketone, this method was validated over the range of 60-270 mg/m³ at an atmospheric temperature and pressure of 25°C and 754 mm Hg, using a nominal 10 l sample. The precison (CV_T) for the total analytical and sampling method in the range of 60 to 270 mg/m³ was 0.01043.

2.3.2. Biological Monitoring

There are no data available on biological monitoring of 2-heptanone, 3-heptanone, ethylamylketone and methylisoamylketone. On the other hand, the following may be true for ketones as a whole. The ketones of industrial importance are usually volatile liquids that may enter the organism by inhalation of vapours or through direct skin contact with the liquid form. They are rapidly eliminated from the body either unchanged in the urine and expired air or after biotransformation. The parent compound or its metabolites can also be detected in blood.

3. SOURCES OF EXPOSURE

3.1. Natural occurrence

2-Heptanone occurs naturally in oil of cloves and in Ceylon cinnamon oil. Verschueren (28) reported that ethylamylketone is produced in nature by Streptomyces cinnamoneuslike organisms and contributes to characteristic odours of actinomyces cultures. No data are available on the natural occurrence of the other ketones.

3.2. Man-made sources

3.2.1. Production

Large amounts of ketones are produced annually for industrial use in the United States. No data are available on the production in Europe. Those with the highest production volumes include acetone, methylethylketone, methylisobutylketone, cyclohexanone, 4-hydroxy-4-methyl-2-pentanone, isophorone, mesitylketone and acetophenone (16). 2-Heptanone, 3-heptanone, ethylamylketone and methylisoamylketone are probably produced in smaller amounts.

3.2.2. Uses

Some of the applications of the ketones in the industry are determined by the solvent properties, rate of evaporation, boiling point, viscosity and availability. Ketones are used as chemical intermediates in chemical manufacturing industries; as solvents for natural and synthetic resins in coating industries, as components in formulations such as inks, adhesives and dyes, as extraction agents for lubricating oils, in wax refining and for rare metal flotation in refining processes (21). Particularly for 2-heptanone, the NIOSH (21) reported its use as a solvent in synthetic resin finishes, particularly for metal roll coating. For methylisoamylketone, its use is reported as a solvent for nitrocellulose, cellulose acetate, and acrylic and vinyl copolymers.

4. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURES

4.1. Environmental levels

No data are available.

4.2. Human exposure

The NIOSH (21) estimated that 67000 workers in the United States are potentially exposed to 2-heptanone, and about 19000 workers to methylisoamylketone. An estimate of the number of workers who are potentially exposed to 3-heptanone and ethylamylketone is not available. No data are available for the populations at risk in the Netherlands.

5. NATIONAL OCCUPATIONAL STANDARDS OF 7/8-CARBON CHAIN ALIPHATIC MONOKETONES IN mg/m³ OR BETWEEN BRACKETS IN ppm.

	2-Heptanone	3-Heptanone	Ethylamylketone	Methylisoamylketone
Denmark (1988)	(50)	(50)	(25)	(50)
Fed. Rep. of Germany - DFG (1989)	-	-	-	-
Finland (1987)	230 (50)	230 (50)	130 (25)*	460 (100)
France - Cahiers de notes documentaires (1988)	235 (50)	230 (50)	130 (25)	240 (50)
Iceland (1978)	465 (100)	230 (50)	130 (25)	475 (100)
Netherland (MAC-twa 8h) - Arbeidsinspectie P145 (1989)	465 (100)	230 (50)	130 (25)	205 (50)
Norway (1989)	115 (25)	115 (50)	100 (20)	115 (25)
Sweden - Ordinance AFS (1989)	-	-	-	-
United Kingdom (1987)	-	230 (50)	130 (25)	240 (50)
United States - ACGIH (1988) - OSHA (1989) - NIOSH (1978)	235 (50) 465 (100) 465 (100)	230 (50) 230 (50) -	130 (25) - -	240 (50) 240 (50) 230 (50)
USSR (1978)	-	-	-	-

* sec. amyl

6. TOXICOKINETICS

6.1. Absorption

In the occupational setting the primary routes of exposure to ketones are inhalation and skin contacts, ingestion is rare (16). No data are available on the degree of absorption in man, but in view of the high solubility in water, the fractional absorption is estimated to be high.

Lynch et al (17) exposed male Cynomolgus monkeys to 2-heptanone for 6 h/d, 5d/w, 10 months the compound was detected both in serum and urine. In exposure of three monkeys to 610 mg/m³ (= 131 ppm) in air they found a concentration of ND - 7.4 mg/l in the serum. At a level of 4777 mg/m³ (= 1025 ppm) in air they found in four monkeys a mean 2-heptanone level in serum of 15.6 ± 6.5 mg/l with a range of 3.5 - 27.2 mg/l. On two control monkeys the concentration of 2-heptanone in serum was below the detection limit. In the same publication 6 rats exposed to 610 mg/m³ (= 131 ppm) for 6 h/d, 5 d/w, 10 months had a mean level of 11.6 ± 2.9 mg/l 2-heptanone in serum, and exposure of four rats to 4777 mg/m³ at the same duration produced a mean level of 27.0 ± 3.6 mg/l 2-heptanone in serum. The serum samples from the monkeys and the rats were collected 1 hour after termination of exposure. The concentration of 610 mg/m³ (= 131 ppm) 2-heptanone 6 h/d in air was selected in order to correspond with the current NIOSH/ OSHA occupational standard of 465 mg/m³ (= 100 ppm), 8 h/d.

Katz et al. (15) exposed rats to 700 ppm (= 3262 mg/m³) 3-heptanone by inhalation weekly for 72 h per week with two 20 h and two 16 h intervals. These subsequent exposures were performed to give animals 8 h non-exposure intervals. The mean serum concentration of 3-heptanone after 30 exposures (or 7.5 week) was 0.6 mg/l.

In 1986, Katz et al. (14) studied the uptake and clearance of methylisoamylketone (MIAK) in rat following single oral dose or a single 6 h inhalation exposure, by determining the levels of MIAK in serum. Peak serum concentrations were observed at 1 h (94 ± 13 mg/ml) after oral administration of 1830 mg/kg and at 4 h (138 ± 11 mg/ml) during inhalation exposure to 1950 ppm (9087 mg/m³). The corresponding elimination half-lives ($t_{\frac{1}{2}}$) were 5.3 hours for the gavage exposure and 0.7 hours for the inhalation exposure.

6.2. Distribution

No data are available on the distribution of ketones in humans.

Lynch et al. (17) performed tissue distribution studies with ^{14}C-labeled 2-heptanone by both intraperitoneal and respiratory routes of exposure of rats. The mean air concentration for the 6 hour inhalation exposures was 132 ± 6.2 ppm (615 ± 29 mg/m³). At all time intervals studied (2 - 72 h) and regardless of the route of administration, the liver had the highest level of radioactivity, followed, in general, by kidney, pancreas and lung. The tissue distribution of 2-heptanone did not correspond to any observed gross or histopathological damage. Suspected target tissues, e.g. brain, had low levels of radioactivity, and the activity in portions of sciatic nerves was below the limit of detection at all time intervals studied.

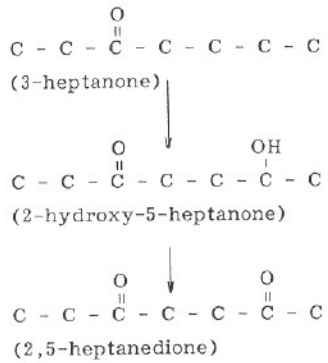
6.3. Metabolic transformation and elimination

Generally, when ketones are absorbed into the bloodstream, they may be eliminated unchanged in the expired air, reduced to secondary alcohols, or oxidized to hydroxyketones, diketones and carbon dioxide by a variety of metabolic pathways. Recent studies indicate that carbonyl reduction, and ω-1 oxidation, decarboxylation and transamination play important roles in the metabolism of aliphatic ketones. Aliphatic ketones may be conjugated with glucuronic acid, sulfuric acid or glutathione prior to excretion in the urine. Glucuronic and sulfuric acid conjugation usually occur after ketone is reduced to a secondary alcohol or oxidized to a carboxylic acid. Of the various conjugation mechanisms that occur, glucuronic acid conjugation appears to be the predominant pathway (16).

Biotransformation of 2-heptanone. It is reported that 2-heptanone undergoes carbonyl reduction to a secondary alcohol and ω-1 oxidation to a hydroxyketone which is further oxidized into

2,6-heptanedione (16). Lynch et al. (17) studied the excretion of 2-heptanone in rats after a single intraperitoneal administration of [^{14}C] MAK. The labeled compound was diluted with unlabeled MAK and mixed with corn-oil to yield a concentration of 2.5 mg MAK/ml of treatment solution. The administered dose was 10 mg MAK/kg b.w. Urinary excretion peaked at 12 h and remained relatively constant through 48 h. About 25% of the administered dose appeared in the urine within 12 hours. Fecal excretion through 72 hours after dosing represented less than 2% of the administered dose. Due to the vapour pressure of the compound, a significant amount of the dosage was probably eliminated in expired air.

Biotransformation of 3-heptanone. Analysis of the sera of rats exposed to 3-heptanone revealed the presence of 2-hydroxy-6-heptanone and 2,5-heptanedione (16). This means that 3-heptanone follows a metabolic pathway similar to that of methyl-n-butylketone (MBK):



Katz et al. (15) reported on rats exposed to 700 ppm (= 3262 mg/m^3) 3-heptanone in air for 24 weeks produced a mean serum concentration of 6.8 ± 4.0 mg/l 2,5-heptanedione and 5.4 ± 2.3 mg/l 2-hydroxy-5-heptanone. In an inhalation study, O'Donoghue et al. (22) reported rats exposed to 700 ppm (= 3262 mg/m^3) four times resulted in mean serum 2,5-heptanedione levels of 10 mg/l, which is rather simular to that of Katz et al. (15). On the other hand, when exposure to 700 ppm 3-heptanone was combined with exposure to 700 ppm or 1400 ppm methylethylketone (MEK), it

produced a 2.5 fold increase in the serum concentration of 2,5-heptanedione.

O'Donoghue et al. (22) reported the biotransformation of 3-heptanone into 2,5-hexanedione. In a gavage study, they administered rats at 24 h intervals for 2 days with doses of 1 or 2 g/kg. At 1 g/kg b.w. they found the 48 hour total urine excretion of 0.42 mg 2,5-hexanedione and 0.86 mg 2,5-heptanedione. At the dose of 2 g/kg b.w., they found the total urine excretion of 0.40 mg 2,5-hexanedione and 1.74 mg 2,5-heptanedione. Other possible pathways of excretion are by way of expired air of 3-heptanone itself or through the digestive tract.

No data are available on the biotransformation and excretion pathways of ethylamylketone and methylisoamylketone.

6.4. Biological monitoring

There are no data available.

7. EFFECTS

7.1. Observation in man

7.1.1. Effects on the respiratory system

The principal hazard associated with exposure to ketone vapours is irritation of eyes, nose and throat. Many ketones have excellent warning properties and can be easily detected by the olfactory sense. Accidental overexposure should be relatively rare provided the warning properties are not ignored and olfactory fatigue does not occur. The classic symptoms produced by overexposure to ketones include, progressively, irritation of the eyes, nose, and throat, headache, nausea, vertigo, incoordination, central nervous system depression, narcosis and cardiorespiratory failure. These data were given by Krasavage et al. (16) without information on the source.

The NIOSH (1978) reported that a number of investigators have studied the irritating effects of ketones in humans. Most studies examined the irritating concentration (concentration that caused irritation in the majority of subjects) on eyes, nose and throat at exposure to various ketone compounds, but no experiments using 2-heptanone, 3-heptanone, methylisoamylketone or ethylamylketone were reported. Due to chemical similarities between the compounds, one must suspect that these compounds also exert similar effects.

7.1.2. Effects on the nervous system

Prockop et al. (24) reported severe neuropathy in seven men who repeatedly sniffed a commercially available lacquer thinner for the euphoric sensation ("high") it produces. This lacquer was later analysed as containing 11 organic compounds (26). One of the compounds was 2-heptanone which was 15.5% of the composition. The onset in all seven white men aged 17 to 22 years began with weakness in the extremities and numbness that progressed in an ascending direction. All patients admitted habitual "sniffing". The symptoms, predominantly motor, continued for three to eight weeks after cessation of inhalation. Extensive laboratory evaluations were conducted, including analysis of cerebrospinal fluid, electroencephalogram, electrocardiogram, urine analysis of heavy metals, tests for viral antigens, lupus erythematosis preparations and electromyography. Results of all studies were normal except for nerve conduction rates which were less than 30 meters per second (normal 42 to 55 m.p.s.) and evidence of acute denervation of varying degrees. The decrease in nerve conduction rates correlates with the severity of clinical involvement in each case. The difficulties in this report is the multitude of compounds these cases may be exposed to. Beside of 2-heptanone, there was also n-hexane (0.5%), toluene (3.9%), xylene (43.6%) and 2-nitropropane (5.8%) in the composition.

7.1.3. Other effects

Krasavage et al. (16) cited a study in which no positive reactions were reported in a skin sensitization study on 26 human volunteers, using 2-heptanone at a concentration of 4% in petrolatum. The same may be true of 3-heptanone, when tested on 25 volunteers. This compound produced no irritation to human skin after 48 h under an occlusive patch in a concentration of 4% in petrolatum.

7.2. Animal experiments

7.2.1. Acute effects

The following acute toxicity data were reported by the NIOSH Registry of Toxic Effects of Chemical Substances (1977), and supplemented with more recent information:

2-Heptanone

Rat oral	LD50 = 1670 mg/kg
Rat inh.	LC10 = 4000 ppm/4 h (18640 mg/m³)
Mouse oral	LD50 = 730 mg/kg
Rabbit skin	LD50 = 13 g/kg
Mouse oral	LD50 = 2407 (95% CL = 1807-3207) mg/kg (Tanii et al., 1986)

3-Heptanone

Rat oral	LD50 = 2760 mg/kg
Rat inh.	LC10 = 2000 ppm/4 h (9320 mg/m³)

Ethylamylketone

Rat oral	LD50 = 3500 mg/kg
Rat inh.	LC10 = 3404 ppm/8 h (18570 mg/m^3)
Mouse oral	LD50 = 3800 mg/kg
Mouse inh.	LC10 = 3484 ppm/4 h (18570 mg/m^3)
Guinea pig oral	LD50 = 2500 mg/kg

Methylisoamylketone

Rat oral	LD50 = 4760 mg/kg
Rat inh.	LC10 = 2000 ppm/4 h (9320 mg/m^3)
Mouse oral	LD10 = 3200 mg/kg
Rabbit skin	LD50 = 10 g/kg
Mouse oral	LD50 = 2542 (95% CL = 2012-3213) mg/kg (Tanii et al., 1986)

More recently, De Ceaurriz et al. (4) studied the irritation properties on the upper respiratory airways of 2-heptanone and methylisoamylketone by measuring the decrease of the respiratory rate in mice following short-term inhalation exposures.

For 2-heptanone, after inhalation of 535-1225 ppm (2493-5708 mg/m^3) for 15 min, they found a reduction of 20-63% of the respiratory rate. The RD_{50} was 895 with 95% CL of 820-990 ppm (4171 with 95% CL of 3821-4613 mg/m^3).

For methylisoamylketone, after inhalation of 416-1515 ppm (1938-7060 mg/m^3) for 15 min, they found a reduction of 27-61% of the respiratory rate. The RD_{50} was 1222 with 95% CL of 1002-1708 ppm (5694 with 95% CL of 4669-7959 mg/m^3). From these data it may be concluded that 2-heptanone is more irritant than methylisoamylketone.

7.2.2. Effects of the cardiopulmonary system

Lynch et al. (17) exposed Cynomolgus monkeys to 2-heptanone at concentrations of 131 or 1025 ppm (610 mg/m^3 or 4777 mg/m^3) 6 h/d, 5 d/w, for 10 months. Lung function tests were carried out including those on compliance and resistance, lung volumes, flow-volume dynamics etc., on all monkeys prior to the start of exposures and after 6 months exposure. A standard six-lead ECG-

examination was also conducted on all monkeys at the same time intervals as the pulmonary function testing. The results showed that the dynamic compliance, inspiratory capacity, expiratory flow maximum at 90% of vital capacity over vital capacity, and diffusion capacity over total lung capacity all exhibited no significant differences within or between the control and the two exposure groups after six months of 2-heptanone exposure. There were also no changes in the ECG's which could be attributed to 2-heptanone. From this experiment it may be concluded that 2-heptanone has no effect on the cardiovascular system at the doses used on monkeys. No data are available on the other ketones.

7.2.3. Effects on the nervous system

A summary of the effects of 2-heptanone, 3-heptanone and methylisoamylketone on experimental animals is presented in Table 2. There are no data on the effects of ethylamylketone.

Analysis on the data of neurotoxicity induced by exposure to 2-heptanone on experimental animals showed some comparable results. From the experiments using rats, various methods of administration were used. To make comparison between these experiments accessible, all doses given to the animals were extrapolated into mg on 1 kg bodyweight basis per day. It was assumed that a 200 g rat has a minute volume of 125 cm^3/min (CIVO institutes TNO, 1985) and the retention of the compound by inhalation is the same as the fractional absorption by gastrointestinal tract. No effects on the neural system were found on rats at doses of:

137 mg/kg/d (~610 mg/m^3, 6 h/d) (12)
400 mg/kg/d (19)
500 mg/kg/d (~0.5% in drinking water) (26)
1075 mg/kg/d (~4777 mg/m^3, 6 h/d) (12)
2097 mg/kg (~6990 mg/m^3, 6-8 h) (1).

Consistent effects on the behavior occurred at levels higher than 2202 mg/kg/d (~7340 mg/m^3, 6 h) were found by Anger et al. (1).

For the determination of the no-adverse-effect level the preference lies for the results from the experiment performed by Johnson

Table 2. The effects of 7/8-carbon chain aliphatic monoketones on the nervous system of experimental animals.

Compound used	Concentration and mode of administration	Duration of exposure	Species of animal (number per group)	Results	Comments	Reference
2-heptanone	0.5% in drinkingwater (500 mg/kg/d)	12 weeks	SD rats (n=5)	No effects on pathological examination of peripheral nervous system. Normal weight gain and clinical signs.		26
2-heptanone	610 mg/m³ 4777 mg/m³ in air (131 and 1025 ppm)	6 h/d, 5 d/w, 9 months	SD rats (n=10)	No effects on maximum motor nerve conduction velocity of sciatic-tibial nerve and ulnar nerve, and amplitude of evoked muscle action potentials.		11, 12
			monkeys (Macaca fascicularis; (n=8)	- idem - Also no effect on EEG and visually evoked potentials.		
2-heptanone	18,37,74 and 175 mg/kg i.p. injection	single injection 15 min	SD rats (n=6)	A dose-related decrease in the response rates on a multiple fixed-ratio, fixed-interval schedule of reinforcement (behavioural parameter).	Estimated no-adverse effect level is 18 mg/kg by i.p. injection.	1
	2383-8807 mg/m³ (490-1890 ppm) in air	6-8 h	SD rats (n=6)	Consistent changes in behaviour occurred at levels higher than 7340 mg/m³, 8 h.	Estimated no-adverse effect level is 6990 mg/m³ (1500 ppm).	
2-heptanone	400 mg/kg/d subcutaneous injection	5 d/w 15 weeks	Donryu rats (n=7)	No effects on neurological signs, growth, and nerve conduction velocity and motor distal latency.		19
3-heptanone	1000 mg/kg/d via drinking-	120 days	Wistar rats (n=?)	No significant neurologic alterations.		10
3-heptanone	3262 mg/m³ (700 ppm) in air	72 h/w during two 20 h and two 16 h intervals, for 24 weeks	rats (n=5)	No clinical and neuropathological evidence of neurotoxicity.	No signs of neurotoxicity (at serum level of 2,5-heptanedione of 6.8 ± 4.0 mg/l and 2-heptanone of 0.6 ± 0.8 mg/l).	15
3-heptanone	250,500,1000 2000 and 4000 mg/kg/d by gavage	5 d/w, 14 weeks	CRL-rats (total 44 rats)	At 2000 and 4000 mg/kg/d the animals developed central nervous system depression or narcosis, and high mortality. Clinical neurotoxicity was present at 2000 mg/kg/d, also a typical "giant" axonal neuropathy. At 1000 mg/kg/d it was not neurotoxic, but a decrease in the weight gain and food consumption was observed.	The estimated no-adverse effect level for neurotoxicity is 1000 mg/kg/d by gavage administration.	22
methylisoamylketone	9320 and 4660 mg/m³ (2000 and 1000 ppm) by inhalation	6 h/d, 5 d/w, 2 weeks (12 exposures)	SD rats (n=5)	At 9320 mg/m³ slight lethargy and decrease of aural response.	The estimated minimal adverse effect level on the effects on central nervous system is 4660 mg/m³ (1000 ppm).	14
	9320, 4660 and 932 mg/m³ (2000, 1000 and 200 ppm) by inhalation	6 h/d, 5 d/w, 90 days (69 exposures)	SD rats (n=15)	Moderate decrease of aural response and lethargy at 9320 mg/m³ and slight in the 4660 mg/m³ group.		
methylisoamylketone	1258-2968 mg/m³ (270-637 ppm) by inhalation	4 h	Swiss OFI mice (n=10)	26 to 68% decrease in the duration of immobility in mice subjected to a "behavioural despair" swimming test.	The significane of this test is unknown. This test is used to study antidepressant drugs.	4

et al. (12) than that from Anger et al. (1), because the former exposed the animals (rats and monkeys) 6 h/d for 9 months and the latter exposed rats only for 6-8 hours. Therefore it may be concluded that the NAEL on the neurotoxicity of 2-heptanone on experimental animal will be in the order of magnitude of 1000 ppm (4660 mg/m³) in inhaled air for a period of several months (for details see Table 2).

From the experiments on rats exposed to 3-heptanone the same similarities in results were shown, although at different order of exposure. The experiment from Homan and Maronpot (10) on rats concluded that at 1000 mg/kg/d via drinking water did not show any sign of neurotoxicity. Katz et al. (15) reported at 3262 mg/m³, 72 h/w (~ 1258 mg/kg/d) for 24 weeks was non-toxic to the nervous systems. From the experiments performed by O'Donoghue et al. (22) it is estimated that the no-adverse effect level for neurotoxicity is about 1000 mg/kg/d for 14 weeks by gavage. At 2000 mg/kg/d for 14 weeks clinical toxicity was present and also a typical "giant" axonal neuropathy. From these data it may be concluded that the no-adverse-effect level (NAEL) on the neurotoxicity of 3-heptanone rats should be about 1258 mg/kg/d, or 3262 mg/m³ (700 ppm) for 24 weeks in inhaled air (for details see Table 2).

Comparison of the neurotoxicity of 2-heptanone and 3-heptanone permits to conclude that 3-heptanone is more toxic than 2-heptanone.

This difference in neurotoxicity may be explained when we look at the structure activity of the metabolites. 2-Heptanone undergoes biotransformation to a secondary alcohol and ω-1 oxidation to hydroxyketone which is further oxidized to 2,6-heptanedione. 2,6-Heptanedione has been tested and shown not to be neurotoxic (16). However, 3-heptanone is metabolized by rats to 2,5-heptanedione which, like its 6-carbon counterpart, 2,5-hexanedione, has been shown to be neurotoxic. Therefore, it may be assumed that the induction of neurotoxicity is strongly associated with the levels of 2,5-heptanedione in the target organs or serum.

The effects of methylisoamylketone on the central nervous system of rats were also studied by Katz et al. (14). The rats were exposed by inhalation to 9320, 4660 and 0 mg/m³, 6 h/d, 5 d/w for 2 weeks (equivalent to 2000, 1000 and 0 ppm). In another group of rats, they were exposed to 9320, 4660, 932 and 0 mg/m³ (equivalent to 2000, 1000, 200 and 0 ppm) for 6 h/d, 5 d/w for 90 days. From these experiments they found a moderate decrease of aural response and a lethargy to the rats at levels of 9320 mg/m³ and only slight effects at 4660 mg/m³. It can be concluded that the estimated minimal-adverse-effect level of methylisoamylketone on the central nervous system must be about 4660 mg/m³ (1000 ppm) for 2 weeks. De Ceaurriz et al. (4) studied the effect of methylisoamylketone on the central nervous system by a method originally developed for detecting the efficacy of antidepressant drugs. They calculated the effect by measuring the duration of immobility in mice subjected to a "behavioural despair" swimming test. Exposure to 1258-2968 mg/m³ (270-637 ppm) for 4 hours reduced the duration of immobility during a 3 min "behavioural despair" swimming test for 26-68%, the ID50 (Median active level producing a 50% decrease) for methylisoamylketone was calculated to be 2078 mg/m³ (446 ppm). For comparison, in a similar experiment with 2-heptanone ID50 was 2097 mg/m³ (450 ppm). The significance of this experiment in determining the grade of toxicity is unknown, one can only surmize that with this method the ID50 from methylisoamylketone is about the same as that of 2-heptanone.

7.2.4. Effects on the liver and the kidney

A summary of the effects of 2-heptanone and methylisoamylketone is presented in Table 3. There is no data on the effects of 3-heptanone and ethylamylketone.

On the effects of 2-heptanone on the liver and kidneys, there is only one experiment known in which the exposure was performed by inhalation. In a subchronic inhalation study, Lynch et al. (17) exposed SD rats to 0, 466 and 4660 mg/m³ (0, 100 and 1000 ppm) 2-heptanone, 6 h/d, 5 d/w for 10 months. The liver function was examined by studying the liver microsomal enzyme induction potential by injecting pentobarbitalsodium (25 mg/kg) ip into rats after inhaling 2-heptanone for 10 months and comparing the sleeping times. They found no significant differences in sleeping times

between the groups. There also were no sign of toxicity on the animals and no gross or microscopic changes in organs and tissues were found. In the same study in which Cynomolgus monkeys were exposed with the same concentrations and duration as the rats, and blood was taken at 1, 3 and 6 months of exposure; the authors found no dose-related alterations in the clinical chemistry profile. The following parameters were examined: glutamate-oxaloacetate transaminase, lactic dehydrogenase, alkaline phosphatase, total bilirubin, albumine, total protein, cholesterol, uric acid, BUN, glucose, inorganic phosphate and calcium. From this study it may be concluded that the possible no-adverse-effect level for effects on the liver and kidneys could be higher than 4660 mg/m³ (1000 ppm) in exposure by inhalation for 10 months.

A few papers mentioned that 2-heptanone may enhance the liver and kidney toxicity induced by chloroform (9,8,3). The results support the hypothesis that administration of ketonic substances increases the susceptibility of the liver and kidney to the toxic effects of halo alkanes. To date the relevance of these data in the risk evaluation of a single compound, is still unknown. Moreover, 2-heptanone had been administered as a single oral dose, which does not comply with that of a chronic exposure.

The effects of methylisoamylketone exposure to the liver and kidneys of rats have been reported by Katz et al. (14). In two different studies, one with 2 weeks duration and the other with 90 days duration, they found that the rats exposed to 4660 and 9320 mg/m³ (1000 and 2000 ppm) in inhaled air, 6 h/d, 5 d/w, showed a slight increase of the absolute and relative kidney and liver weights. At 9320 mg/m³, the changes in the liver were characterized as minimal to moderate eosinophilic cytoplasmic change (11/15, male rats), minimal to moderate hypertrophy of hepatocytes (14/15 male, 15/15 female rats), and minimal to minor necrosis (10/15, male rats). In the kidneys the changes were characterized as minor to moderately increased cytoplasmic basophilia interpreted as regeneration of tubular epithelium (8/15 male, 6/15 female rats) and a possible increase of the severity of hyaline droplet degeneration in the proximal convoluted tubules of males. At 4660 mg/m³ the same changes were seen in the liver and the kidneys, however, with lower incidences. No compound related changes were

Table 3. The effects of 2-heptanone and methylisoamylketone on the liver and the kidney of experimental animals.

Compound used	Concentration and mode of administration	Duration of exposure	Species of animal (number per group)	Results	Comments	Reference
2-heptanone	0,20,100 and 500 mg/kg/d; oral intubation	13 weeks	SPF rats (15 male and 15 female)	Increase of liver and kidney weight at 100 and 500 mg/kg/d. Also increase of number of cells excreted in the urine. At 20 mg/kg/d only traces of ketone bodies in the urine.	The estimated no-adverse effect level by oral intubation is 20 mg/kg/d.	5
2-heptanone	0,466 and 4660 mg/m³ (0,100 and 1000 ppm) by inhalation	6 h/d, 5 d/w, 10 months	SD rats (n=50); Cynomulgus monkeys (n=8)	No liver microsomal enzyme induction when evaluated by pentobarbital (25 mg/kg, i.p.) sleeping time. No abnormalities in the blood clinical chemistry in both species, neither gross/microscopic changes in organs.	Possible no-adverse effect level should be higher than 4660 mg/m³.	17
2-heptanone	1713 mg/kg, by oral administration	a single dose	rats (n=15)	No appreciable degree of kidney damage as examined in the BUN content and PAH S/M ratio. But the response to chloroform chalenge dose was increased when pretreated with MAK.		7
2-heptanone	1713 mg/kg, by oral administration (gavage)	a single dose	SD rats (n=15)	No marked liver injury as examined in the plasma GPT and OCT activity. However, it potentiated the chloroform-induced liver damage.	At this dose there is an increase of the relative liver weight.	8
2-heptanone	1713 mg/kg, by oral administration	a single dose	Fischer rats (n=7)	Treatment of rats did not alter, renal cortical slice PAH accumulation or plasma creatinine concentration. But it potentiates chloroform-induced kidney injury. MAK did not produce a marked degree of hepatic dysfunction, examined from the plasma GPT activity.		3

methyliso-amylketone	9320 and 4660 mg/m³ (2000 and 1000 ppm) by inhalation	6 h/d, 5 d/w, 2 weeks (12 exposures	SD rats (n=5)	Slight increase in absolute and relative kidney and liver weight. Histologic examination showed hyalin degeneration within cells of the proximal convoluted tubular epithelium of the kidneys.	The estimated no-adverse effect level of MIAK by inhalation is 932 mg/m³ (200 ppm)
	9320, 4660 and 932 mg/m³ (2000, 1000 and 200 ppm) by inhalation	6 h/d, 5 d/w 90 days (69 exposures)	SD rats (n=15)	There were histological changes in the liver and kidneys at 9320 and 4660 mg/m³. No compound related changes were observed at exposure to 932 mg/m³.	

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observed in male and female rats following exposure to 932 mg/m³ (200 ppm). From these experiments it may be concluded that the no-adverse effect level of methylisoamylketone on the liver and kidney of rats by respiratory exposure is about 932 mg/m³ (200 ppm) for 90 days.

7.2.5. Effects on the skin

Smyth et al. (25) reported that 2-heptanone induced moderate irritation on the clipped skin of each of five albino rabbits within 24 hours of uncovered application of 0.01 ml of an undiluted sample. Krasavage et al. (16) cited that the undiluted compound in quantities from 5 to 20 ml/kg when held in contact with the depilated skin of guinea pigs under an occlusive wrap for 24 h produced slight to moderate irritation. The same effect on the skin was also reported for methylisoamylketone, 3-heptanone and ethylamylketone.

7.2.6. Data on carcinogenicity, mutagenicity and effects on the reproduction

No data have been found on the parent compounds. The possibility of effects on the reproduction by their metabolites should be kept in mind. 2,5-Hexanedione is a metabolite from 3-heptanone (see 6.3), also from 2-hexanone. Peters et al. (23) exposed pregnant rats to a totigestational exposure of 500, 1000 or 2000 ppm (2050, 4100 and 8200 mg/m³ respectively) of 2-hexanone by inhalation for six hours a day. In fetal tissues 2-hexanone, 2,5-hexanedione and pentanone were identified, indicating that 2-hexanone and its metabolites reach the fetal circulation and/or that 2-hexanone is metabolized in the fetus. Female rats exposed to 2000 ppm (8200 mg/m³) 2-hexanone delivered significantly less pups per litter than did pair-fed controls (7.0 and 10.6 pups/litter respectively). Also the mean weight of pups of the dams exposed to 2000 ppm (8200 mg/m³) were significantly lower as compared to the offspring of control rats (3.0 and 5.0 grams respectively). A definite dose-dependent decrease in weight gain was seen in male offspring of the 1000 and the 2000 ppm (4100 and 8200 mg/m³ respectively) exposed rats which persisted throughout life. How-

ever, this was not the case with female offspring. Behavioural testing of the offspring showed some significant treatment effects, but these results were not uniform. Also clinical tests showed a few treatment effects, but these were difficult to interpret. Hematological tests revealed no differences at all between the groups and as compared to controls. Since the exposure concentrations cause effects in the parent animals, no conclusions can be drawn from this experiment.

7.2.7. Other effects

Katz et al. (15) reported decrease of total blood cell counts in rats following exposure to 700 ppm (3262 mg/m^3) 3-heptanone, 72 h/w for 24 wk. The authors argumented the importance of this finding is uncertain in view of the absence of other changes, including effects on the bone marrow.

7.3 Summary

In general the effects of ketone compounds on man and experimental animals may be distinguished into:

1. Effects on the upper respiratory airways caused by irritation.
2. The systemic effects.

ad 1 Irritation of the respiratory tract

No human data were available for the specific compounds; there were data for other ketone compounds. Due to chemical similarities one should suspect the existence of this property in the ketones under discussion. The irritation properties of 2-heptanone and methylisoamylketone have been studied in experimental animals by calculating the RD_{50} (the dose used to induce 50% reduction of the respiratory rate) of mice. For 2-heptanone an RD_{50} of 4171 mg/m^3 (895 ppm) and for methylisoamylketone an RD_{50} of 5694 mg/m^3 (1222 ppm) was established. It may be concluded that 2-heptanone appears to have a greater irritative potential than that of methylisoamylketone.

ad 2 The systemic effects

The target organs for the ketones and their metabolites are the nervous system, the liver and the kidneys. Other possible effects are on the white blood cells and on the reproduction.

Effects on the nervous system

There has been reports of peripheral neuropathy on men after sniffing commercially available lacquer thinner for the euphoric sensation. However these data are difficult to interpret due to the multitude of chemicals in its composition. It was reported that the composition contained 15.5% 2-heptanone. The dose was not measured.

There are more data on effects on the central nervous system in animal experiments. For 2-heptanone there appeared to be a dose-dependent influence on the behaviour of rats. Daily doses between 610 mg/m^3 (6 months on rats) and 6990 mg/m^3 (one day only) by inhalation do not show any effects, but consistent effects on the behaviour occurred at levels higher than 2202 mg/kg/d (equivalent to 7340 mg/m^3, 8 h). From these experiments it may be concluded that the NAEL of 2-heptanone on the central nervous system of experimental animals will be in the order of magnitude of 1000 ppm (4660 mg/m^3) in inhaled air for a period of several months.

3-Heptanone seemed to be more neurotoxic than 2-heptanone. At doses of 2000 and 4000 mg/kg/d administered by gavage on rats showed development of CNS depression or narcosis. Clinical neurotoxicity was present at 2000 mg/kg/d for 14 wk and also "giant" axonal neuropathy. At 1258 mg/kg/d (or equivalent to 3262 mg/m^3) for 24 wk, no signs of neurotoxicity were found, although there was a decrease of total white blood count with no change of differential count. From the accumulated data it may be concluded that the NAEL on the neurotoxicity of 3-heptanone in rats is about 3262 mg/m^3 (700 ppm) in inhaled air for a period of 24 wk exposure.

The difference in the neurotoxicity between 2-heptanone and 3-heptanone has been assumed to be due to the different metabolites these compounds produce. In the rat 2-heptanone undergoes biotransformation into 2,6-heptanedione, while 3-heptanone is

metabolized into 2,5-heptanedione. The latter, which is like its 6-carbon counterpart 2,5-hexanedione, has been shown to be neurotoxic, in contrast to 2,6-heptanedione. There are no data on biotransformation in humans. This should be studied in man.

Experiments in rats also showed that exposure to methylisoamylketone produces effects on the central nervous system as shown in the decrease of the aural response and lethargy. The estimated MAEL of methylisoamylketone on the central nervous system of rats is 4660 mg/m³ (1000 ppm) by inhalation exposure during 6 h/d, 5 d/w, for 2 weeks.

Comparison on the effects of 2-heptanone and methylisoamylketone on mice by using the "behavioural despair" swimming test, a test originally developed for detecting the efficacy of antidepressant drugs, showed that the effective dose (ID50) of 2-heptanone and methylisoamylketone is about similar.

There are no data on the effects of ethylamylketone on the central nervous system.

Effects on liver and kidney

There seemed to be a difference between the effects of 2-heptanone on the liver and on the kidneys, depending on the method of administration. Oral administration of 2-heptanone is reported to have an effect on the organ weights at doses of 100 and 500 mg/kg/d for 13 weeks. Furthermore, the number of cells excreted in the urine is increased. The NAEL by oral intubation is estimated at 20 mg/kg/d for 13 wk on rats. On the other hand, inhalation exposure of rats to 466 and 4660 mg/m³ (100 and 1000 ppm), 6 h/d, 5 d/w, 10 months has no influence on the liver microsomal enzyme induction as evaluated by the sleeping time after i.p. injection of pentobarbital. On the assumption of a 200 g rat having a minute volume of 125 cm³/min, this means a daily dose of 1049 mg/kg/d. The result of this experiment means that by inhalation exposure the NAEL for the liver microsomal enzyme induction would be higher than 4660 mg/m³ (1000 ppm), 6 h/d, 5 d/wk, 10 months.

For methylisoamylketone, effects on the liver and kidneys are reported in rats after inhalation exposure to 4660 and 9320 mg/m³ (1000 and 2000 ppm) 6 h/d, 5 d/w for 90 days. The effects are

seen in the increase of absolute and relative liver and kidney weights and pathological changes in both organs. The NAEL of methylisoamylketone on the liver and kidneys of rats by respiratory exposure is estimated at 932 mg/m³ (200 ppm) 6 h/d, 5 d/wk, 90 days.

No data on the effects of 3-heptanone and ethylamylketone are available.

Other effects

It has been reported that ketones may cause slight to moderate irritation of the clipped skin of experimental animals.

No data are available on the carcinogenicity, mutagenicity and effects on the reproduction of 2-heptanone, 3-heptanone, methylisoamylketone and ethylamylketone.

8. PREVIOUS EVALUATION BY NATIONAL BODIES

As shown in chapter 5, only the ACGIH and the NIOSH have made an evaluation on the various 7/8-carbon chain aliphatic monoketones.

2-heptanone (methylamylketone)

The ACGIH recommended a change of the TLV from 100 to 50 ppm in 1979 and a reduction of the STEL from 150 to 100 ppm. This was adopted in 1981. The change was made in absence of information on the concentration at which this compound starts to exert irritation in humans. Later on the committee recommended deletion of the STEL until additional toxicological data and industrial hygiene experience becomes available.

The NIOSH recommended a concentration of 465 mg/m^3 (100 ppm) 2-heptanone, in a 10-hour workshift, 40-hour week, in 1978. It concluded that the standard should be based on its irritating properties, because repeated exposures to rats and monkeys did not provide any evidence of peripheral neuropathy. Because 2-heptanone was at least as irritating to animals as methylpropylketone, they recommended that the standard should be at least as low as that for methylpropylketone (= 2-pentanone).

3-heptanone (ethylbutylketone)

The recommended standard as proposed by ACGIH of 50 ppm 3-heptanone was assumed to be low enough to prevent narcosis and also prevent significant eye irritation, the chief recognized effects of exposure. Obsolete data from 1949 have been quoted, e.q. no rats died when exposed for 4 hours to 2000 ppm and all rats died in exposure to 4000 ppm.

Ethylamylketone (EAK)

The ACGIH recommended a TLV of 25 ppm (130 mg/m^3) as a comfortable level for unconditioned workers. They based this standard on unpublished data:

> "Shell Chemical Corp. prevented the following observations in respect to sensory responses reported by unconditioned personnel during or following 5-min exposures to vapour:
> - threshold, odour - 6 ppm
> - 50% threshold, eye irritation - 50 ppm
> - 50% threshold, nose irritation - 50 ppm.
>
> No illness caused by industrial handling of EAK have been reported. Workers may complain of odour and transient eye irritation when handled in poorly ventilated areas when concentration exceeds 25 ppm, but experience shows that transient responses do not lead to significant systemic effects."

Methylisoamylketone (MIAK)

The ACGIH recommended a reduction of the TLV from 100 to 50 ppm (240 mg/m^3) in 1980, based on the value adopted for MIBK. There is no toxicological evaluation at hand. This lower TWA was adopted in 1982.

9. EVALUATION OF HUMAN HEALTH RISK

9.1. Groups at risk

There are no specific groups which might be designated as groups at risk.

9.2. Assessment of health risk

2-Heptanone (methylamylketone)

The critical effect for exposure to 2-heptanone is the upper respiratory tract irritation. The effects on the central nervous system, the liver and the kidneys should as well be taken into consideration.

With respect to irritation in experimental animals the RD_{50} is 4171 mg/m³ (895 ppm) in mice. On the other hand, there is a dose-dependent effect on the nervous system as well as increased liver and kidney weights are reported. A dose-effect relationship may be constructed (see Table 4).

Table 4. Dose-effect relationship of 2-heptanone.

Dose (mg/kg/d)	Method of administration on rats	Notation
20, for 13 wk	oral	NAEL liver and kidney weights
100 and 500, for 13 wk	oral	increased liver and kidney weights
1049, for 10 mo (4660 mg/m³; 1000 ppm)	inhalation	no effects on liver microsomal enzyme induction (pentobarbital sleeping time)
about 1049, for 9 mo (4660mg/m³; 1000 ppm)	inhalation	probable NAEL on effects of the CNS
2202, for 6 h (7340 mg/m³; 1575 ppm)	inhalation	consistent changes in the behaviour

In the evaluation of toxicological data with the objective to determine the occupational exposure limit, inhalation exposure data are more relevant than oral exposure data. An overall NAEL of 4660 mg/m³ (1000 ppm) has been taken as a starting point.

3-Heptanone

No recent data on the irritation property of 3-heptanone have been found. The critical effect for exposure to 3-heptanone is effects on the nervous system. 3-Heptanone seems to be more neurotoxic than 2-heptanone. Clinical neurotoxicity is present at 2000 mg/kg/d for 14 wk.

The estimated NAEL on the neurotoxicity in rats is about 3262 mg/m³ (700 ppm) for 24 wk in inhaled air. There are no data on the effects of 3-heptanone on the liver and the kidneys.

Ethylamylketone

No (recent) toxicological data are available, therefore no critical effect can be assessed. The present TLV as recommended by ACGIH of 130 mg/m³ (25 ppm) is based on occupational hygiene experience from a chemical company.

Methylisoamylketone

Methylisoamylketone has many similarities in its biological activities as 2-heptanone (methylamylketone). In the irritation property to the respiratory airways it is shown to have an RD_{50} of 5694 mg/m³ (1222 ppm), which is smaller than that of 2-heptanone.

Experiments on rats showed that methylisoamylketone decreased the aural response and induced lethargy in rats. The estimated NAEL was 4660 mg/m³ (1000 ppm) for 2 wk by inhalation exposure. Effects on the liver and kidneys were also reported. For these effects, the NAEL was estimated at 932 mg/m³ (200 ppm) 6 h/d for 90 d by inhalation exposure.

The critical effect is thus likely to be effects on the liver and kidneys.

10. RECOMMENDATION FOR RESEARCH

- There is a paucity of data on the chronic effects of ketones, particularly in the areas of carcinogenicity, mutagenicity and effects on the reproduction.

- Effects in exposures to various mixtures of ketones should be studied, particularly in their ability to act synergistically to produce toxic effects.

- Epidemiological studies are required on occupational groups exposed for long duration.

- Biological monitoring techniques on occupationally exposed workers should be studied.

11. SUMMARY

11.1. Summary in English

A.A.E. Wibowo: DEC and NEG basis for an occupational health standard 7/8-Carbon chain aliphatic monoketones. Arbete och Hälsa 1990:2, pp 1-45.

The four types of 7/8-carbon chain aliphatic monoketones in discussion are 2-heptanone (MAK), 3-heptanone (EBK), ethylamylketone (EAK) and methylisoamylketone (MIAK). They are liquids of low volatility with a specific penetrating odour. Ketones are used mostly as chemical intermediates, solvents, components of formulations and as extraction agents. In occupational settings, exposure takes place by inhalation and skin contacts, ingestion is rare. After absorption they may be eliminated unchanged in expired air, or diketones and carbon dioxide. There are no data on biological monitoring.

The principal hazard of acute exposure to ketone vapours is irritation of eyes, nose and throat. Systemic effect on the central nervous system has been reported. There are many similarities on the biological activities of MAK and MIAK. The critical effect for exposure to MAK is the upper respiratory tract irritation, although effects on CNS, liver and the kidneys should also be taken into consideration. MIAK is considered less irritant than MAK. The critical effect of EBK is effects on the nervous system, no data are available on effects of the liver and kidneys. As for EAK, no data are available on which to assess the critical effects.

Key-words: 2-heptanone, 3-heptanone, ethylamylketone, methylisoamylketone, occupational standard, health assessment.

30 References

11.2. Summary in Swedish

A.A.E. Wibowo. DEC and NEG basis for an occupational health based standard - 7/8-Carbon chain aliphatic monoketones.
Arbete och Hälsa 1990:2, sid 1-45.

De fyra 7/8-kols alifatiska monoketoner som diskuteras är 2-heptanon (MAK), 3-heptanon (EBK), etylamylketon (EAK) och metylisoamylketon (MIAK). De är svårförångade vätskor med en specifik genomträngande lukt. Ketonerna används huvudsakligen som lösningsmedel, exktraktionsmedel och intermediärer i kemisk industri. Yrkesmässigt kan exponering ske genom inhalation och hudkontakt, medan nedsväljning är ovanligt. Efter absorption kan de elimineras oförändrade eller som diketoner och koldioxid. Det saknas data för biologisk monitorering.

Den främsta effekten vid akut exponering är irritation i ögon, näsa och hals. Systemeffekter på centrala nervsystemet har rapporterats. Det är stora likheter mellan MAK:s och MIAK:s biologiska aktivitet. Den kritiska effekten vid exponering för MAK är irritation i övre luftvägarna, men hänsyn bör även tagas till effekter på CNS, lever och njure. MIAK anses mindre irriterande än MAK. Den kritiska effekten av EBK är effekter på nervsystemet. Det föreligger inte några data om effekter på lever och njure. Vad beträffar EAK saknas data för att man skall kunna fastställa den kritiska effekten.

Nyckelord: 2-heptanon, 3-heptanon, etylamylketon, metylisoamylketon, hygieniskt gränsvärde, hälsoffekter.

Pa engelska, 30 referenser.

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b kapitel ur bok

3 Birmingham DJ. Occupational dermatoses. In Clayton GD, Clayton FE (Eds). Patty's Industrial Hygiene and Toxicology. John Wiley & Sons, New York, 3rd ed Vol 1 (1978) 203–235.

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6 Toropkov V. The toxicology of trimellitic acid. Prof Zabol 4 (1968) 12–16 (på ryska, engelskt abstract).

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