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Methyl Isobutyl Ketone
CAS: 108-10-1

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Joint Assessment of Commodity Chemicals

No. 8

METHYL ISOBUTYL KETONE

CAS: 108-10-1

European Chemical Industry
Ecology & Toxicology Centre

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JACC Report No.8

THE ECETOC SCHEME FOR THE "JOINT ASSESSMENT OF COMMODITY CHEMICALS" (JACC)

This report has been produced as part of a programme for making critical reviews of the toxicology, including ecotoxicology, of selected industrial chemicals.

A number of organisations, world-wide, have produced and are continuing to produce such reviews with the aim of ensuring that, based on an up-to-date knowledge of the toxicological and other relevant information regarding existing chemicals they can continue to be produced and used safely. ECETOC is contributing to this activity with its JACC reviews.

In general, commodity chemicals, i.e. those produced in large tonnage by several companies and having widespread and multiple uses, are reviewed jointly by experts from a number of the companies concerned. Before it is decided to review a chemical, every effort is made to discover whether an adequate review exists already, in which case no work is necessary.

It should be noted that in a JACC review only the uses of the chemical as such are considered, i.e. its occurrence as an impurity in other products is not normally taken into account.

In this document a critical assessment of the toxicology and ecotoxicology of methyl isobutyl ketone is presented. Whenever good scientific reviews on certain toxicological or ecotoxicological aspects exist, their conclusions are summarised and in these cases only the subsequent literature has been assessed.

CONTENTS

1. SUMMARY AND CONCLUSIONS

Methyl isobutyl ketone (MIBK) is widely used as a solvent. It readily evaporates into the atmosphere where it is rapidly phototransformed. MIBK volatilises from upper soil layers when accidentally spilled and is readily biodegradable. This may be the reason for the absence of quantitative data on the presence of MIBK in the environment. Its moderate water solubility and low octanol/water partition coefficient indicate that MIBK has a low bioaccumulation potential.

MIBK is of low acute systemic toxicity by the oral and inhalation routes. Liquid MIBK and vapour concentrations above 100 ppm are irritant to the eye and mucous membranes of the upper respiratory tract. Prolonged or repeated skin contact may cause drying and flaking of the skin. Aspiration of liquid MIBK will cause chemical pneumonitis.

In short-term (90d) inhalation studies in rats and mice concentrations up to 1000 ppm resulted in no toxicologically significant effects. In a number of studies MIBK concentrations below 1000 ppm induced microsomal enzyme metabolism in the liver.

MIBK is not teratogenic or embryotoxic in rats and mice at exposure levels which are maternally non-toxic. Maternal and foetal toxicity but no teratogenic effects were seen at 3000 ppm. Exposure to MIBK at the current occupational exposure limit is not considered to pose a reproductive risk.

Results from a number of short-term assays indicate that MIBK is not genotoxic. The results of the short-term and mutagenicity/genotoxicity studies suggest that it is unlikely that MIBK will pose a chronic toxic or a carcinogenic hazard. Chronic toxicity or carcinogenicity studies have not been reported.

MIBK induces symptoms which are consistent with a reversible depressive effect on the central nervous system activity (e.g. headache, nausea, narcosis); there is no evidence it produces a permanent damage to the nervous system.

MIBK has a low toxicity to aquatic organisms and micro-organisms.

The relative high volatility of MIBK, its rapid atmospheric phototransformation, ready biodegradability and low mammalian and aquatic toxicity indicate that the environmental hazards of this substance are negligible.

2. IDENTITY, PHYSICAL AND CHEMICAL PROPERTIES, ANALYTICAL METHODS

2.1 Identity

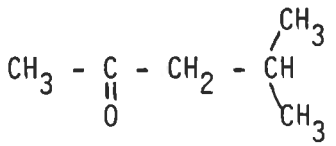
Chem. Abstr. Services Reg. No. : 108-10-1

EEC No. : 606-004-00-4

RTECS No. : SA 9275000

Synonyms: : MIBK, M.I.K., 4-methyl-2-pentanone, hexanone, hexone, isopropyl-acetone, 4-methyl pentan-2-one, 4-methyl-2-pentanone, 4-methyl-2-oxopentane, 2-methyl propyl methyl ketone.

Formula: : $C_6H_{12}O$;



A typical sample of MIBK has a purity of 99% (wt); it may contain the following main impurities:

dimethyl heptane	:	< 0.3%
water	:	< 0.1%
methyl isobutyl carbinol	:	< 0.06%
mesityloxide	:	< 0.03%
acidity as acetic acid	:	< 0.002%
non-volatiles	:	< 0.002%

2.2 Physical and Chemical Properties

Verschuuren (1983)

Molecular weight	: 100.16
Physical form	: liquid
Colour	: colourless
Odour/taste	: sweet
Odour threshold value, ppm	: from 0.4 onwards (Ruth, 1986)
Boiling point, °C at 1013.10^2Pa (range)*	: 116.2 (116/119)*
Freezing point, °C (range)*	: -80.26 (-80/-85)*
Specific gravity (20°C/4°C)	: 0.8017
Refractive index, n_D^{20}	: 1.395 - 1.397
Viscosity, mPa.s at 20°C	: 0.58-0.61
Vapour density (air = 1)	: 3.45
Vapour pressure, mbar (kPa) at 20°C	: ±19.9 (1.99)
Concentration in saturated air, g/m³ at 20°C and 1013.10^2Pa	: 27
Flashpoint, °C (closed cup)	: 14
Auto ignition temp., °C	: 460
Explosion limits in air at 1013.10^2Pa,% vol	: 1.4-7.5
Solubility in water, g/l at 20°C	: 17.0

* For commercial products.

2.3 Conversion factors

- 1 ppm = 4.1 mg/m³
- 1 mg/l = 244 ppm

2.4 Analytical Methods

2.4.1. Environmental Media

Gas chromatography (GC) is currently the best developed technique for analysing trace quantities of MIBK (Analytical Quality Control, 1972; Webb et al., 1973). Flame ionisation detection (FID) is the most sentitive detection technique (Webb et al.,1973).

- In air

An analytical method for measuring MIBK in air was described by NIOSH (1984). The method involves sampling on charcoal, silicagel and some chromatographic column packings, desorption with carbon disulfide and further analysis via gas chromatography with flame ionisation detection. The sample volume is 10 to 12 litres at a rate of 0.2 l/min. The measurable concentration range is 4-45 mg/m^3 (1-11 ppm).

- In water

Since water is not a suitable solvent for GC analysis, techniques such as headspace sampling, when there is no interference (Corwin, 1969), liquid - liquid extraction (Keith, 1974; Austern et al., 1975), distillation or stripping with an inert gas stream (Webb et al.,1973; Ellison and Wallbank, 1974) have been used. The use of synthetic resin GC columns gives low detection limits (ppb range) and high recovery; they have been used, for example, in the analysis of traces MIBK of drinking water (Burnham et al.,1972). Ellison and Wallbank (1984) removed MIBK from waste water and waste sludges by steam distillation and partitioning into cyclohexanone before GC analysis.

2.4.2. In Urine

The presence of methyl isobutyl ketone and other 2-pentanones in 24-h urine samples of unexposed men and women was demonstrated using GC and mass spectrometry (Zlatkis and Liebich, 1971) but no method for biological monitoring of individuals exposed to MIBK has been described.

3. PRODUCTION, STORAGE, TRANSPORT AND USE

MIBK is produced commercially by acetone condensation followed by catalytic hydrogenation in a one step catalytic process. The annual production worldwide was estimated by the OECD (1977) to be 250,000 tonnes worldwide and by Lande et al. (1976) to be 80,500 tonnes in the US in 1975. No production data are available for Europe alone.

MIBK is stable and steel containers are adequate for storage. It is transported in drums, rail tank cars and road tankers.

MIBK may be one of the component ketones in lacquers, such as cellulose lacquers and polyurethane lacquers (Sabroe and Olsen, 1979). MIBK can also be a minor component of paint solvents used including car and industrial spray paints (Elofson et al., 1980; Hänninen et al., 1976).It is also used as an extraction agent for pharmaceuticals.

4. ENVIRONMENTAL DISTRIBUTION AND TRANSFORMATION

4.1 Environmental Distribution

No experimental data are available on transport, mobility and concentration of MIBK in the environment. MIBK is soluble in water and may volatilise only slowly from soil and from surface waters. MacKay and Wolkoff (1973) calculated a half-life of 33 days in a waterbody with a depth of 1 m.

4.2 Biotransformation

- Biodegradation

  Bridié et al. (1979-a) using the standard dilution method with a sludge from a biological sanitary waste treatment plant found a BOD^{*}_{5} for MIBK of 76% of the ThOD**; MITI (1978) confirmed MIBK to be readily biodegradable. MIBK was also shown to be biodegradable, 53% biodegraded in 20 days in synthetic seawater (Price et al.,1974).

  No information is available on the breakdown of MIBK in soil.

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* BOD_5 = Biological oxygen demand after 5 days at 20°C.

** ThOD = Theoretical oxygen demand

- Abiotic degradation

Methyl isobutyl ketone is subject to atmospheric degradation by OH-radicals. Cox et al. (1980) and Atkinson et al. (1982) found k_{OH}. reactivity constants of 14.0 X 10^{-12} and 14.5 X 10^{-12} cm^3. mole. sec^{-1} respectively, which correspond to half lives of 0.57 and 0.55 days. The major phototransformation product is acetone which has a k_{OH}. of 0.5 X 10^{-12} cm^3.mole.sec^{-1} corresponding to a half-life of 16 days (Cox et al., 1980).

- Photochemical smog reactivity

There exists some experimental evidence on how the ketones participate in the photochemical smog cycle as free-radical chain initiators. While their relative contribution to overall smog generation has not been established, it is thought to be minor (Lande et al., 1976).

- Bioaccumulation

No experimental information is available on the ability of MIBK to accumulate in biological material. Its moderate solubility in water and a calculated and measured log octanol/water partition coefficient (log Pow) of 1.2, and 1.38 (Leo and Weininger, 1984) respectively suggest that MIBK has a low potential to bioaccumulate (OECD, 1984).

5. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

5.1. Environmental Levels

5.1.1. Air. MIBK may be released into the atmosphere during its production through fugitive emissions and incomplete removal of vapours from reaction gases before they are vented or disposed of in a scrubber. The closed production systems ensure that the exposure of workers in MIBK manufacturing plants is well below the recommended occupational exposure limits. Emissions which occur when MIBK is used as a solvent e.g. in paints and lacquers are less easily controlled. Hänninen et al.(1976) reported a mean time weighted average (TWA) concentration of 1.7 ppm (range of 1-39 ppm) in the breathing zone of spray painters in car repair shops in Helsinki. In an occupational health study of house painters,

personal air sampling during 6-8 h demonstrated exposures up to 11 ppm of MIBK (Triebig, 1985).

5.1.2. Water. MIBK may be released during the discharge of spent scrubbing water. Traces (not quantified) of MIBK have been found in American tap water (CEE, 1976).

5.1.3. Soil. MIBK may contaminate soil as a result of accidental spillage or disposal of solid wastes or sludges (Basu et al.,1968); no data are available on levels which may occur in soil.

5.2 Hygiene Standards - Occupational Exposure Levels

A Threshold Limit Value, 8h TWA, of 50 ppm (205 mg/m^3) with a Short-Term Exposure Limit of 75 ppm (300 mg/m^3) has been adopted by ACGIH (1986-87). The German MAK value (DFG - 1986) is 100 ppm (400 mg/m^3). The majority of countries have adopted the ACGIH TLV values.

6. EFFECTS ON ORGANISMS IN THE ENVIRONMENT

6.1 Microorganisms

The concentrations of MIBK which are without effect on growth are listed in Table 1. They show that MIBK has a low toxicity to microorganisms.

Table 1

Toxicity of MIBK to Microorganisms

Species	No-observed-Effect-Level, (growth inhibition) mg/l; (duration of experiment)	Reference
Protozoa		
Saprozoic flagellate (Chilomosas paramaecium)	>800 (48h)	Bringmann and Kühn (1981)
Bacteriovorous flagellate (Entosiphon sulcatum)	450 (72h)	Bringmann and Kühn (1981)
Bacteriovorous ciliate (Uronema parduczi)	950 (20h)	Bringmann and Kühn (1981)

6.2 Aquatic Organisms

Information on the acute toxicity of MIBK on fish, invertebrates and algae is summarised in Table 2. MIBK appears to have a low toxicity for aquatic organisms and microorganisms.

Table 2

Acute Toxicity of MIBK to Aquatic Organisms

Species	LC_{50} mg/l	Reference
Freshwater Fish		
Golden Orfe (Leuciscus idus melanotus)	675-750 (48h)	Juhnke and Lüdemann (1978)
Goldfish (Carassius auratus)	460 (24h)	Bridié et al. (1979-b)
Invertebrates		
Freshwater		
Water flea (Daphnia magna)	4300 (24h)	Bringmann and Kühn (1977-a)
Marine		
Brine shrimp (Artemia salina)	1250 (24h)	Price et al. (1974)
Freshwater Algae	No observed effect concentration (total biomass) mg/l	
Green algae (Scenedesmus quadricauda)	725 (8d)	Bringmann and Kühn (1977-b)
Bluegreen algae (Microcystis aeruginosa)	140 (8d)	Bringmann and Kühn (1978)

6.3 Terrestrial Organisms

No experimental data are available. Because of its relative high vapour pressure and the chemical and biological degradation which occurs in the environment, MIBK is "not expected to pose a hazard to terrestrial animals"(Fed. Reg., 1979).

7. KINETICS AND METABOLISM

7.1 Human

No data are available.

7.2 Experimental

Following intraperitoneal injection of 450 mg/kgbw of MIBK, two metabolites were found in guinea pig serum. The major metabolite, 4-hydroxy-4-methyl-2-pentanone, was formed by oxidation of MIBK; a minor metabolite, 4-methyl-2-pentanol, was formed by reduction of MIBK. The serum half-life and total clearance time as calculated by the authors for parent MIBK were 66 minutes and 6 hours, respectively. 4-Hydroxy-4-methyl-2-pentanone was cleared in 16 hours. The hydroxylation product such as 4 methyl-2-pentanol formed by MIBK are usually conjugated and excreted in the urine or enter intermediary metabolism. The metabolites of MIBK in the guinea pig are different from those of methyl n-butyl ketone and n-hexane which have neurotoxic properties (Di Vicenzo et al. , 1976).

A number of studies have indicated indirectly (Vernot et al.,1971; Mac Ewen et al.,1971; Dodd et al.,1982) or directly (Vezina et al.,1985; Abou-Donia et al.,1985) that MIBK has the potential to induce microsomal enzyme metabolism in the liver.

8. EFFECTS ON EXPERIMENTAL ANIMALS AND IN VITRO TEST SYSTEMS

8.1 Acute Toxicity

Table 3 summarises information available on the lethal dose and lethal concentration of MIBK and shows that MIBK is of low acute toxicity by the oral and inhalation routes.

Table 3

LD_{50} - LC_{50} Values for MIBK

Route	Species	Sex	LD_{50} - LC_{50}	Reference
Oral (LD_{50})	Rat	NS	4570 mg/kgbw	Smyth et al.(1951)
	Rat	NS	4600 mg/kgbw	Batyrova (1973)
	Mouse	NS	2850 mg/kgbw	Batyrova (1973)
	Mouse	NS	1900 mg/kgbw	Zakhari et al. (1977)
Inhalation (LC_{50})	Rat (4 h)	NS	>2000, <4000 ppm	Smyth et al.(1951); Smyth (1956)
	Mouse (2h)	NS	± 5000 ppm	Batyrova (1973)

NS : not specified.

Smyth et al. (1951) reported that 15 min. was the maximum time for which rats could be exposed to a saturated atmosphere of MIBK without dying. Six rats survived a 4-h exposure to 2000 ppm MIBK but following a 4-h exposure to 4000 ppm all six animals died within 14 days.

Specht (1938) and Specht et al. (1940) exposed female (F) guinea pigs to concentrations of 1000, 16,800, and 28,000 ppm MIBK for up to 24 h. The 1000-ppm level caused little or no ocular or nasal irritation in the animals. The decreased respiratory rate which occurred during the first 6 h of exposure was attributed to a low-grade narcosis. The 16,800 ppm level 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 h of exposure. Complete recovery could be effected by removal from exposure at any but the terminal stages The highest concentration (28,000 ppm) killed 50 percent of the animals within 45 min and only a few animals survived 6u min of exposure. Autopsy and histopathological assessment of tissues from some animals which died

showed fatty livers and congestion of the brain, lungs, and spleen ; the heart and kidneys were not affected.

A single intraperitoneal dose of 500 mg/kgbw MIBK induced no changes in the serum ornithine-carbamyl transferase level and no histopathological changes in the liver of guinea pigs. An injection of 1000 mg/kgbw killed one of four animals and a slight increase in the serum enzyme level was observed in the survivors. Histopathologically, there was an equivocal evidence of lipid accumulation in liver cells but no evidence of liver damage (Di Vincenzo and Krasavage, 1974).

A single oral dose of MIBK to male (M) Sprague-Dawley rats enhanced the hepatotoxic potential of a single intraperitoneal dose of chloroform given 24 h later. The non- and minimal effect dose of MIBK were 375 and 560 mg/kgbw respectively (Vezina et al.,1985). It was suggested that ketone potentiation of haloalkane induced hepatonecrosis is due largely to the enhanced bioactivation of the haloalkane mediated by increased cytochrome P-450 activation induced by the ketone (Branchflower et al.,1983).

8.2 Subchronic Toxicity

8.2.1. Inhalation

Inhalation studies in rats resulted in increased kidney weights after exposure to 100 ppm for 2 weeks and an increase in liver and kidney weights after exposure to 200 ppm for 2 weeks or 100 ppm for 90 days. Histopathological examination revealed toxic nephrosis (Vernot et al., 1971; MacEwen et al., 1971). Rats, dogs and monkeys were exposed to MIBK (410 mg/m^3 or 100 ppm in 65% O_2 at 260 mm Hg) continuously for 90 days. Liver and kidneys weights were increased in rats after 90 days. Hyaline droplets were observed in rat kidney epithelium from 15 days onwards and this effect was reversible after 3 to 4 weeks recovery period. No histopathological changes were observed in monkeys or dogs (MacEwen et al., 1971).

Batyrova (1973) reported that exposure of rats to 20-25 ppm MIBK for 4 h/d for 4.5 months interfered with the detoxifying function of the liver, although no experimental details are given.

Four groups of each 6 M, 6 F F344 rats and 6 M, 6 F B6C3F1 mice were exposed to 0, 101, 501 and 1996 ppm MIBK 6h/d, 5d/wk for nine days at a normal atmospheric pressure (Dodd et al., 1982). Clinical observations were made, the body weight and the organ weights of the liver, lungs, kidneys and testes determined and opthalmological, pathological and histopathological evaluations carried out. The only consistent clinical observation was lacrymation in the 1996 ppm-treated rats. No ophthalmological lesions or alterations in body weight gain were found in MIBK-exposed animals throughout the study. Liver weight, expressed as a percentage of body weight, was increased in M and F rats and F mice exposed to 1996 ppm of MIBK. Liver weight was also increased in M rats exposed to 501 ppm. Increased kidney weight was observed in M rats and F mice exposed to 1996 ppm of MIBK. Only M rats of the 501 ppm group exhibited a mild increase in kidney weight but this was not statistically significantly different from controls. Hyaline droplet formation and epithelial regeneration of the proximal convoluted tubules was seen in the kidneys of M rats of the 1996 ppm group. Hyaline droplets were also seen in the kidneys of M rats exposed to 501 ppm of MIBK. There were no histopathological findings in animals exposed to 101 ppm of MIBK. In conclusion, increases in liver and kidney weights and limited histopathologic lesions in the kidney were associated with exposure of rats and mice to MIBK at 501 or 1996 ppm. A concentration of 101 ppm was considered a clear no-effect level (Dodd et al., 1982).

In a subsequent study, four groups of 14 M and 14 F F344 rats and 14 M and 14 F B6C3F1 mice were exposed to 0, 50, 250 and 1000 ppm MIBK for 6 h/d, 5 d/wk for 90d. No clinical effects or growth retardation of rats or mice were observed during the study. Male rats and mice exposed to 1000 ppm MIBK showed a slight increase in liver weight and in liver weight/body weight ratio. Liver weight was also slightly increased in M mice exposed to 250 ppm. No gross or microscopic hepatic lesions were observed. In M rats exposed to 250 to 1000 ppm of MIBK, there was an increase in the number of hyaline droplets within proximal tubular cells of the kidney. No other gross or microscopic changes were observed. The authors concluded that, overall, exposure of F344 rats and B6C3F1 mice to 50, 250 or 1000 ppm MIBK for 90 days resulted in no toxicologically significant effects (Dodd and Eisler, 1983).

Groups of five hens were continuously exposed to either 1000 ppm MIBK or 1000 ppm n-hexane for 50 d or to a mixture of 1000 ppm of each of MIBK and n-hexane for 30 d. Inhalation of n-hexane alone had no effect on hepatic microsomal enzymes, whereas inhalation of MIBK or MIBK/n-hexane significantly increased the aniline hydroxylase activity and cytochrome P-450 content of the liver (Abou-Donia et al.,1985).

Plaa and Ayotte (1985) reported that three daily oral doses of 375 or 1500 mg/kgbw of MIBK to rats reduced bile flow produced by an i.v. injection of 20 mg/kgbw taurocholate . It was suggested that this cholestatic effect may not be associated with metabolic induction but may reflect a separate mechanism of action.

In conclusion, several 90d inhalation studies with several species indicate that exposure up to 1000 ppm MIBK does not cause systemic toxicological effects.

8.2.2. Parenteral

In an unpublished study cited by Krasavage et al.(1982) rats (number not mentioned) were administered parenteral injections of MIBK or a mixture of methyl ethyl ketone and MIBK (9/1 by volume), 5 times/wk for 35 weeks. The dose levels of 10, 30 and 100 mg/kgbw were doubled after 2 weeks of treatment. Except for body weight suppression, seen after 3 to 4 weeks of treatment, the only effect noted was transient narcosis during the first month in the 200 mg/kgbw animals.

8.3. Skin, Respiratory and Eye Irritation; Sensitivation

8.3.1. Skin irritation

In an unpublished study made available for this review and cited by Krasavage et al. (1982), a single occluded application of MIBK for a period of 10h to the shaved skin of rabbits produced erythema which was evident immediately after the exposure and persisted for 24 hours. Daily applications of 10 ml on 10 cm^2 skin for 7 days caused drying and flaking of the surface. Undiluted MIBK (5 and 10 ml) held in contact with the depilated skin of guinea pigs under an occlusive wrap for 24h produced slight irritation with no clinical evidence of absorption. Other studies

showed that 500 mg MIBK was moderately irritant to rabbit skin after 24h exposure. MIBK or methyl ethyl ketone/MIBK (9/1), with or without dimethyl sulfoxide, dropped on the backs of guinea pigs in amounts up to 2 ml twice daily for 31 weeks produced skin desquamation.

8.3.2. Respiratory irritation

Batyrova (1973) reported an irritation threshold of 60 to 120 ppm following a 15 min exposure to MIBK based on the measurement of salivation by use of a parotid fistula in cats.

8.3.3. Eye irritation

The work quoted by Krasavage et al. (1982) and made available for the present review, showed that undiluted MIBK (0.1 ml) produced some irritation within 10 min when instilled in the rabbit eye. Inflammation and conjunctival swelling occurred within 8h; the inflammation, swelling, and exudate present at 24h had regressed by 60 h.

8.3.4. Sensitisation

No experimental studies have been reported.

8.4 Mutagenicity

MIBK has been examined by 5 mutagenicity tests (Haworth, 1984).

Ames Salmonella Pre-Incubation Assay. An assay was conducted at dosage levels from 0.04 to 4 µl/plate both in the presence and absence of a metabolic activation system prepared from a rat liver homogenate (S-9 fraction). Four tester strains were used; TA-98, TA-100, TA-1537 and TA-1538. Precautions were taken to prevent the escape of MIBK vapour and assure prolonged exposure of the bacteria to the test substance. There was no indication that MIBK caused an increase in reverse gene mutation.

L 51784 TK+/- Mouse Lymphoma Assay. The preliminary assay was carried out in the presence and absence of a metabolic activation system at doses of 0.001 up to 100 µl/ml. The non-activated cultures showed 3 to 157 percent total relative growth, while the cultures containing the rat liver S-9 fraction had a relative growth of 23 to 95 percent when compared with untreated control cultures. No increase in mutation frequencies was observed in cultures containing the

metabolic activation system. In the non-activated cultures, a two-fold increase above controls was seen at two non-consecutive doses. An increase in mutation frequency of approximately 5 times the concurrent control occurred at only one test concentration. This concentration also caused 97 percent cell death. In the absence of a dose-related effect, this result was considered equivocal and the assay was repeated.

The repeat assay was performed using duplicate cultures and a narrower range of doses (0.4 to 6 µl/ml). The total relative growth ranged from 1 to 80 percent in non-metabolically activated cells and from 28 to 63 percent in cultures which contained the S-9 fraction. None of the activated cultures revealed increased mutation frequencies. A borderline positive result was found at the highest dose level but different mutation frequencies occurred in the duplicate cultures and 96-99% of the cells were killed. It is concluded that MIBK did not produce repeatable genotoxic effects in the mouse lymphoma assay except at highly toxic doses.

Unscheduled DNA Synthesis in Primary Rat Hepatocytes In Vitro. MIBK was tested at five dose levels ranging from 100 µl/ml to 0.01 µl/ml in a single assay. Under the conditions of this test there was an increase of less than 5 in labeled nuclear grains in cells treated with MIBK when compared to cells of the solvent control plates. MIBK was considered not to have altered unscheduled DNA synthesis.

Mouse Micronucleus Assay. M and F mice were administered MIBK by intraperitoneal injection at the maximum tolerated dose level of 0.73 ml/kgbw. Bone marrow polychromatic erythrocytes were estimated 12, 24 and 48h following injection. There were no significant differences between the treated and control animals in the ratio of polychromatic to normochromatic erythrocytes . The number of micronucleated polychromatic erythrocytes per 1000 cells was not significantly increased in the MIBK treated animals. Therefore, under the conditions of this test there was no evidence that MIBK produced chromosomal effects resulting in production of erythrocyte micronuclei.

Cell Transformation Assay. MIBK was tested in the Balb/3T3 morphological transformation assay. In the original assay, doses of 2.4, 3.6 and 4.8 µl/ml of MIBK were added to the culture medium in the absence of a metabolic activation system and 1, 2 and 4 µl/ml of MIBK were added in the presence of a metabolic

activation system (S-9 fraction from a rat liver homogenate). MIBK produced a positive response in the non-activated cultures only. A confirmatory study was conducted with doses of 2, 3, 4 and 5 µl/ml and 4, 5, 6 and 7 µl/ml respectively in the presence and absence of S-9 fraction . No significant increase in the number of transformed foci was found in this second study, either in the presence or absence of the metabolic activation system. Thus, the effect of MIBK on cell transformation was not reproducible in the two assays.

Overall the mutagenicity assays do not suggest that MIBK has any mutagenic activity.

8.5 Chronic Toxicity and Carcinogenicity

No information from long-term studies is available.

8.6 Reproduction, Embryotoxicity, and Teratogenicity

Groups of 35 pregnant Fischer 344 rats and 30 pregnant CD-1 mice were exposed to 300, 1000, or 3000 ppm MIBK on the 6th to 15th days of gestation inclusive. The animals were sacrificed on day 21 (rats) or 18 (mice) of gestation and foetuses were examined for external, visceral and skeletal alterations (Tyl, 1984).

In the rats, exposure to 3000 ppm resulted in maternal toxicity (as shown by clinical signs, decreased body weight gain, increased relative kidney weight and decreased food consumption) and foetotoxicity (reduced foetal body weight per litter and delays in skeletal ossification). No increase in foetal malformations was observed in any exposure group. At the 300 and 1000 ppm dose levels, there was no maternal, embryo or foetal toxicity or malformations. The reduced foetal body weight observed at the 300 ppm dose level in rats was confounded by litter size and was not dose-related and was thus not considered to be treatment related.

In the mice, exposure to 3000 ppm produced maternal toxicity (increased mortality,clinical signs and increased absolute and relative liver weight), and foetotoxicity (increased incidence of dead foetuses, reduced foetal body weight per litter and delayed or reduced ossification). Although findings were not

statistically significant, there was some indication of foetotoxicity at 1000 ppm. No treatment-related embryotoxicity was seen. No treatment-related increases in foetal malformations were seen at any exposure concentration tested.

It is concluded that MIBK is not teratogenic or embryotoxic in rats and mice at exposure levels which are maternally non-toxic.

8.7 Neurotoxicity

Rats were administered intraperitoneal injections of MIBK or a mixture of methyl ethyl ketone and MIBK (9/1 by volume), 5 times/wk for 35 weeks. The dose levels of 10, 30 and 100 mg/kgbw were doubled after 2 weeks of treatment. Transient narcosis was noted during the first month in the 200 mg/kgbw animals. No toxic neuropathy was detected. Electromyographic examination of dogs administered 300 mg/kgbw/d MIBK subcutaneously for 11 months revealed no evidence of neurotoxicity (unpublished study quoted by Krasavage et al., 1982).

Spencer and Schaumburg (1976) treated cats subcutaneously with 150 mg/kgbw/d MIBK or a mixture of methyl ethyl ketone/MIBK (9/1) twice daily, 5 times/wk for up to 8.5 months. They detected no nervous system damage. No neurotoxic changes were found in beagle dogs receiving treatment similar to that of the cats (Krasavage et al., 1982).

Spencer et al. (1975) reported on groups of male rats exposed to 1300 ppm methyl n-butyl ketone for 4 months or 1500 ppm MIBK for 5 months. Methyl n-butyl ketone produced a toxic distal axonopathy. MIBK produced some minimal distal axonal changes but this may have been due to the 3 percent methyl n-butyl ketone present as a contaminant in the MIBK or, more likely, to a compression neuropathy caused by the design of cages used (Spencer et al., 1975; Spencer and Schaumburg, 1976). Animals exposed to MIBK were slightly narcosed but bodyweight gain was normal and there were no clinical signs of neurological dysfunction after 5 months.

Geller et al. (1978) reported that rats exposed for 3 hours to 25 ppm MIBK showed a 58% increase in pressor lever response which had not returned to control levels 7 days after exposure. The discriminatory behaviour and memory of baboons was not impaired by exposures of 20 to 40 ppm. Geller et al. (1979)

reported delayed behavioural response times in baboons exposed for 7 days to 50 ppm of MIBK alone, but no alteration of response was seen when MIBK was combined with methyl ethyl ketone (100 ppm). It was postulated that this effect could represent an early manifestation of the incoordination and narcosis which are observed at much higher doses.

The effect of MIBK on n-hexane-induced neurotoxicity was investigated by Abou-Donia et al. (1985) in inhalation studies in hens. A continuous exposure period of 90 d was followed by a 30 d observation period. One group was exposed to 1000 ppm n-hexane and another group to 1000 ppm MIBK. Four additional groups were exposed simultaneously to 1000 ppm of n-hexane and to 100, 250, 500, or 1000 ppm MIBK. A control group was exposed similarly to ambient air in an exposure chamber. Hens continuously exposed to 1000 ppm MIBK developed leg weakness with subsequent recovery, while inhalation of the same concentration of n-hexane produced mild ataxia. Exposure of hens to 1000 ppm n-hexane in combination with 250, 500 or 1000 ppm MIBK produced clinical signs of neurotoxicity including paralysis; the severity depended on MIBK concentration. Hens continuously exposed to 1000/100 ppm (n-hexane/MIBK) were severely ataxic throughout the observation period. Histopathological examination of hens exposed simultaneously to n-hexane and MIBK showed large swollen axons and degeneration of the axon and myelin of the spinal cord and peripheral nerves. No histopathological abnormalities were detected in the CNS of hens exposed to MIBK alone. The results indicate that, although MIBK is not neurotoxic, it potentiates the neurotoxic action of n-hexane. The results of a subsequent study in which hens were exposed for 50 d to MIBK (1000 ppm) or n-hexane (1000 ppm) , or for 30 d to a mixture of 1000 ppm of MIBK and 1000 ppm n-hexane suggest that the synergistic action of MIBK on n-hexane neurotoxicity is related to the ability of MIBK to induce liver microsomal cytochrome P-450, resulting in increased metabolism of n-hexane to its neurotoxic metabolites (see sections, 7.2 and 8.2.1.).

In contrast to methyl n-butyl ketone and n-hexane, MIBK caused little or no cytopathological or growth inhibiting effects in cultured mouse neuroblastoma cells (Selkoe et al., 1978).

It is concluded that MIBK, in common with other organic solvents, may induce reversible depressive effect on the central nervous system activity. It produces no neurotoxic but does enhance the neurotoxic effects of n-hexane.

9. EFFECTS ON MAN

9.1 Acute Toxicity

Vapours of methyl isobutyl ketone inhaled at very high concentrations (above 1000 ppm) produces central nervous system depression and narcosis (Krasavage et al., 1982).

Silverman et al. (1946), in a study on sensory threshold, subjected 12 "subjects of both sexes" to various concentrations of MIBK for a 15 min. period. This period permitted an accurate observation of olfactory fatigue and an appraisal of increasing or decreasing irritation of mucous membranes. One hundred ppm was a sensory response limit. A majority of subjects found the odour objectionable at 200 ppm and the vapour was irritant to the eyes. The low odour threshold (from 0.4 ppm onwards; Ruth, 1986) and its irritant effects warn of the presence of high concentrations and help to avoid acute overexposure. When swallowed, MIBK may, because of its low viscosity, be aspirated into the lungs causing chemical pneumonitis (Panson and Winek, 1980).

9.2 Subchronic Toxicity

Elkins (1959) reported that a group of workers exposed to 100 ppm MIBK complained of headache and nausea. Tolerance was said to be acquired during the working week, but was lost over the weekend. Another group exposed at a similar level complained only of respiratory irritation. Introduction of an exhaust system reduced the exposure to 20 ppm and largely eliminated the complaints.

9.3 Irritation and Sensitisation

9.3.1. Skin irritation. No reports are available on the irritant properties of MIBK on the human skin.

9.3.2. Eye and respiratory irritation. Silverman et al. (1946) reported that exposure to a concentration of 200 ppm MIBK for 15 min. period caused eye irritation in 12 human volunteers. Undiluted MIBK splashed in the eyes may cause painful irritation (Shell, 1957). Batyrova (1973) reported (without supplying experimental evidence) an irritation threshold of 8-24 ppm for a one-minute inhalation exposure. Elkins (1959) reported that a

group of workers exposed to 100 ppm of MIBK complained of respiratory tract irritation; these effects were not noted at 20 ppm.

9.3.3. Skin sensitisation. No cases of skin sensitisation in man have been reported.

9.4 Mutagenicity

No data are available.

9.5 Chronic Toxicity and Carcinogenicity

Workers near a centrifuge were exposed up to 500 ppm of MIBK for 20-30 min/d Elsewhere in the room the level was 80 ppm. Over half of the 19 workers complained of weakness, loss of appetite, headache, burning in the eyes, stomach ache, nausea, vomiting and sore throat. Insomnia, somnolence, heartburn, intestinal pain and some unsteadiness were experienced by a few of the workers. Four had slightly enlarged livers and six had complaints indicative of a nonspecific form of colitis. Clinical chemistry tests on all the workers were normal. The wearing of respirators for the centrifuging process reduced MIBK exposure considerably. Five years later it was found that work practices had greatly improved and that the MIBK concentration near the centrifuge was 100-105 ppm and elsewhere in the room was 50 ppm. Workers were required to wear respiratory protection but a few still complained of gastrointestinal and central nervous system effects. Slight liver enlargement had persisted in two workers, but earlier symptoms had disappeared (Armeli et al., 1968).

No other studies have been reported on the chronic toxic or carcinogenic effects of MIBK exposure in humans.

9.6 Reproductive Toxicity

MIBK was one of the 27 volatile organic compounds which has been demonstrated in maternal and umbilical cord blood samples from 11 patients using a mass-spectrometric method (Dowty et al., 1976), indicating that MIBK can cross the placenta.

9.7 Neurotoxicity

A few isolated cases of peripheral neuropathy have been reported after exposure to spray paint or lacquer thinner which contained MIBK and other hydrocarbon solvents (Au Buchon et al., 1979; Oh and Kim, 1976). In recent years a number of epidemiological studies carried out on painters and other groups exposed to a wide range of solvents, in particular hydrocarbon solvents, have led certain investigators to conclude that prolonged exposure to low levels of such materials may cause irreversible effects on the central nervous system. The signs and symptoms reported are ill-defined and non-specific, e.g. headache, loss of memory, fatigue and alternations in behaviour and emotional response as shown by psychological tests. The condition has been given a variety of names, such as organic solvent syndrome, pre-senile dementia, painters syndrome, psycho-organic syndrome and neuraesthenic syndrome.

These epidemiological studies suffered a number of methodological deficiencies, including the lack of quantitative exposure data, ill-defined exposures to known neurotoxic and neuroactive chemicals such as lead and mercury compounds and the use of unmatched control populations. In the majority of studies insufficient attention has been given to confounding factors that could influence brain function e.g. the use of drugs and alcohol and advancing age (Grasso et al., 1984). An international workshop on the neurobehavioural effects of solvents concluded that further research is needed to establish the prevalence and incidence of these disorders, to relate them to specific solvents or mixtures and to elucidate the pathogenesis of this type of disorders (CIIT, 1985). The existence of the disease is not reported outside Scandinavian countries (Dayan, 1986).

There are no specific studies which implicate MIBK as a human neurotoxin.

10. FIRST AID AND SAFE HANDLING ADVICE

10.1. First Aid and Medical Treatment

Eye contact

Irrigate the eyes thoroughly with eyewash solution or water for up to 10 minutes. Medical attention should be obtained.

Skin contact

Contaminated clothing should be removed and the affected area of the skin thoroughly flushed with water and soap if available. If skin irritation occurs, medical attention should be obtained.

Inhalation

The patient should be removed to fresh air and kept warm and at rest. If breathing ceases or becomes weak and irregular artificial respiration should be applied and oxygen administered. Obtain medical attention.

Ingestion

Vomiting should not be induced but medical attention should be obtained, since aspiration into the lungs will lead to chemical pneumonitis.

10.2 Safe Handling

Personal protection

Atmospheric levels should be kept below the recommended occupational exposure limits. Suitable respiratory protection should be readily available. Skin and eye protection should be worn where exposure to liquid is likely to occur.

Flammability/explosion hazards

Adequate ventilation should be provided and smoking prohibited. Electrical equipment should be explosion protected and of a type meeting local legal requirements.

Storage

Drums should be stored in a well-ventilated area away from sources of ignition and heat. The storage temperature should not exceed 40°C.

Transport precautions

The flow of MIBK, e.g. by pumping, may generate electrostatic charges and therefore all equipment should be adequately earthed. Compressed air should not be used for filling, discharging or handling operations.

10.3 Management of Spillage and Waste

Spillage

Naked flames should be extinguished and smoking and the generating of sparks should be avoided. Contact with the skin, eyes and clothing should be avoided by wearing gloves, goggles, face shield and boots. Liquid should be prevented from entering sewers, basements and workpits. As the vapours are heavier than the air and may spread along the floors, there is a risk of explosion in enclosed areas.

Small-scale spillages should be absorbed on paper towels and the paper burned away from other combustible materials.

For medium-scale spillages the liquid should be absorbed with sand or earth and all material should be removed to a safe place for subsequent incineration. The contaminated area should be washed out with plenty of water.

For large-scale spillages, the spilt liquid should be prevented from spreading by the use of sand or earth. The liquid should be transfered to a salvage tank if possible, otherwise it should be treated as for medium-scale spillages. The local authorities (particularly the fire service) should be informed at once if the spilt liquid enters the surface water drains since there may be an explosion hazard.

Disposal

Residues containing MIBK, whether from road or rail tanks, bulk storage or shipment, should be collected for controlled disposal e.g. through re-use or incineration. The residues should not be buried or dumped in a landfill.

Fire

Fire extinguishers containing carbon dioxide, dry chemical or foam are recommended. Flashback along a vapour trail may occur.

BIBLIOGRAPHY

- Abou-Donia, M.B., Lapadula, D.M., Campbell, G., Timmons P.R. (1985). The synergism of n-hexane-induced neurotoxicity by methyl isobutyl ketone following subchronic (90 days) inhalation in hens: induction of hepatic microsomal cytochrome P-450. Toxicol. and Appl. Pharmacol. 81, 1.
- ACGIH (American Conference of Governmental Industrial Hygienists, 1986-87). TLVs, Treshold Limit Values and Biological Exposure Indices.
- Analytical Quality Control Lab.(1972). Handbook for analytical quality control in water and waste water laboratories. Nat. Environ. Res. Center. Cincinnati - Ohio.
- Armeli, G., Linari, F. and Mastorano, G. (1968). Rilievi clinici ed ematochimici in operai esposti all'azione di un chetone superiore (MIBK) ripetuti a distanza di 5 anni. Lavoro Umano, 20,9.
- Atkinson, R., Aschmann, S.M., Carter, W.P.L. and Pitts, J.N., Jr. (1982). Rate constants for the gas-phase reaction of OH radicals with a series of ketones at 299 - 2°K. Int. J. Chem. Kin., 14, 839.
- AuBuchon, J., Robins, H.I. and Viseskul, C.(1979). Peripheral neuropathy after exposure to methylisobutyl ketone in spray paint. The Lancet, August 18, 363.
- Austern, B.M., Dobbs, R.A. and Cohen, J.M.(1975). Gas-chromatographic determination of selected organic compounds added to waste water. Environ. Sci. Technol., 9(6), 588.
- Basu, P., Carpenter, J., Chen, C., Nelson, H., Perry, W., Shoclet, A., Taylor, D. and Zafran, F.(1968). JRB Inc. TSCA Section 4, Human exposure asssessment. Methyl isobutyl ketone. Draft final report. DOW No.11. U.S. Environmental Protection Agency. Contract 68-01.4839. Cited in Fed. Reg., 47(150), 58026.
- Batyrova, T.F. (1973). Substantiation of the maximum permissible concentration of methylisobutyl ketone in air of workrooms. Gig. Tr. Prof. Zabol. 17 (11), 52.
- Branchflower, R.V., Schulick, R.D., George J.W. and Pohl, L.R. (1983). Comparison of effects of methyl n-butyl ketone and phenobarbital on rat liver cytochromes P-450 and the metabolism of chloroform to phosgene. Tox. Appl. Pharmacol., 21, 414.
- Bridié, A.L., Wolff, C.J.M. and Winter, M. (1979-a). BOD and COD of some petrochemicals. Water Res. 13, 627.
- Bridié, A.L., Wolff, C.J.M. and Winter, M. (1979-b). The acute toxicity of some petrochemicals to goldfish. Water Res. 14, 231.
- Bringmann, G. and Kühn, R. (1977-a). Befunde der Schadwirkung wassergefährdender Stoffe gegen Daphnia magna. Z. Wasser-Abwasser Forsch., 10 (5), 161.
- Bringmann, G. and Kühn, R. (1977-b). Grenzwerte der Schadwirkung wassergefährdender Stoffe gegen Bakterien (Pseudomonas putida) und Grünalgen (Scenedesmus quadricauda). Z.Wasser-Abwasser Forsch., 10 (3.4), 87.
- Bringmann, G. and Kühn, R. (1978). Grenzwerte der Schadwirkung wassergefährdender Stoffe gegen Blaualgen (Microcystis aeruginosa) und Grünalgen (Scenedesmus quadricauda) im Zellvermehrungshemmtest. Vom Wasser 50, 45.
- Bringmann, G. and Kühn, R. (1981). Vergleich der Wirkung von Schadstoffen auf Flagellate sowie Ciliate bzw. auf holozoisch bakterienfressende sowie saprozoische Protozoen. GFW-Wasser/Abwasser 122 (7), 308.
- Burnham, A.K., Calder, G.V., Fritz, J.S., Junk, G.A., Svec, H.J. and Willis, R.(1972). Identification and estimation of neutral organic contaminants in potable water. Anal. Chem., 44, 139.
- CEE (Commission of the European Communities) (1976). Analysis of organic micropollutants in water (Cost 64b bis).
- CIIT (1985). International workshop on neurobehavioural effects of solvents. October 13-16, 1985, Raleigh, North Carolina, USA. Neurotoxicology, 6(4), 99.

- Corwin, J.F.(1969). Volatile oxygen-containing organic compounds in sea water : determination. Bull. Mar. Sci., 19(3), 504.
- Cox, R.A., Derwent, R.G.and Williams, M.R. (1980) Atmospheric photooxidation reactions. Rates, reactivity and mechanism for reaction of organic compounds with hydroxyl radicals. Environ. Sci. and Technol., 14, 57.
- Dayan, A. (1986). Critique of the solvent syndrome. European meeting of Toxicology Forum, Sept.22-26, 1986, Geneva, 229.
- DFG (Deutsche Forschungsgemeinschaft, 1986). Maximale Arbeitsplatzkonzentrationen und Biologische Arbeitstofftoleranzwert 1985. Mitteilung XX der Senatskommission zur Prüfung gesundheitsschädlicher Arbeitsstoffe.
- Di Vincenzo, G. D. and Krasavage, W.J. (1974). Serum ornithine carbamyl transferase as a liver response test for exposure to organic solvents. Am. Ind. Hyg. Assoc. Journal, Jan., 21.
- Di Vincenzo, G. D., Kaplan, C.J., Dedinas, J. (1976). Characterization of the metabolites of MnBK, MiBK and MEK in guinea pig serum and their clearance. Tox. Appl. Pharmacol. 36, 511.
- Dodd, D.E., Longo, L.C., Eisler, D.L. (1982). Nine-day vapour inhalation study on rats and mice. Bushy Run Research Center. Report 45-501 submitted to Environmental Protection Agency by Chemical Manufacturers Association.
- Dodd, D.E. and Eisler, D.L. (1983). Methyl isobutyl ketone ninety-day inhalation study on rats and mice. Bushy Run Research Center. Report 46-504 submitted to Enviromental Protection Agency by Chemical Manufacturers Association.
- Dowty, B.J., Laseter, J.L., Storer, J. (1976). The transplacental migration and accumulation in blood of volatile organic constituents. Pediat. Res. 10, 696.
- Elkins, H.B. (1959). Chemistry of industrial toxicology. John Wiley and Sons, New York, 121.
- Ellison, W.K. and Wallbank, T.E.(1974). Solvents in sewage and industrial waste waters. Identification and determination. Water Pollut. Control, 73(6), 656.
- Elofsson, S.A., Gamberale, F., Hindmarsh, T., Iregren, A., Isaksson, A., Johnson, I., Knave, B., Lydahl, E., Mindus, P., Persson, H.E., Philipson, B., Steby, M., Struwe, G., Söderman, E., Wennberg, A., Widen, L. (1980). Exposure to organic solvents : a cross-sectional epidemiologic investigation on occupationally exposed car and industrial spray painters with special reference to the nervous system. Scand. J. Work Environ. & Health, 6, 239.
- Federal Register (1979). Methyl isobutyl ketone. Recommended studies. 44, 31868.
- Geller, I., Rowlands, J.R., Kaplan, H. L. (1978). Effects on ketones on operant behaviour of laboratory animals. DHEW Publ. Adm 79-779, Voluntary inhalation of industrial solvents, p 363.
- Geller,I. , Gause, E., Kaplan, H., Hartmann, R.J. (1979). Effects of acetone, methyl ethyl ketone, and methyl isobutyl ketone on a match to sample task in the baboon. Pharmacol. Biochem. Behav., 11, 401.
- Grasso, P., Sharratt, M., Davies, D.M. and Irvine, D.(1984). Neurophysical and psychological disorders and occupational exposure to organic solvents. Food Chem. Toxicol., 22(10, 819.
- Hänninen, H., Eskelinen, L., Husman, K. and Nurminen, M.(1976). Behavioural effects of long-term exposure to a mixture of organic solvents. Scand. J. Work Environ. & Health, 4, 240.
- Haworth, S. (1984). Microbiological associates. Mutagenicity studies performed for Chemical Manufacturers Association. Salmonella, study T 1827.502003; Mouse lymphoma, study T 1827.701005; UDS, study T 1827.380003; Mouse Micronucleus, study T 1827.121001; Cell transformation, study T 1827.302001.
- Juhnke, I. and Lüdemann, D. (1978). Ergebnisse der Untersuchung von 200 chemischen Verbindingen auf akute Fischtoxizität mit dem Goldorfentest. Z. Wasser-Abwasser-Forsch., 11 (5), 161.
- Keith, L.H.(1974). Chemical characterisation of industrial waste waters by gas chromatography - mass spectrometry. Sci. Total Environ., 3(1), 87.

- Krasavage, W. J., O'Donoghue, J. L. and Di Vincenzo, G.D. (1982). Methyl isobutyl ketone. In: Patty's industrial hygiene and toxicology. Vol. 2e, 4747. Eds Clayton and Clayton. John Wiley & Sons, New York.
- Lande, S. S., Durkin, P. R. , Christopher, D. H. , Howard, P. H. , Saxena, J. (1976). Investigation of selected potential environmental contamination: ketonic solvents. Center for Chemical Hazard Assessment, Syracuse. Research Corporation, Syracuse, 252.
- Leo, A. and Weininger, D.(1984). CLOGP Version 3.2 User reference manual. Medicinal Chemistry Report. Pomona College, Claremont, CA.
- MacEwen, J.D., Vernot, E.H., Haun, C.C. (1971). Effect of 90-day continuous exposure to methyl isobutyl ketone on dogs, monkeys, and rats. U.S.N.T.I.S. AD Rep., Issue N° 730291.
- MacKay, I.D. and Walkoff, A.W.(1973). Rate of evaporation of low solubility contaminants from water bodies to atmosphere. Environ. Sci. Technol., 7(7), 611.
- MITI (1978). Chemical Products Safety Division - Basic Industries Bureau. Ministry of International Trade and Industry, Japan. The biodegradability and bioaccumulation of new and existing chemical substances.
- NIOSH (National Institute of Occupational Safety and Health)(1984). NIOSH manual of analytical methods. Ketones I, number 1300, issued 15.2. 85. Third Ed., Vol.2, NIOSH, Cincinnati, Ohio.
- OECD (Organisation for Economic Cooperation and Development) (1977). The assessment of environmental chemicals: production figures and use patterns for some high volume chemicals. ENV/Chem./77.6.
- OECD (Organisation for Economic Cooperation and Development) (1984). Data Interpretation Guides. For Initial Hazard Assessment of Chemicals (Provisional), 31.
- Oh, S.J. and Kim J.M.(1976). Giant axonal swelling in "Huffer's" neuropathy. Arch. Neurol., 33, 583.
- Panson, R.D. and Winek, C.L.(1980). Aspiration toxicity of ketones. Clin. Toxicol., 17(2), 271.
- Plaa, G.L. and Ayothe, D. (1985). Taurolithocholate - induced intrahepatic cholestases : potentiation by methyl isobutyl ketone and methyl n-butylketone in rats. Toxicol. Appl. Pharmacol., 80, 228.
- Price, K.S., Waggy, G.T., Conway, R.A. (1974). Brine shrimps bioassay and seawater BOD of petrochemicals. J.Water Pollut. Control Fed., 46 (1), 63.
- Ruth, J.R.(1986). Odour threshold and irritation levels of several chemical substances : a review. Am. Ind. Hyg. Assoc. J., 47, A 142.
- Sabroe, S. and Olsen J.(1979). Health complaints and work conditions among lacquerers in the Danish furniture industry. Scand. J. Soc. Med., 7, 97.
- Selkoe, D.J., Luckenbill Edds, L. and Shelanski, M.L. (1978). Effects of neurotoxic industrial solvents on cultured neuroblastoma cells: methyl n-butyl ketone, n-hexane and derivatives. J. Neuropath. Exp. Neurol. 37 (6), 768.
- Shell Chemical Corporation (1957). Methyl isobutyl ketone: industrial hygiene bulletin. SC: 57 - 112. Shell Chemical Corporation, N.Y.
- Silverman, L., Schulte, H. F., First, M.W. (1946). Further studies in sensory response to certain industrial solvent vapours. J. Ind. Hyg. Toxicol., 28, 262.
- Smyth, H.F. (1956). Hygienic standards for daily inhalation. Amer. Ind. Hyg. Assoc. J., 17, 129.
- Smyth, H. F., Carpenter, C. P., Weil, C.S. (1951). Range finding toxicity data: list IV. Arch. Ind. Hyg. Occup. Med., 4, 119.
- Specht, H. (1938). Acute response of guinea pigs to inhalation of methyl isobutyl ketone. U.S. Public Health Rep., 53, 292.
- Specht, H., Miller, J.W., Valaer, P.J., Sayers, R.R. (1940). Acute response of guinea pigs to the inhalation of ketone vapors. U.S. Public Health Service, NIH Bull., N° 176, Div. Ind. Hyg., 1.
- Spencer, P.S., Schaumburg, H. H., Raleigh, R. L., Terhaar, C.J. (1975). Nervous system degeneration produced by the industrial solvent methyl n-butyl ketone. Arch. Neurol., 32, 219.

- Spencer, P.S. and Schaumburg, H.H. (1976). Feline nervous system response to chronic intoxication with commercial grades of methyl-n-butyl ketone, methyl isobutyl ketone and methyl ethyl ketone. Toxicol. Appl. Pharmacol. 37, 301.
- Triebig, G.(1985). New studies of the situation of occupational medicine in the painter's trade. Lecture given on May 22nd, 1985 in Mainz.
- Tyl, R.W. (1984). A teratologic evaluation of methyl isobutyl ketone in Fischer 344 rats and CD-1 mice following inhalation exposure. Bushy Run Research Center, Project Rep. 47.505.
- Vernot, E.H., MacEwen, J.D., Harris, E.S. (1971). Continuous exposure of animals to methyl isobutyl ketone. U.S.N.T.I.S., AD Rep., Issue N° 751443.
- Verschueren, K.(1983). Handbook of Environmental Data on Organic Chemicals. 2nd Edition, New York, Van Nostrand Reinhold. Comp. .
- Vezina, M., Ayothe, P. and Plaa, G.L.(1985). Potentiation of necrogenic and cholestatic liver injury by 4-methyl-2-pentanone. Canad. Fed. Biol. Soc., 28, 221.
- Webb, R.G., Garrison, A.W., Keith, L.H. and McGuire, J.H.(1973). Current practice in GC-MS analysis of organics in water. USEPA R2-73-277, Washington, D.C., US - Nat. Tech. Inform. Serv., PB 224.
- Zakhari, S., Levy, P., Liebowitz, M., Aviado, D.M. (1977). Acute oral, intraperitoneal, and inhalation toxicity of methyl isobutyl ketone in the mouse. In: Isopropanol and ketones in the environment, L. Goldberg, Ed. CRC Press, Cleveland.
- Zlatkis, A. and Liebich, H.M. (1971). Profile of volatile metabolites in human urine. Clin. Chem., 17(7), 592.

APPENDICES

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