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Joint Assessment of Commodity Chemicals

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METHYL ETHYL KETONE

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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 ethyl ketone (MEK) is presented. MEK was chosen as one of four varied chemicals on which trial exercises were carried out to aid in developing the JACC scheme.

CONTENTS

A. CHEMICAL IDENTITY AND PHYSICAL-CHEMICAL PROPERTIES

Methyl ethyl ketone (syn. 2-butanone, MEK)

CH_3-CO-CH_2-CH_3

1. Physical Properties

MEK is a colourless volatile liquid with an acetone-like smell detectable at about 25 ppm in air.

physical form	: volatile liquid
colour	: water clear
odour threshold	: about 25 ppm
irritation threshold	: approx. 200 ppm
relative molecular mass	: 72.11
density, kg/m³ at 20°C	: 804-806
boiling range, °C	: 79-80.5
boiling point, pure compound, °C	: 79.60
freezing point, °C	: - 86.4
viscosity, mPa.s at 15°C	: 0.423
vapour pressure, mbar at 20°C	: 1033
vapour density (air=1)	: 2.41
concentration in saturated air, ppm at 20°C and 760 mm Hg	: 93,000
flash point (Abel), °C	: -4
auto ignition temp., °C	: 514
explosion limits in air, %	: 1.97-10.2
solubility in water, g/l at 10°C	: 353

2. Composition

The technical product is typically greater than 99.5% pure, the main impurities being alcohols (principally sec-butyl), ketones (acetone and C_5 ketones) and water. See Appendix 1 for a typical composition.

3. Analysis

Collection and concentration of MEK on absorbant materials such as charcoal and porous polymers are generally required prior to analysis of the vapour or aqueous samples. Following thermal or solvent desorption, MEK can be analysed using gas chromatography with a flame ionisation detector which may need to be coupled to a mass spectrometer to identify the compound. Techniques are also available for the

detection and determination of MEK in food, urine, blood and other tissues (NIOSH, 1980; Munies and Wurster, 1965; Zlatkis et al.,1973; Urich et al.,1977).

B. PRODUCTION AND USES

About half-a-million tons of MEK are manufactured world-wide either by the dehydrogenation of 2-butanol obtained from the hydration of n-butenes, or by the catalytic oxidation of butane. The nature and amount of impurities are similar in the product from both processes. It is widely used: as a solvent in plastics, resins, varnishes, cosmetics and pharmaceuticals production; as a solvent cleaner; and as a chemical intermediate.

C. HUMAN AND ENVIRONMENTAL EXPOSURE

Exposure in industry is chiefly by inhalation of vapour, and by skin and eye contact with liquid and vapour. Exposure is less during the production of MEK and its use as a chemical intermediate (where it is handled in closed systems) than when it is used in solvent systems open to the air.

No information is available about the number of people exposed worldwide, but NIOSH estimated that about 2.5 million workers could be exposed in the USA (NIOSH,1978). The occupational hygiene control limit (8 hr TWA) is 200 ppm (590 mg/m^3) in Europe and the USA. Published figures suggest that exposures to MEK are below this limit in many industries (NIOSH, 1980) although exposures above the limit have also been recorded (NIOSH,1980; Smith and Meyers,1944; Billmaier et al.,1974).

In the environment, MEK will disperse mainly into water and air.

D. TOXICOLOGICAL DATA

1. Human

1.1. Clinical observations

At concentrations above about 200 ppm MEK has an objectionable smell and causes irritation of the eyes, nose and throat. In

addition, headaches have been reported following exposure to 300 ppm, and levels in the region of 400-550 ppm have been reported to cause nausea and gastrointestinal disturbance, mental confusion, loss of consciousness and convulsions (Smith and Meyers, 1944; Elkins,1959; Glatt, 1977; Levy et al.,1969). Numerous cases of peripheral neuropathy have been reported following industrial exposure or abuse of solvent mixtures containing MEK but in these cases simultaneous exposure to the known neurotoxins n-hexane or methyl butyl ketone had occurred (Billmaier et al.,1974; Altenkirch et al.1977; Oh and Kim, 1976) or other possible causes for the neuropathy had not been fully investigated (Viader et al.,1975).

No skin irritation occurs on occasional short contact with MEK but dermatitis has been reported following repeated contact, probably consequent upon defatting of the skin (Rowe and Wolf,1963; Smith and Meyers, 1944).

1.2. Experimental studies

Volunteers exposed for 3 to 5 minutes to MEK vapour complained of slight nose and throat irritation, and mild eye irritation at 200 ppm. These symptoms became unacceptable at 300 ppm (Nelson et al.,1943). A concentration of 10,000 ppm was intolerable after several inhalations, and 33,000 and 100,000 ppm were intolerable even on momentary exposure (Patty et al.,1935).

The importance of skin absorption as a route of exposure was demonstrated by measuring MEK concentrations in exhaled breath following application of liquid MEK to the skin of volunteers (Munies and Wurster, 1965). Another study showed that the MEK concentration in exhaled breath in the first 30 minutes after exposure to the vapour was reasonably proportional to the exposure concentration (Tada et al.,1972).

MEK, as a 20% solution in petrolatum, showed no potential to cause allergic skin sensitisation in the Kligman maximisation procedure used on 24 volunteers (Epstein, 1975) .

Men and women exposed to 90-270 ppm MEK for 4 hours a day, for 4 days, were examined for their ability to estimate 5, 10 and 30 second time-periods every 30 minutes during exposure. Men tended to

shorten their estimates and women increased their variability on exposure, suggesting that at these exposure levels there was some effect on the CNS function (Nakaaki, 1974).

1.3. Epidemiological studies

Following an unpublished report of a US study (Enterline, 1978), Alderson and Rattan (1980) undertook a retrospective study on 446 men who worked in MEK dewaxing plants in the UK. The average time of follow-up was 14-years, and 46 men died during the period studied. The value of the studies was limited by the small numbers in the cohorts and the short duration of the study period. Nevertheless, there was no clear evidence of a cancer hazard. An extension of the studies with a longer follow-up period would be needed before a firm conclusion could be reached.

2. Experimental

2.1. Acute toxicity

2.1.1. Lethal dose

Route/species	Lethal dose or concentration	References
oral, rat adult	LD_{50}, 2,800-5,600 mg/kgbw	Rowe and Wolf,1963; Kimura et al.,1971; Smyth et al.,1962.
oral, rat 14-day old	LD_{50}, 2,500 mg/kgbw	Kimura et al.,1971
oral rat, newborn	LD_{50}, 810 mg/kgbw	Kimura et al.,1971
oral, mouse	LD_{50}, 3,100 mg/kgbw	Zakhari et al.,1977
dermal, rabbit	LD_{50}, 5,000-13,000 mg/kgbw	Rowe and Wolf,1963; Smyth et al.,1962; Moreno, 1975; General Electric, 1979.
intraperitoneal, mouse	LD_{50}, 610-1,700 mg/kgbw	Zakhari et al.,1977;NIOSH,1975.
inhalation, rat	Death soon after exposure to 11,700 ppm, 4 hr.	LaBelle and Brieger, 1955.
inhalation, rat	2-4/6 deaths within 14 d., after 4 hr exposure to 2,000 ppm.	LaBelle and Brieger, 1955.
inhalation, rat	3/6 deaths within 14 d, after 8 hr. exposure to 8,000 ppm	Carpenter et al.,1949
inhalation, mouse	Lethal concn., 72,000 ppm for 45 min.	Patty et al.,1935
inhalation, mouse	Lethal concentration, 103,000 ppm for 43 min.	LaBelle and Brieger, 1955

2.1.2. Effects of intoxication. In common with other organic solvents, excessive exposure to MEK leads to depression of the central nervous system, shown by loss of coordination, reflexes and

consciousness. Depression of respiratory rate and body temperature (Moreno, 1975) and the development of reversible corneal opacity (Patty et al.,1935) have been described in animals exposed to 100,000 ppm. Signs of irritation of the eyes and nose are seen soon after commencement of exposure to the vapour. At lethal doses, marked congestion of blood vessels occurs in internal organs (e.g. kidney, brain and lung). A weak hepatotoxicity potential has been demonstrated 24 h. after an intraperitoneal injection of MEK into guinea pigs: a dose of 2000 mg/kgbw produced a moderate increase in ornithine-carbamyl-transferase and histological evidence of a moderate accumulation of lipid in liver cells (Di Vincenzo and Krasavage,1974). Administration of MEK increases the activity of some microsomal enzymes and the smooth endoplasmic reticulum content of liver cells, and enzyme stimulation has been demonstrated in rats exposed for 7 days to 750 ppm MEK in air (NIOSH,1975; Traiger and Bruchner,1976; Couri et al.,1977).

2.1.3. Skin irritancy. When applied (occluded or un-occluded) for 24 h. to rabbit skin, MEK produces signs of mild to moderate irritancy (Rowe and Wolf,1963; Smyth et al.,1962; Moreno,1975; Weil and Scala,1971).

2.1.4. Eye irritancy. Liquid MEK instilled into the rabbit eye produces injury which is not completely reversible in all animals after several days. Corneal opacity with ulceration and vascularisation, conjunctivitis, and iritis have been described (Weil and Scala,1971; Exxon, 1980; Larson et al.,1956). 0.1 ml of a 1% solution in water or propylene glycol instilled into the eye of 6 rabbits elicited severe irritation, corneal dullness, opacity, epithelial sloughing and vascularisation (Smyth et al.,1962). Exposure to 100,000 ppm vapour for 30 minutes produced corneal opacity (Patty et al.,1935).

2.1.5. Cutaneous sensitisation. No evidence from animal experiments is available.

2.1.6. Aspiration. In common with other organic solvents of low viscosity, MEK causes acute pneumonitis on aspiration into the lungs. A single dose of 810 mg/kgbw killed most of a group of

rats when the MEK was administered so as to enter the lungs, signs of chemical pneumonitis occurring (Panson and Winek, 1980).

2.2. Sub-chronic and chronic toxicity

Exposure of a small number of rats and guinea pigs to MEK vapour at a concentration of 235 ppm in air for 7 hours a day, 5 days a week for 12 weeks failed to demonstrate adverse effects (LaBelle and Brieger,1955). No indication of injury to the nervous system was seen in rats exposed to 1,125 ppm MEK for 5 months (Saida et al.,1976); in rats exposed to 500 ppm for 22 hours a day, 7 days a week for 6 months (Egan et al.,1980); or in rats, mice or chickens exposed to 1500 ppm for 7 to 9 weeks (NIOSH,1975). A recent study in which rats were exposed to 1,250 to 5,000 ppm MEK in air for 6 hours a day, 5 days a week for 90 days, failed to demonstrate pathological changes attributable to MEK in a wide range of organs and tissues studied (Toxigenics Inc.,1981). A dose-related increase in the weight of the livers was found to be statistically significant at the 5,000 ppm exposure level. The lack of liver pathology strongly suggests that this increase was due to stimulation of microsomal enzymes.

2.3. Carcinogenicity

Horton et al.(1965) studied possible skin-tumour promotion in C3H/He mice by sulphur and its organic compounds. A 0.1% solution of benz(a)pyrene in MEK, used as a positive control, induced papilloma at the site of application in all animals. Mixtures of 70% dodecylbenzene and 25 and 29% of MEK with 5% of benzyl disulphide or 0.2% of 2-phenylbenzthiophene respectively, induced tumour formation in only 1 of 10 animals, in the latter case after 27 weeks. After 51 weeks exposure to 50% dodecylbenzene, 33% decalin and 17% MEK, 1 out of 15 mice developed a tumour. Although the study does not preclude MEK as a skin carcinogen it demonstrates that it is unlikely to be potently carcinogenic.

2.4. Metabolism, pharmacokinetics and biochemistry

A number of human, animal and in vitro studies have been performed to examine the absorption, metabolism, excretion and biochemical effects of MEK. The liquid is readily absorbed through the skin (Munies and Wurster, 1965) and gastrointestinal tract (Munies and Wurster, 1965; Traiger and Bruckner,1976), and the vapour is

rapidly absorbed through the lungs (NIOSH, 1975; Tada et al.,1972). Although there is no direct evidence on the distribution of absorbed MEK in the body, its presence has been demonstrated in the blood following exposure (Traiger and Bruckner, 1976), and its toxic actions and routes of elimination demonstrate that it can reach the nervous system (LaBelle and Brieger,1955; Altenkirch et al.,1978; Altenkirch et al.,1979), lungs (Munies and Wurster, 1965; Tada et al.,1972; De Castiglia et al.,1972), liver (Traiger and Bruckner, 1976; Traiger et al., 1975; White and Bus, 1980), and kidneys (Tada et al.,1972; De Castiglia et al.,1972; Sanoyeshi, 1911). The hydro- and lipo-philic properties of MEK also suggest that it would be widely distributed in the body following absorption.

Studies on guinea pigs (Di Vincenzo et al.,1976) and rats (Deitz and Traiger, 1979) have demonstrated, by gas chromatographic/mass spectrometric analyses of serum samples, that MEK is metabolized to 2-butanol, 3-hydroxy-2-butanone and 2,3-butanediol. Possible metabolites of smaller chain-length have not yet been demonstrated to occur.

Excretion of MEK takes place through the kidneys (Tada et al.,1972; De Castiglia et al.,1972; Sanoyeshi, 1911) and lungs (Munies and Wurster, 1965; Tada et al.,1972; De Castiglia, 1972). MEK is also normally present in exhaled air (Conkle et al.,1975) and urine (Zlatkis et al.,1973; Tsao and Pfeiffer, 1957; Przyrembel et al.,1979), possibly as a result of the metabolism of isoleucine (Tsao and Pfeiffer, 1957; Przyrembel et al.,1979). The half-life of MEK in serum was found to be 4.5 hours in guinea pigs administered the liquid intraperitoneally, and the clearance time was 12 hours (Di Vincenzo et al.,1976) . The clearance time of the three known metabolites was 16 hours (Di Vincenzo et al.,1976). The data point to a relatively rapid clearance of absorbed MEK from the body.

Several studies have demonstrated that, because of the increase in hepatic microsomal enzyme activity brought about, repeated exposure to MEK can alter the rate at which other substances (e.g. carbon tetrachloride, n-hexane, drugs) are metabolised (NIOSH, 1975; Traiger et al.,1975; Traiger and Bruckner, 1976; Couri et al.,1977; Smith and Meyers, 1944).

2.5. Mutagenicity

Several studies on the mutagenic potential of MEK have given negative results. In studies on a series of pesticides dissolved in MEK, no mutagenic activity was seen in B. Subtilis and E. Coli strains with and without metabolic activation systems (Kada et al.,1974; Shirazu, 1976; Shirazu et al.,1976). It was also tested (Nestmann et al.,1980) in S. Typhimurium strains with and without activation and at concentrations of up to 10 mg/plate, with negative results. A similar study in which the test strains were exposed to liquid before incubation, or to vapour, also gave negative results (Trueman, 1981).

2.6. Reproductive toxicity

Only teratological studies have been carried out. In an earlier study (Schwetz et al.,1974; Leony et al.,1974) in which 23 Sprague-Dawley female rats were exposed to 1000 or 3000 ppm MEK vapour for 7 hr/d from days 6 to 15 of pregnancy, the occurrence of 4 young with unusual congenital deformities, but without evidence of maternal toxicity, suggested that MEK may have a teratogenic action at the 3000 ppm exposure level. In a more recent study (Deacon et al.,1981) in which pregnant rats of the same strain were exposed to 400, 1000 or 3000 ppm MEK, there was no increase in major foetal malformations. The occurrence of minor skeletal variants in the 3000 ppm group confirmed the occurrence of retarded foetal development at this exposure level, but there was no indication of embryotoxic or teratogenic activity at 3000 ppm.

2.7. Neurotoxicity

In common with many other organic solvents, exposure to high concentrations of MEK causes reversible depression of CNS activity (LaBelle and Brieger, 1955; Altenkirch et al.,1978; Altenkirch et al.,1979). No pathological effects on the nervous system have been found in rats (Couri et al.,1978; Saida et al.,1976; Egan et al.,1980; NIOSH, 1975), and mice, cats or chickens (NIOSH, 1975) following repeated exposure to MEK vapour for several months. However, it has been demonstrated that MEK enhances the neurotoxic effect of n-hexane and methyl butyl ketone when simultaneous exposure occurs, potentiating their effect or decreasing the time of onset of the effect (Duckett et al., 1974; Saida et al.,1976; Altenkirch et al.,1978).

No effects were found on neurological function (posture, gait, functional muscular tone or symmetry, 4 neuromuscular reflexes) when rats (15 M, 15 F) were exposed to MEK at concentrations of up to 5000 ppm in air, 6 h/d, 5d/wk for 90 days (Toxigenics, Inc., 1981).

E. ECOTOXICOLOGICAL DATA

1. Environmental Distribution

The water-solubility and volatility of MEK suggest that in the environment it would be distributed in the air and water. No reliable data on MEK concentrations in these compartments were found. The ready biodegradability of MEK and its ability to photodegrade indicate that it is not likely to reach harmful concentrations in water or air after normal dispersion, ie. with the possible exception of local discharge points.

2. Degradation

Chemical degradation. The carbonyl group of saturated ketones is not susceptible to nucleophilic attack, and significant degradation by hydrolysis, oxidation and reduction in the environment is therefore unlikely.

Biodegradation. Extensive data demonstrate that MEK is readily biodegradable. Determinations in freshwater (Anon, 1951; Dore et al.,1974; Price et al.,1974; Bridié et al.,1979-b) and seawater (Price et al.,1974) demonstrated that the BOD was a high percentage of the theoretical oxygen demand, and studies on activated sludge showed that MEK is easily degraded and is not toxic to sludge microorganisms in concentrations up to 800 µg/litre (Dojildo, 1977).

Photodegradation. Although MEK is less reactive in smog than many other organic chemicals, it does undergo significant photodecomposition (Levy et al.,1969; Laity et al.,1973) probably because of a combination of direct photolysis and OH radical reactions. In the presence of 5 ppm NO, and with 35-40% relative humidity and 10 ppm MEK, a photodecomposition half-life of 9.8 hours was found (Dilling et al.,1976). Winer et al.(1976) calculated that the half-life of MEK in urban conditions is likely to be about 5.5 hours.

3. Toxicity to Aquatic Organisms

The high LC_{50} figures for MEK show that it will pose no hazard to fish or aquatic invertebrates in situations other than accidental discharge. At above 100 mg/litre it may inhibit the growth of blue algae but such concentrations are unlikely to be reached except for

short periods, again following accidental discharge. Data are summarised below.

Species	Conditions	LC_{50} mg/litre	Ref.
Mosquito fish (Gambusia affinis)	Turbid water, 96 hr.	5,600	Wellen et al.,1957
Bluegill (Lepomis macrochirus)	48 hr.	5,640	Turnbull et al.,1954
Goldfish (Carassius auratus)	24 hr.	>5,000	Bridié et al.,1979-a
Golden Orfe (Leucisus idus)	96 hr.	4,600-4,880	Juhnke and Lüdemann,1978
Water flea (Daphnia magna)	24 hr.	8,890	Bringmann and Kühn,1977-a
Water flea (Daphnia magna)	48 hr.	>520	Leblanc, 1980
Brine shrimp (Artemia salina)	24 hr.	1,950	Price et al. (1976)
Green Algae (Scenedesmus quadricauda)	incipient inhibition of cell multiplication	4,300	Bringmann and Kühn,1977-b
Blue algae (Microcystis aeruginosa)	"	100-120	Bringmann and Kühn,1976 Bringmann and Kühn, 1978.

4. Bioaccumulation

No direct information is available on the ability of MEK to accumulate in biological material. However, metabolic studies in man (see section D.2.4.) demonstrate that concentrations likely to be present in the environment will not lead to accumulation in human tissues. Its high water solubility, rapid degradation by aquatic bacteria, and low octanol-water partition coefficient of 0.26 (Turnbull et al.,1954) suggest that it is unlikely to concentrate in aquatic species (Metcalf et al.,1973; Chiou et al.,1977).

5. Toxicity to Plants

A concentration of 900 mg/l of MEK in water caused a 50% inhibition of the germination of lettuce (lactuca sativa) seeds (Reynolds, 1977).

F. SUMMARY AND CONCLUSIONS

Exposure to MEK is widespread in user industries, mainly via contact of the skin with liquid, and the respiratory tract with vapour. The acute lethal dose to animals is about 3 g/kgbw. Exposure to the liquid or vapour depresses central nervous system activity. The vapour is irritant to the eyes, nose and throat and the liquid can cause severe eye damage. Aspiration of the liquid produces acute pneumonitis.

MEK is weakly hepatotoxic . Short-term exposure of rats to concentrations of up to 5,000 ppm causes liver enlargement associated with an increased metabolic capacity of the liver. Such a change is unlikely to be of significance to man at normal exposure levels. Bacterial mutagenicity studies gave negative results. Epidemiological studies, although limited, have failed to demonstrate any carcinogenic activity. No long-term carcinogenicity study in animals has been performed, although the use of MEK during a study of skin-tumour promotion suggested that it has little or no carcinogenic activity. An adequate reproduction study has not been carried out, but teratogenicity studies in one species of animal have given conflicting results. MEK potentiates the action of neurotoxic solvents such as n-hexane and methyl butyl ketone. The metabolism and pharmacokinetics have been reasonably fully studied.

MEK is readily biodegraded in fresh- and salt-water systems, and the vapour appears to photodegrade. There is no evidence to suggest that it accumulates in the environment. It has a low acute toxicity to fish and other aquatic species.

Thus, MEK is of low toxicity to man and the environment and under normal conditions of use poses no undue problems to them.

A summary of studies in progress on MEK is given in Appendix 2.

APPENDIX 1 : TYPICAL COMPOSITION OF METHYL ETHYL KETONE

	mean wt.%
Methyl ethyl ketone	99.677
Low-boiling substances (isopropanol, C_4 and C_5 alkanes)	0.046
Acetone	0.018
Sec-butyl ether	0.002
Intermediate boiling unknowns (probably C_5 alcohols)	0.022
Sec-butyl alcohol	0.205
Higher-boiling unknowns (C_5 ketones)	0.030

APPENDIX 2 : RECENT OR CURRENT WORK

Sponsor	Type of Study	Species	Conc.	Duration	Results	Reference
1. CIIT	Pharmacokinetics	F-344 rat	500 1500 5000 ppm	6 hrs	- linear kinetics	CIIT (1980)
	Subchronic	F-344 rat	1250 2500 5000 ppm	6 hrs/d 5d/wk 13 wks	- lack of toxicity with the exception of wt. loss at high dose	Toxigenics (1981)
2. NTP (NIOSH)	Neurobehavioural	man	200 ppm MEK or 200 ppm MEK/ 100 ppm toluene	3.5 hrs	- test development to demonstrate usefulness of reflex response lacking in toxic assessments	Anger (1982)
3. Exxon Corp.	Neuropathy	S/D rat	500 ppm	22 hrs/d 7d/wk 6 months	- negative at clinical and sub-clinical levels	Egan et al. (1980)
4.	Liver induction	S/D rat	800 ppm	4 wks	- increased liver wt - no effect on cyt P450	Toftgard et al. (1981)
5. Exxon Corp.	Neuropathy (in vitro)	-	10-600 g/ml	< 8 wks	- MEK not neuro-toxic alone to CMS/PMS nerve unit	Veronesi et al. (1982)
6.	Neuropathy (interaction)	rat	500 ppm-n-hexane+ 200 ppm-MEK	8 hrs/d 7d/wk 40 wks	- no neuropathy detected clinically or sub-clinically	Altenkirch et al. (1982)
7. CIIT	Pharmacokinetics	rat	2000 ppm (1000-n-hexane + 1000 MEK)	6 hrs	- single exposure : no significant changes as compared to n-hexane repeated exposure : study planned	White & Bus (1980)

(cont'd)

Sponsor	Type of Study	Species	Conc.	Duration	Results	Source
8. Duke Univ.	Neuropathy : interaction with 5-nonanone	rat	(MEK) 750 mg/kgbw 1500 mg/kgbw	7 d/wk 14 wks	- authors claim that MEK enhances 5-nonanone neuropathy.	Shifman et al.(1981)
9. E. Kodak	Neuropathy : interaction 5-nonanone	rat	-	14 weeks	- MEK does not enhance 5-nonanone neuropathy	O'Donaghue et al. (1982)
10.	Neuropathy MEK, n-hexane	man (64 workers)	n-hexane: 33-320 ppm cyclohexane: 30-185 ppm MEK: 0-40 ppm ethyl acetate: 0-130 ppm	1 to 24 years	- subclinical effects reported	Mutti et al. (1981) (1982)
11.	Pharmacokinetics n-hexane, MEK	man			- 2,5-hexadione responsible for neuropathies in man	Perbellini et al. (1980)

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