Appendix B
Section L

METHYL ETHYL KETONE
HEALTH-BASED MAXIMUM CONTAMINANT LEVEL
SUPPORT DOCUMENT

Office of Science and Research

New Jersey Department of Environmental Protection

Prepared by
Lubow Jowa

EXECUTIVE SUMMARY

Methyl ethyl ketone (MEK) is a ketonic solvent commonly used, in the manufacture of plastics and adhesives. From the information available concerning the acute and chronic toxicity of MEK in both animals and humans, it appears that MEK has a low order of toxicity. In subchronic studies of MEK exposure, animals displayed toxicity at exposure levels of 5,000 ppm and higher. However, to most humans MEK is irritating at concentrations above 300 ppm; it can be detected in air at concentrations as low as 10 ppm. At these concentrations MEK also was reported to cause dermatosis of the face and numbness of the extremities. MEK has been shown also to augment the neuropathy attributed to co-exposure with methyl n-butyl ketone or n-hexane. A health-based maximum contaminant level of 270 ug/L MEK is proposed.

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BACKGROUND INFORMATION AND PROPERTIES

Chemical Properties

Chemical Name	Methyl Ethyl Ketone (MEK)
Synonyms	2-Butanone, Ethyl Methyl Ketone, MEK
CAS #	78-93-3
Chemical structure	CH_3-C-CH_2-CH_3
Molecular weight	72.11
Physical state	liquid colorless
Melting point	-86.35 ^{o}C
Boiling point	79.6^{o}C at 1 atmosphere
Vapor pressure	70.6 mmHg at 20 ^{o}C
Specific gravity, density	0.805 at 20 ^{o}C/4 ^{o}C
Water solubility	12.5% at 25 ^{o}C
Odor threshold, air	10 ppm
Conversion factors	100 ppm (285 mg/m^3)

Production and Use

Methyl ethyl ketone (MEK) is used mainly as a solvent for nitrocellulose formulations. Other uses include: manufacture of barrier coatings from acrylic resins, smokeless powder, cements, adhesives, and dewaxing of lubricating oils. MEK is an intermediate in drug manufacture (NIOSH, 1978).

MEK can be used as a food additive because of its ketonic odor and taste (Furia, 1986). MEK is produced by three firms in the U.S. and is probably the most widely used ketone.

Guidelines, Regulations, and Standards

The Occupational Safety and Health Administration has set a Time Weighted Average (TWA) level of 200 ppm (590 mg/m^3) which is the threshold for eye and nose irritation (ACGIH, 1980), and a short term exposure limit of 300 ppm (885 mg/m^3) was set (ACGIH, 1980).

The Office of Drinking Water, United States Environmental Protection Agency (1985) issued Health Advisories for MEK in drinking water. The one-day and ten-day Health Advisory determined for a 10 kg-child was 75,000 ug/L and 7,500 ug/L, respectively. The longer term Health Advisory for MEK was 2,500 ug/L for the 10-kg child and 8,000 ug/L for an adult. A level of 172 ug/L MEK was derived for the lifetime Health Advisory assuming that drinking water would contribute 20% of the total daily exposure to MEK.

ENVIRONMENTAL EXPOSURE

Fate and Transport

No information is available.

Ambient Levels

Approximately 2005.18 metric tons are estimated to be emitted into the air over Bergen County in one year; 1931.14 metric tons were emitted over Middlesex County in one year (1984) (PIPQUIC, 1985).

No studies have been done to detect MEK in New Jersey ground or potable water.

METABOLISM AND PHARMACOKINETICS

Absorption, Distribution, and Excretion

Munies and Wurster (1965) found that MEK (100 mL) when applied to normal, hydrated, and dehydrated human skin could be detected in expired air at 3.6 ug/L, 15 minutes after exposure. MEK reached a steady state level of 6.5-6.6 ug/L in 2 to 3 hours.

A study of the uptake and kinetics of MEK in Italian shoeworkers mainly exposed to MEK and hexanes was conducted (Perbellini et al. 1984). They found that alveolar MEK concentration was approximately 30% of the environmental MEK concentration, and blood MEK concentration was 104 to 116 times greater than the alveolar concentration, and 31 to 35 times greater than the environmental concentration. The mean urinary MEK concentration was 4.8 times the mean environmental MEK concentration. Urinary excretion of MEK and its metabolite, acetylmethylcarbinol (3-hydroxy-2-butanone), amounts to 0.1% of the alveolar uptake. In two heart attack victims among the workers, the tissue (brain, kidney, lung, fat, heart, muscle, and liver) concentration of MEK was similar to the amount found in the blood.

Dietz and Traiger (1979) reported that after a single oral dose of MEK (355 mg/kg) given to rats, the concentration of MEK alone in the serum was: 94 mg/100 mL, after 4 hours and 6.2 mg/100 mL after 18 hours.

In humans exposed to MEK, approximately 30-40% is eliminated in the respired air (Browning, 1965).

Metabolism

MEK is readily reduced by rat metabolism to form 2-butanol, 3-hydroxy-2-butanone and 2,3-butanediol (Divincenzo and Krasavage, 1976).

DiVincenzo and coworkers (1976) reported that after a single intraperitoneal dose of MEK (450 mg/kg), the metabolites observed after 16 hours were: 2-butanol, 3-hydroxy-2-butanone and 2.3 butanediol. Dietz and Traiger (1979) detected the same metabolites described by DiVincenzo et al. (1976) after a single oral dose of 355 mg/kg MEK administered to rats.

Human Exposure and Body Burden

Human exposure to MEK occurs primarily through inhalation and dermal contact during manipulation of MEK containing substances. Little is known about the contribution of MEK through the diet or by drinking water.

HEALTH EFFECTS

Overview

MEK is a relatively nontoxic compound. Animals are able to withstand very high exposures with no apparent permanent effects. Studies of human exposure to MEK report irritation to eyes, nose and throat, dermatosis and mild neurological effects.

Human

Acute and Chronic. Workers have been exposed to 700 ppm without suffering permanent injury. Exposure to 500 ppm has been reported to produce nausea and vomiting, while 350 ppm produced irritation to eyes, nose and throat (Enc. Occup. Health and Safety, 1971).

Vapors of MEK are extremely irritating to mucous membranes and conjuctiva. Smith and Mayers (1944) studied a factory where MEK was used as a solvent for weatherproofing raincoats. Some workers immersed their unprotected hands in the solvent: the workers were exposed by inhalation (300-600 ppm) and dermally. Several workers had severe dermatitis, two of them had no direct contact with the solvent. Several workers experienced numbness of the fingers and arms. One worker had numbness of the legs.

In 1971, Berg reported a case of retrobulbar neuritis in an 18 year old seaman exposed to MEK while removing paint. The seaman experienced

dull headaches, mild vertigo and substantially diminished vision. Blood tests at 10 hours revealed methanol and formaldehyde. At 36 hours normal vision returned, blood analysis revealed no formaldehyde and decreasing amount of methanol. Berg proposed that the subject had optic nerve toxicity induced by methanol formed during the metabolism of MEK. Toxic neuropathy was attributed to MEK alone in the case of one French plastics worker (Viader, 1975 as cited in Yang, 1986).

Animal

Acute. In Table I are several reported LD_{50} and LD_{50} values for MEK exposure.

Chronic. Labelle and Brieger (1955) exposed rats to 235 ppm (691 mg/m^3) MEK alone and as a component of a composite solvent for 7 hours per day, 5 days per week for 12 weeks; controls were exposed to air alone. Changes observed in the differential blood cell counts with exposure to MEK compared with the solvent and controls were not significant. No significant gross or microscopic pathologic changes were observed in either of the three groups, although details of the experimental protocol were not specified.

Cavender et al. (1983) exposed male and female F344 rats to MEK at air concentrations of 0, 1250, 2,500 and 5,000 ppm (6 hours per day, 5 days per week) for 90 days. There were no treatment related effects at 1,250 ppm level. An increase in SGPT levels (serum glutamic pyruvaic transaminase) was seen in females at the 2,500 ppm level but not at lower levels; at that level no liver histopathology was observed. At the 5000 ppm level significant changes were observed in body weight, liver weight, liver to body weight ratio, and liver to brain weight ratio. In addition, the authors noted decreased SGPT activity, and increased alkaline phosphatase, potassium and glucose levels in females.

Most of the MEK toxicology literature is devoted to the study of the effects from the interaction of MEK with other substances rather than to MEK alone. This is due to these factors: outbreaks of peripheral neuropathies in the 1970s due to solvent abuse (MEK as a component of these solvents); the realization the MEK alone could not induce neuropathy, but rather potentiated it; and finally the role of MEK as inducer of liver microsomal drug-metabolizing enzymes, which could potentiate the effects of various toxicants (Yang, 1986).

Smith and Mayers (1944) first suggested that MEK could potentiate acetone toxicity. In a plant that used both MEK and acetone for weather proofing raincoats, there were two episodes of acute toxicity. In another plant which used MEK only, and had the same airborne concentrations of MEK as the first plant, no acute toxicity episodes were reported.

In a study of the effect of ketones and ketogenic substances, MEK was found to potentiate the hepatobiliary toxicity of chloroform (Hewitt et al., 1986). MEK has been known to also potentiate the hepatotoxicity of chloroform (Dietz and Trager, 1979) in male Sprague-Dawley rats.

Table I

Acute LD_{50} and LC_{50} values for MEK

Animal species	Route	LD_{50} or LC_{50}	Reference
rat	oral	2.9 g/kg	Kimura, 1971
rat	inhalation	5.9 g/m^3 (2,000 ppm/4 hrs)	Carpenter, 1979
rabbit	dermal	78 g/kg	Smyth, 1962

Acute exposure studies with MEK were conducted in guinea pigs by Patty et al. (1935). The animals were exposed to 3,300 ppm, 10,000 ppm, 33,000 or 100,000 ppm for up to 14 hours. A level above 10,000 ppm, MEK was reported to produce irritation of the nose and eyes, tearing, respiratory distress, incoordination, and narcosis. The exposure to 100,000 ppm MEK for 30 minutes produced corneal opacity that appeared to be reversible. Pathologic examination of animals that died during exposure, or were sacrificed immediately after exposure to MEK, indicate that exposures above 3,300 ppm produced congestion of liver, kidney, lungs, and brain. In animals allowed to survive several days after exposure, no congestion was observed in the visceral organs.

In another study guinea pigs were administered a single intraperitoneal dose of 750 mg/kg, 1,500 mg/kg or 2000 mg/kg MEK (DiVincenzo and Krasavage, 1974). Twenty-four hours later higher levels of ornithine carbamyl transferase, an enzymatic marker of liver injury was observed at the 2,000 mg/kg level. Lipid accumulation in the liver was seen at the 1,500 mg/kg and 2,000 mg/kg exposure level.

Behaviorial and Central Nervous System

Saida et al. (1976) studied the neurotoxicity of methyl n-butyl ketone (MBK) at 225 ppm, MEK at 1125 ppm, and MBK and MEK combined at 225 ppm and 1125 ppm, respectively in Sprague-Dawley rats exposed continuously for 24 hrs per day for 5 months. No clinical signs of neuropathy were observed in the MEK exposed group. MEK in combination with MBK did cause signs of neuropathy.

Couri et al. (1974) (as cited in Yang, 1986) exposed Sprague-Dawley rats, chickens, cats, and mice (strain unknown) to MEK alone, and in combination with MBK. The exposure of 150/1500 ppm MBK/MEK was for 24 hours per day, 7 days per week, for 4 to 8 weeks with a few interuptions. There were no clinical paralyses or neuropathies detectable in the MEK exposed group alone. However, MEK-potentiated neurotoxicity of MBK was suspected in rats and cats, while mice appeared to be unaffected.

Takeuchi et al. (1983) examined the ability of MEK to potentiate n-hexane neurotoxicity. Groups of 8 rats were exposed to 100 ppm n-hexane, 200 ppm MEK, 100 ppm n-hexane with 200 ppm MEK, or fresh air for 12 hours per day for 24 weeks. From each group one rat was examined histopathologically. Body weight, motor nerve conduction velocity, distal motor latency and mixed nerve conduction velocities were measured at four week intervals. Exposure to 200 ppm MEK significantly increased motor nerve conduction velocity and mixed nerve conduction velocities at four weeks but not thereafter; no significant changes over controls were seen in any parameter with MEK alone. However, the MEK with hexane groups showed significant changes in several parameters within 24 weeks. The degree of these changes was greater than that which was seen in n-hexane groups.

Thus MEK alone has not been shown to produce significant neurological effects *in vivo* in animals, but it does appear to enhance the neuropathologic effects of other chemicals.

There has been a report of reproducing neurotoxic effects of MEK *in vitro*. Veronesi (1984) treated explants of mouse spinal cord and attached dorsal root ganglia with MEK at 300 ug/mL for 7 weeks, and sampled them intermittently for electron microscopic examination. MEK was found to induce axonal damage which was characterized by early and persistent morphological changes in the cytoplasm of both the motor and the sensory neurons. The author speculates that the reason that neurotoxicity was observed *in vitro* versus *in vivo* may be the result of differental rates of biotransformation by neural cell cultures.

Reproductive, Embryonic and Teratogenic

Two studies on the reproductive effects of MEK were conducted by the Dow Chemical Company. In the first study, Schwetz et al. (1974) exposed pregnant Sprague-Dawley rats to concentrations of 1126 ppm or 2618 ppm MEK for 7 hours per day on days 6 through 15 of gestation. MEK at either dose level did not affect the number of implantation sites, the number of live fetuses per litter or the number of corpora lutea per dam. There was a decrease of fetal body weight at 1126 ppm but not at 2618 ppm. The individual incidence of skeletal anomalies (skull, vertebral and sternebral) was not significantly elevated over controls ($p \leq 0.05$). A significant difference ($p \leq 0.05$) was observed in the incidence of skeletal defects of the sternum in the controls and 2618 ppm group but not in the 1126 ppm group. A higher incidence of visceral anomalies, including dilated ureters and subcutaneous edema, was seen in the offspring of the 2618 ppm group.

In the other study, Deacon et al.(1981) exposed pregnant Sprague-Dawley rats to 0, 400, 1000 and 3000 ppm MEK for 7 hours per day on days 6 through 15 of gestation. There was evidence of maternal toxicity by a decrease body weight gain and increased food consumption at 3000 ppm. (There was an indication of this as well in Schwetz et al., 1974, however it was not significant). There was an increase in two minor skeletal variants (extra ribs and delayed cervical central ossification) at the 3000 ppm level, but not at any lower levels. Maternal toxicity could have accounted for these variations. There are several ambiguities, including a significant difference in the frequency of variations observed between the control groups of the Deacon et al. (1981) and Schwetz et al. (1977) studies. Also, the frequencies of skull variations were observed to be higher in the control group compared with any of the MEK-exposed groups in the Deacon et al. (1981) study.

Deacon et al. (1981) concludes:

> Exposure to 3000 ppm of MEK, a slightly maternally toxic level, resulted in some minor variations in the development of the fetal skeleton in rats, a slight fetotoxic effect. Neither significant embryotoxicity nor a teratogenic effect was discerned in rats inhaling up to 3000 ppm MEK for 7 hours per day during the period of major organogenesis.

Genetic

MEK is assumed to be nonmutagenic, and has been employed as a control for the mutagenic testing of pesticides (Smiarsu, 1976) at one dose concentration. However, no unusual number of revertants were observed in Salmonella typhimurium TA 1535, TA 1537, TA 1536, TA 1538 or

in Escherichia coli WP2. MEK was shown to be nonmutagenic in the other Salmonella strains TA98, 100, 102, 1535, and 1537 with and without the S-9liver activation (Florin et al., 1980, Nestmann et al.; 1980, Marnett et al., 1985, as cited in Yang, 1986). However, a recent paper of Zimmerman et al. (1985) indicates that MEK strongly induced aneuploidy, but not recombination or point mutation, in yeast strain D61.M test system.

Carcinogenicity

Horton et al. (1965) applied topically 50 mg of a 17% MEK solution to the skin of C3H male mice twice a week, for one year. No skin tumors appeared to be induced (as cited in Yang, 1986).

QUANTITATIVE RISK ASSESSMENT

Studies Useful for Risk Assessment

There are no chronic MEK ingestion studies available in animals or humans. Therefore, a risk assessment for MEK must be performed with inhalation studies.

Human toxicity from MEK exposure has been characterized by irritation of the skin and respiratory tract, and also symptoms of neuropathy. Only one human study was identified which could be considered for risk assessment, Smith and Mayers (1944). In this study, workers exposed to levels of 300-600 ppm MEK were reported to have symptoms which could be interpreted as neuropathy. These symptoms could have been the result of higher levels of MEK exposure from direct contact with the solvent, however, the airborne concentration of MEK must contribute significantly to the body burden of MEK and be considered as capable of producing symptoms of neuropathy alone. The airborne levels of 300-600 ppm MEK appear to produce dermatitis.

Examination of animal subchronic studies with MEK reveal that most of the studies (Labelle and Brieger, 1955; Takeuchi et al. 1983; Saida et al., 1976) describe no apparent toxicity with MEK exposure. Cavender et al., 1983 describes an elevation of SGPT at 5000 ppm which was not correlated with liver histopathology. The authors believe that the elevation of SGPT was the result of an adaptive mechanism, and not of liver toxicity. The studies of Schwetz et al. (1972) and Deacon et al. (1981) fail to prove that MEK has reproductive or teratogenic effects, but rather a slight fetotoxic effect that could have been the result of maternal stress. In summary, subchronic animal studies failed to describe clear evidence of systemic toxicity with MEK, especially neuropathy; any effects observed which could be attributed to MEK were at exposure levels that would have been intolerable for humans. These

studies appear to indicate that experimental animals were relatively insensitive to MEK exposure, and that the MEK subchronic studies performed with them would not predict the risk of MEK exposure to human health.

However, animal studies might be predictive of the synergistic effects of MEK upon the toxicity of other substances. In the studies of Hewitt et al. (1986) as well as other described in Yang (1986), MEK potentiates the toxicity of n-hexane, MBK, chloroform, and carbon tetrachloride. Since humans are ordinarily exposed to a multitude of chemicals including those having toxicity known to be potentiated by MEK, it is necessary to propose an additional safety factor to protect human health from the synergistic effects of MEK.

Smith and Mayers (1944) is the only appropriate study for risk assessment that predicts an MEK level at which no toxic effects would be seen in the human. An intermittent dose level of 300 ppm (the lower bound on the inhalation dose) could be identified as the lowest-observed-adverse-effect-level (LOAEL). An acceptable daily level can be calculated as follows:

Calculation of Acceptable Daily Intake (ADI)

300 ppm = 870 mg/m^3

$$ADI = \frac{(870\ mg/m^3)\ (20 m^3/day)\ (5\ days/week)\ (7\ hours/day)\ (0.75)}{10 \times 10 \times 10 \qquad (7\ days/week)\ (24\ hrs)\ (70\ kg)}$$

ADI = 0.386 mg/kg or 39 ug/kg

Calculation of the Health-Based Maximum Contaminant Level

$$MCL = \frac{ADI\ (0.2)(70\ kg)}{2\ L} = 270\ ug/L$$

where:
- 870 mg/m^3 = LOAEL
- 20 m^3/day = assumed adult respiratory rate
- 0.75 = pulmonary absorption factor (Krasavage, et al. 1983)
- 0.2 = assumed contribution from drinking water
- 5 days/week = days/week exposed
- 7 days/week = days/week
- 7 hours/day = hours/day exposed
- 10 = convert LOAEL to NOAEL
- 10 = to protect the most sensitive individual in the exposed population
- 10 = to prevent MEK augmented toxicity of other substances
- 24 hrs = number of hours/day
- 70 kg = average weight of adult male
- 2 L = water consumption per day

Assumptions and Uncertainty

The Smith and Mayers study (1944) as well as other human case reports reviewed here indicate that neuropathy is the only observable systemic toxicity which can be attributed to MEK exposure. From the Smith and Mayers study (1944) it can also be inferred that these toxic effects result largely from inhaling 300-600 ppm MEK. It is assumed that a level as low as 300 ppm of MEK can produce these effects in humans, and that humans are as sensitive to effects of MEK by ingestion as they are by inhalation.

It is also assumed that the extra factor of 10 will protect against the possible MEK enhancement of neurotoxic effects from chemicals, such as n-hexane and MBK, available in drinking water or through other sources of exposure. This extra factor of 10 is also necessary to prevent possible enhancement of hepatonecrosis by MEK prior to the haloalkane exposure.

Conclusion

A health-based MCL for MEK has been recommended of 270 ug/L in drinking water. This level was developed based on MEK toxicity seen in occupational settings.

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