Fact Sheet Date: 4/9/93

NEW YORK STATE
- HUMAN HEALTH FACT SHEET -

Ambient Water Quality Value for
Protection of Sources of Potable Water

SUBSTANCE: Methyl Ethyl Ketone **CAS REGISTRY NUMBER:** 78-93-3

AMBIENT WATER QUALITY VALUE: 50 ug/L

BASIS: General Organic Guidance Value [6 NYCRR 702.15(a)(1)(ii)]

SUMMARY OF INFORMATION

Introduction:

Methyl ethyl ketone, also called MEK or 2-butanone, is used as a solvent in processes involving resins, gums, cellulose acetate and cellulose nitrate (USEPA, 1988). This synthetic organic substance is also used extensively in production of paraffin wax and high-grade lubricating oil, in the synthetic rubber industry and in household products such as lacquer and varnishes, paint remover and glues. It has a formula of C_4H_8O and a molecular weight of 72.2 (RTECS, 1992).

Pharmacokinetics:

ATSDR (1992) notes that reports by Kopelman and Kalfayan (1983) and Sakata et al. (1989) provide qualitative but not quantitative evidence that MEK is absorbed in humans following oral exposure . ATSDR (1992) further notes that rat data by Dietz and Traiger (1979) and Dietz et al. (1981) indicate that MEK is quickly absorbed and eliminated following oral administration. Humans exposed to MEK via the inhalation route showed a pulmonary uptake of 41-56% of the inspired amount (Liira et al., 1988a, 1988b, 1990; all as cited by ATSDR, 1992).

Of MEK given orally to rats, about 30% was converted to 2,3-butanediol, 4% to 2-butanol and 4% to 3-hydroxy-2-butanone (Dietz et al., 1981; as cited by ATSDR, 1992). DiVincenzo et al. (1976; as cited by ATSDR, 1992) reported that metabolites of MEK in guinea pigs (route of administration not specified) were excreted in urine as O-sulfates or O-glucuronides. Schwetz et al. (1991) reports the rate of elimination from the blood to be independent of the route of exposure.

Effects from Short-Term Exposure:

Lethality data for MEK are shown in Table 1.

Table 1

Lethality Data for MEK

Route	Type	Value	Species	Reference
Oral	LD_{50}	800 mg/kg	Rat (newborn)	*
Oral	LD_{50}	2500 mg/kg	Rat (weanling)	*
Oral	LD_{50}	2737 mg/kg	Rat	RTECS, 1992
Oral	LD_{50}	4050 mg/kg	Mouse	RTECS, 1992
Intraperitoneal	LD_{50}	607 mg/kg	Rat	RTECS, 1992
Intraperitoneal	LD_{50}	616 mg/kg	Mouse	RTECS, 1992
Inhalation	LC_{50}	5.9 g/m^3/4H	Rat	**
Inhalation	LC_{50}	23.5 g/m^3/8H	Rat	RTECS, 1992
Inhalation	LC_{50}	40 g/m^3/2H	Mouse	RTECS, 1992
Skin	LD_{50}	6480 mg/kg	Rabbit	RTECS, 1992

* Kimura et al., 1971; as cited by USEPA, 1988.
** Carpenter et al., 1949; as cited by USEPA, 1988.

Rats given MEK by gavage at 3670 mg/kg and up exhibited clinical signs of central nervous system toxicity (Stillmeadow Inc., 1978; as cited by ATSDR, 1992). Specific signs included labored breathing, lethargy, ptosis, lacrimation, exophthalmos, ataxia, salivation and piloerection, and most of these animals died.

MEK was given in a single intraperitoneal dose at 750, 1,500 or 2,000 mg/kg to guinea pigs (Davidsohn and Wells, 1965; as cited by USEPA, 1988). Liver effects of lipid accumulation in cells at the mid- and high doses and elevated serum ornithine carbamyl transferase (OCT) activity at the high dose were noted.

Oral administration of 1,080 mg/kg MEK to rats resulted in mild renal tubular necrosis (Brown and Hewitt, 1984; as cited by ATSDR, 1992).

Systemic Effects from Intermediate and Long-Term Exposure:

Systemic effects were noted in one oral and several inhalation studies on MEK.

Oral

Ralston et al. (1985; as cited by ATSDR, 1992) treated rats with MEK by gavage for 90 days at a time-weighted average dose of 173 mg/kg/day. Neurobehavioral tests, including hindlimb grasp, hindlimb place, balance beam, and roto-rod revealed no effects. The value of 173 mg/kg/day represents a no-observed-adverse-effect-level (NOAEL).

Inhalation

In a 12-week study, 25 rats were exposed to 235 ppm for 7 hr/day, 5 days/week (LaBelle and Brieger, 1955). According to these authors, any post-exposure differences were of no or questionable biological significance. Both gross autopsy and microscopic findings were "no significant pathological changes." Growth, hemoglobin, red and white blood cells, neutrophilic cells, lymphocytes and monocytes were also measured, but no statistical comparison was provided. Sex, strain or weight information on the rats was not given.

Significantly increased liver weight and liver-to-body weight ratio were noted in rats exposed to 800 ppm MEK 6 hr/day, 5 days/week for 4 weeks (Toftgard et al., 1981).

In another study, male and female rats were exposed to MEK at levels of 0, 1,250, 2,500 or 5,000 ppm for 6 hr/day, 5 days/week for 90 days (Cavender et al., 1983). Liver weights in females at 2500 ppm were increased from controls ($p<.01$). Females at 1250 ppm also showed an increase in liver weight but the authors do not make it clear if this was significantly different from controls. Significant differences at 5000 ppm were noted in several blood parameters and relative organ weight levels.

In a 24-week study, rats exposed to MEK at 200 ppm for 12 hr/day, 7 days/week showed significantly increased motor nerve conduction velocity and mixed nerve conduction velocities and decreased distal motor latency after exposure for four weeks (Takeuchi et al., 1983). However, no significant changes were found in these parameters at later time points.

All five rats exposed to 6000 ppm MEK 7 days/week, 8 hr/day died of severe bronchopneumonia within seven weeks of a planned 15 week exposure (Altenkirch et al., 1978a; as cited by ATSDR, 1992).

No deaths or altered clinical signs were reported in rats exposed continuously at 1,125 ppm MEK for 5 months (Saida et al., 1976; as cited by ATSDR, 1992). According to USEPA (1988), the only endpoint examined in this study was paralysis.

Reproductive/Developmental Effects:

No information on the reproductive effects of MEK was found. Developmental effects were noted in rat and mouse inhalation studies, and concerns raised over human parental exposure.

Schwetz et al., (1974; as cited by USEPA, 1992) exposed pregnant Sprague-Dawley rats to MEK vapor at 0, 3.3 or 7.7 g/m^3 for 7 hr/day on days 6-15 of gestation. Fetotoxicity was indicated by a marked decrease in fetal body weight at the low dose (but not the high dose). At the low dose, the total incidence of skeletal anomalies was significantly increased compared to controls. At the high dose, the incidence of skeletal defects of the sternum was significantly different from controls. The occurrence of visceral anomalies in offspring of rats at the high dose was significantly increased.

Deacon et al. (1981) also exposed pregnant Sprague-Dawley rats to MEK for 7 hr/day on days 6-15 of gestation, but at 0, 400, 1000 or 3,000 ppm (0, 1.2, 3.0 or 8.9 g/m^3). Rats at the highest dose exhibited maternal toxicity and their offspring showed slight fetotoxicity, specifically an increased incidence of two skeletal variants. The levels of 1000 and 3000 ppm represent a NOAEL and LOAEL, respectively (ATSDR, 1992).

In a recent study [Schwetz et al., 1991; Mast et al., 1989 (same study); as cited by USEPA, 1992], Swiss mice were exposed to MEK at 0, 398, 1010 or 3020 ppm for 7 hr/day on days 6-15 of gestation. A reduction in fetal weight, statistically significant in males, was noted at 3020 ppm. This represents a LOAEL, with a NOAEL of 1126[sic] ppm. A statistically significant increase in relative liver to body weight ratio in the mothers was also noted at the 3020 ppm level.

In pregnant rats exposed prenatally (21 days) to 800 ppm MEK (23 hr/day, 7 days/week) less than two thirds brought forth young, compared to all in the controls (Stoltenburg-Didinger et al., 1990). Delayed histogenesis in the cerebellar cortex was also reported.

In a drinking water study, rats were exposed to 2, 1 or 0.3% 2-butanol (FDRL, 1975; as cited by Kodak, 1992). This substance is described as metabolically interchangeable with MEK. At the high dose, weanling rats exhibited a significant depression in growth and evidence of retarded skeletal maturation. Parental rats showed mild toxicity (not specified). NOELs of approximately 1500 mg/kg/day were described for both the parental and first filial generations.

Several studies discuss effects in children of parents exposed to MEK. Peters et al. (1985) found that paternal exposure to solvents including MEK is associated with excess risk of tumors in the central nervous system in children of fathers employed in the aircraft industry. However, quantification of these exposures was not provided.

Lowengart et al. (1987) reported an increased risk (odds ratio = 3.0; p = 0.05) of leukemia for children whose fathers were occupationally exposed to MEK following the birth of the child. Data on exposure concentrations were not provided.

Holmberg and Nurminen (1980) compared case mothers (child with CNS defect) with referent mothers (healthy children). They reported that "case mothers had been exposed more often than referent mothers to organic solvents during the first trimester of pregnancy," a statistically significant result. However, MEK exposure was listed for only one of the nine cases, and was not quantified.

Genotoxicity:

In Salmonella typhimurium strains TA98, TA100, TA1535 or TA1537 with or without rat hepatic homogenates, MEK was not found to be mutagenic (Florin et al., 1980, Douglas et al. 1980; both as cited by USEPA, 1992). No increase in the number of revertants was found when MEK was tested as a solvent control in Escherichia coli WP2 and Salmonella typhimurium strains TA1535, TA1536, TA1537 and TA1538 (Smirasu, 1976; as cited by USEPA, 1988). It did, however, induce aneuploidy in the diploid D61, M strain of Saccharomyces cerevisiae (Zimmerman et al., 1985; as cited by USEPA, 1992). MEK induced a significantly elevated chromosome loss level in Saccharomyces cerevisiae D61.M, postulated to occur via perturbation of microtubular assembly (Whittaker et al., 1990).

Oncogenicity

USEPA (1992) classifies MEK as "D; not classifiable as to human carcinogenicity," based on a lack of human carcinogenicity data and inadequate animal data. No animal data were available to assess MEK carcinogenicity by either the oral or inhalation routes. The presence of a single skin tumor was noted after 27 weeks in one of 10 male C3H/He mice that were dermally treated with 50 mg of a solution containing 29% MEK in 70% dodecylbenzene twice weekly for one year (Horton et al., 1965; as cited by USEPA, 1992). In an equal size group at 25% MEK, no skin tumors were found.

ATSDR (1992) cited two retrospective epidemiological studies of workers chronically exposed to MEK via inhalation. In both studies, workers in dewaxing plants were found to have cancer deaths less than expected (Alderson and Rattan, 1980, Wen et al., 1985; both as cited by ATSDR, 1992). In the Alderson and Rattan study, the incidence of buccal or pharyngeal neoplasms was statistically significant but regarded by those authors as being due to chance (Alderson and Rattan, 1980; as cited by ATSDR, 1992). This incidence was not confirmed in the Wen et al. study.

Interactions with Other Substances:

MEK has been shown to potentiate the hepatotoxicity of chloroform and carbon tetrachloride and the neurotoxicity of n-hexane, ethanol and methyl n-butyl ketone (ATSDR, 1992). The ability of MEK to induce microsomal liver enzymes has been documented by several studies (ATSDR, 1992). Oral administration of MEK to rats for 1-7 days resulted in increased levels of cytochrome P-450, increased activities of cytochrome P-450 dependent monooxygenases (Brady et al., 1989; Raunio et al., 1990, Robertson et al., 1989; Traiger et al., 1989; all as cited by ATSDR, 1992). Such administration also results in the proliferation of the smooth endoplasmic reticulum (Traiger et al., 1989; as cited by ATSDR, 1992).

Other Standards and Guidelines:

Under New York State Department of Health regulations (10 NYCRR Part 5), MEK is an unspecified organic contaminant (UOC) with a maximum contaminant level (MCL) of 50 ug/L in drinking water (NYSDOH, 1990).

USEPA (1988) has derived a Lifetime Health Advisory (HA) for MEK in drinking water of 200 ug/L, based on the 12-week rat inhalation study by LaBelle and Brieger (1955) described above. However, this was calculated using an overly conservative assumption about pulmonary rate to body weight ratios.

DERIVATION OF VALUE

Regulations [6 NYCRR 702.15(a)(1)] require that the ambient water quality value be the more stringent of the values derived using the procedures in sections 702.3 through 702.7 or a "general organic guidance value" of 50 ug/L.

Analysis of the effects data in the "Summary of Information" above was performed according to the procedures in regulation. Short-term data are not appropriate for the development of a value. The only oral animal study of intermediate or greater duration on MEK that showed a systemic effect is that of Ralston et al., which has a NOAEL of 173 mg/kg/day, which yields a potential ambient water quality value of 1200 ug/L. Given the uncertainties and drawbacks of route-to-route extrapolation, potential ambient water quality values were not calculated from the inhalation studies described above. Workplace exposure typically involves multiple substances and it is difficult to quantify an association between a specific substance and a toxicological endpoint. A water quality value cannot be derived from the occupational exposure studies described above.

If one accepts the premise that 2-butanol is a valid surrogate for MEK, a potential ambient water quality value can be calculated for MEK based on the FDRL study as well. Although detailed exposure data were not provided, the value would likely be in the range of 10,000 ug/L.

Although the available non-oncogenic data on MEK and the FDRL study on 2-butanol would yield a value less stringent than 50 ug/L, a substantial data gap exists with respect to oncogenicity. Specifically, MEK is classified as "D; not classifiable as to human carcinogenicity," based on absent or inadequate data. Accordingly, there are not adequate and sufficient data available to justify values greater than 50 ug/L based on both oncogenic and non-oncogenic effects as described in 702.15(a)(1)(ii). The appropriate ambient water quality guidance value for MEK, therefore, is 50 ug/L, based on the "general organic guidance value" [702.15 (a)(1)(ii)].

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SEARCH STRATEGY

The following on-line databases were searched for MEK:

Integrated Risk Information System (IRIS) - Searched March 30, 1992
Registry of Toxics Effects of Chemical Substances (RTECS) - Searched March 23, 1992
Hazardous Substances Data Bank (HSDB) - Searched March 19, 1992

CSS/SS
April, 1993