

Appendix A

OECD SIDS Dossier and SIAR for MEK

DRAFT

SIDS INITIAL ASSESSMENT PROFILE

CAS NO.	78-93-3
CHEMICAL NAME	Methyl Ethyl Ketone
STRUCTURAL FORMULA	CH3 - C - CH2 - CH3) O

RECOMMENDATION OF THE SPONSOR COUNTRY

- currently of low priority for further work
- currently of low priority for further work, but avoid exposure to man and the environment
- requiring further information to assess identified concerns
- candidate for in-depth risk assessment with a view to possible risk reduction activities

Table of Contents	Page
Short Summary	3
Full SIDS Summary	5
1.0 Exposure Assessment	11
1.1 Production Volumes	11
1.2 Major Uses	11
1.3 Manufacturing Process	11
1.4 Distribution	11
1.5 Fugitive Emissions	11
1.6 Workplace Monitoring	12
2.0 Summary of Environmental Fate and Effects	12
2.1 Environmental Fate	12
2.2 Toxicity to Aquatic Organisms	13
2.3 Toxicity to Plants	14
2.4 Toxicity to Terrestrial Organisms	14
3.0 Summary of Health Effects	14
3.1 Acute Toxicity and Primary Irritancy	14
3.2 Effects Resulting from Repeated Exposure	15
3.3 Effects on Reproductive Capabilities	15
3.4 Effects on Developmental Toxicity	16
3.5 Genotoxic Effects	17
3.6 Neurotoxic Effects	18
3.7 Carcinogenicity	21
3.8 Human Studies	21
4.0 Conclusions	21
5.0 References	22

SHORT SUMMARY OF THE REASONS WHICH SUPPORT THE RECOMMENDATION

Methyl ethyl ketone (MEK) is a high production volume chemical which is primarily used in commercial and industrial settings and is rarely found in commercial products. The major use of MEK is as a solvent and chemical intermediate. As a solvent, MEK is used in surface coatings, adhesives, inks, traffic marking paints, cleaning fluids, and dewaxing agents. Its largest use is in vinyl lacquers but nitrocellulose lacquers also consume large volumes of MEK. It is used for the solubilization of acrylic coatings in the surface coatings industry. MEK is also commonly used as a solvent for rubber cements and other natural or synthetic resins for adhesive use. Other important applications include extraction medium for fats, oils, waxes and resins, and as an intermediate in the production of antioxidants, perfumes, smokeless powder and catalysts.

Manufacture of MEK takes place in an enclosed process and transport of the material occurs through enclosed systems or bulk carrier. This condition significantly limits exposure during manufacture and handling. Fence line concentrations are also expected to be negligible.

The estimated annual production of MEK in the United States is in the order of 620 million pounds. Worldwide, it is estimated that 1940 million pounds are produced annually.

Based on physical and chemical properties, MEK is an unlikely environmental contaminant. It undergoes degradation in the atmosphere and in aqueous environments and has a low degree of toxicity to environmental species. MEK may contribute to the formation of photochemical smog.

There are estimates of significant fugitive emissions. Rapid biodegradation in aquatic and terrestrial habitats, and physical degradation in the troposphere occur, indicating that methyl ethyl ketone will not persist in the environment.

MEK has been shown to be of a low order of toxicity following acute oral, dermal, and inhalation exposure. Contact with the eyes, skin or respiratory tract may produce irritation. MEK has not been shown to produce skin sensitization. No significant signs of toxicity were seen following repeated inhalation exposure of rats to MEK at high concentrations. MEK and its metabolic surrogate, 2-butanol, do not appear to present significant risk of adverse reproductive or developmental effects. MEK has been shown to produce central nervous system effects at high concentrations but does not cause damage to the nervous system. It does not show peripheral neurotoxic effects but will potentiate effects by co-exposure with hexacarbons. Human volunteers exposed to relatively high levels of MEK did not demonstrate any significant effects, other than minor irritation and sensory effects. MEK is not genotoxic and is not likely to be carcinogenic. It can enhance the toxicity of other chemicals.

The information obtained from this database allows for the characterization of toxicity hazard of MEK for both human/mammalian and environmental effects. Taken together, these considerations support the conclusion that MEK is a low priority for further work.

FULL SIDS SUMMARY

CAS No: 78-93-3		SPECIES	PROTOCOL	RESULTS
PHYSICAL-CHEMICAL				
2.1	Melting point		ASTM D97	- 85.9 °C
2.2	Boiling point		ASTM D1078	78.5 - 81 °C (at 1012 hPa)
2.3	Density		ASTM D891	0.806 g/cm ³ (6.7 lb./gal)
2.4	Vapor pressure		not known	100 hPa (75 mmHg) at 20 °C 223 hPa (168 mmHg) at 38 °C 436 hPa (327 mmHg) at 55 °C
2.5	Partition coefficient (Log P _{ow})		not known	0.29 at 25 °C
2.6	Water solubility		not known	26.3 wt% at 20 °C
	pH			
	pKa			
2.7	Flash Point			-4 °C (closed cup)
2.8	Auto Flammability			>450 °C
2.9	Flammability			Highly flammable
2.10	Explosive properties			Explosive
2.11	Oxidizing properties			No oxidizing properties
2.12	Adsorption coefficient (Log K _{oc})		calculated	0.58
2.13	Henry's Law constant		calculated	5.60 x 10 ⁻⁵ atm·m ³ /mole at 25 °C 5.67 Pa·m ³ /mole at 25 °C

FULL SIDS SUMMARY (Continued)

CAS No: 78-93-3		SPECIES	PROTOCOL	RESULTS
ENVIRONMENTAL FATE AND PATHWAY				
3.1.1	Photodegradation Atmospheric degradation (OH radical attack)		various	Photolysis is not a significant degradation process $T_{1/2} = 128$ hours in air
3.1.2	Stability in water			Not subject to hydrolysis
3.2	Monitoring data			In air = mg/ m ³ In surface water = ug/l In soil/sediment = ug/g In biota = ug/g
3.3	Transport and Distribution		Calculated (Fugacity Level type 1) (Mackay) (local exposure)	In air 58.7 % In water 41.3 % In sediment 0.0 % In soil 0.0 % In biota 0.0 %
3.5	Biodegradation			
3.6	BOD ₅	aerobic	APHA-219	83 % after 5 days at 20 °C
		aerobic	Standard Methods, 1971	89 % after 20 days (freshwater) 69 % after 20 days (seawater)
3.7	Bioconcentration (BCF)	freshwater fish	calculated	0.7

FULL SIDS SUMMARY (Continued)

CAS No: 78-93-3		SPECIES	REFERENCE	RESULTS
ECOTOXICOLOGY				
4.1	Acute/Prolonged Toxicity to Fish	Carassius auratus Cyprinodon variegatus Gambusia affinis Lepomis macrochirus L. macrochirus Pimephales promelas P. promelas	Jensen, 1978 Heitmuller et al, 1981 Wallen et al, 1957 Buzzell et al, 1968 Turnbull et al, 1954 Brooke et al, 1984 Veith et al, 1983	LC ₅₀ (24 hr) = 2,400 mg/l LC ₀ (96 hr) = 400 mg/l LC ₅₀ (96 hr) = 5,600 mg/l LC ₀ (96 hr) > 10,000 mg/l LC ₅₀ (48 hr) = 5,640 mg/l LC ₅₀ (96 hr) = 3,220 mg/l LC ₅₀ (96 hr) = 3,200 mg/l
4.2	Acute Toxicity to Aquatic Invertebrates	Artemia salina Daphnia magna D. magna D. magna D. magna	Price et al, 1974 Bringmann & Kühn, 1982 LeBlanc, 1980 Randall & Knopp, 1980 Bringmann & Kühn, 1977	EC ₅₀ (24 hr) = 1,950 mg/l EC ₅₀ (24 hr) = 7,060 mg/l LC ₅₀ (48 hr) > 520 mg/l EC ₅₀ (48 hr) = 5,091 mg/l LC ₅₀ (24 hr) = 8,890 mg/l
4.3	Toxicity to Aquatic Plants e.g. Algae	Microcystis aeruginosa Scenedesmus quadricuada	Bringmann & Kühn, 1978 Bringmann & Kühn, 1980	Toxicity Threshold (8 day) = 120 mg/l Toxicity Threshold (7 day) = 4,300 mg/l
4.4	Toxicity to Microorganisms e.g. bacteria	Chilomonas paramaecium Entosiphon sulcatum Pseudomonas putida	Bringmann et al, 1980 Bringmann & Kühn, 1980 Bringmann & Kühn, 1980	Toxicity Threshold (48hr) = 2,982 mg/l Toxicity Threshold (72hr) = 190 mg/l Toxicity Threshold (16hr) = 1,150 mg/l
4.5.1	Chronic Toxicity to Fish			Data not available
4.5.2	Chronic Toxicity to Aquatic Invertebrates			Data not available
4.6.1	Toxicity to Soil Dwelling Organisms			Data not available
4.6.2	Toxicity to Terrestrial Plants			Data not available
4.6.3	Toxicity to Other Non-Mammalian Terrestrial Species (including Birds)			Data not available

FULL SIDS SUMMARY (Continued)

CAS No: 78-93-3		SPECIES	REFERENCE	RESULTS
TOXICOLOGY				
5.1.1	Acute Oral Toxicity	Rat	see Dossier	LD ₅₀ range = 2600 - 5400 mg/kg
		Rat	Topping, 1994	LD ₅₀ = 3 - 7 ml / kg
		Rat	Smyth, 1962	LD ₅₀ = 6.86 ml / kg
5.1.2	Acute Inhalation Toxicity	Rat	see Dossier	LC ₅₀ (4 hr) = > 5000 ppm
		Rat	Smyth, 1962	LC ₅₀ (8 hr) = 8000 ppm
		Rat	Pozzani, 1959	LC ₅₀ (8 hr) = 7970 ppm
5.1.3	Acute Dermal Toxicity	Mouse	La Belle & Brieger, 1955	LC ₅₀ (4 hr, 14 day) = 11,700 ppm
		Mouse	Zakhari, 1977	LC ₅₀ (45 min) = 69,400 ppm
		Guinea Pig	Patty, 1935	LC ₅₀ = > 10,000 ppm
5.2.1	Skin Irritation	Rabbit	see Dossier	LD ₅₀ = 6.4 - 8.0 g / kg
		Rabbit	Smyth, 1962	LD ₅₀ = 10 g / kg
		Rabbit	Opdyke, 1977	LD ₅₀ = 5 g / kg
5.2.2	Eye Irritation	Rabbit	Panson & Winek, 1980	LD ₅₀ = 13 g / kg
		Rabbit	Weil & Scala, 1971;	Mild - Moderate; 24 hr occluded or unoccluded
		Rabbit	Moreno, 1977	
5.2.3	Respiratory Irritation	Rabbit	Weil & Scala, 1971;	Severe (Draize score - 21/110 at 1 and 4 hr; 39/110 at 1 and 2 days; 21/110 at 7 and 10 days; 12/110 at 14 days)
		Rabbit	Exxon	
		Rabbit	Unpublished	
5.3	Dermal Sensitization	Mouse	DeCeaurriz, 1981	RD ₅₀ = 10,745 ppm
		Guinea Pig	Cannelongo, 1978	Not Sensitizing
		Mouse	Descotes, 1988	Not a contact allergen in ear swelling test
5.4	Repeated Dose Toxicity	Rat inhalation	Cavender, 1983	NOEL = 5000 ppm (6 hr/day, 5days/wk, 13 weeks)

FULL SIDS SUMMARY (Continued)

CAS No: 78-93-3		SPECIES	REFERENCE	RESULTS
TOXICOLOGY (cont.)				
5.5	Genetic Toxicity in Vitro Bacterial Test	Salmonella typhimurium & E. coli	Smirasu, 1976; Shimizu, 1985; Zeiger, 1992	Negative (with and without metabolic activation)
	Non-Bacterial (In Vitro) Test	Mouse Lymphoma Chromosome Aberration Unscheduled DNA Synthesis Morph Transform Assay	see Dossier	Negative (with and without metabolic activation) Negative (with and without metabolic activation)
5.6	Genetic Toxicity in vivo	Micronucleus	O'Donoughue, 1988	Negative (Mouse)
		Micronucleus	Basler, 1986	Negative (Chinese hamsters)
5.7	Carcinogenicity	Mice (male)	Horton, 1965	Negative (50 mg of a 17% MEK solution 2X / week for 1 year)
5.8	Toxicity to Reproduction	Rat	see Dossier	NOEL P generation = 1%; ~ 1500 mg / kg / day NOEL F1 generation = 1%; ~ 1500 mg / kg / day (OECD single generation reproductive toxicity / teratology screen with 2-butanol at 0.3, 1.0, and 3.0 % in water)

FULL SIDS SUMMARY (Continued)

CAS No: 78-93-3		SPECIES	REFERENCE	RESULTS
TOXICOLOGY (cont.)				
5.9	Developmental Toxicity/Teratogenicity	Rat (Inhalation)	Schwetz, 1974	NOEL = 3000 ppm (Maternal) NOEL = none (Fetal)
		Rat (Inhalation)	Deacon, 1981	NOEL = 1000 ppm (Maternal) NOEL = 3000 ppm (Fetal)
		Mouse (Inhalation)	Schwetz, 1991	NOEL = 1000 ppm (Maternal) NOEL = 1000 ppm (Fetal)
5.10	Neurotoxicity	Rat (Inhalation)	Cavender, 1983	No direct neurotoxic effects
		Rat (Inhalation)	Altenkirch, 1978	No direct neurotoxic effects
		Rat (Inhalation)	Saida, 1976	No direct neurotoxic effects
		Rat (Inhalation)	Spencer, 1976	No direct neurotoxic effects
		Cat (i.v.)	Egan, 1980	No direct neurotoxic effects Mild eye irritation at 200 ppm (vapor; 3 - 5 min) No ill effects up to 700 ppm (industrial exposure) No effects in psychomotor tests, sensorimotor tests, or test of mood states at 200 ppm Not irritating, not sensitizing in a 48-hour closed-patch test with 20% MEK in a petrolatum mixture
5.11	Experience with Human Exposure			

1.0 Exposure Assessment

1.1 Production Volumes

The estimated annual production of Methyl Ethyl Ketone (MEK) in the United States is in the order of 620 million pounds. Worldwide, it is estimated that 1940 million pounds are produced annually.

1.2 Major Uses

MEK is widely used as a solvent and as a chemical intermediate. As a solvent, MEK is used in surface coatings, adhesives, inks, traffic marking paint, cleaning fluids, and dewaxing agents.

Its largest use as a solvent is in vinyl lacquers but nitrocellulose lacquers also consume large volumes of MEK. In addition, its use for the solubilization of acrylic coatings also contributes to the overall use of MEK in the surface coatings industry. MEK is also commonly used as a solvent for rubber cements and other natural or synthetic resins for adhesive use. Other important applications are as an extraction medium for fats, oils, waxes and resins, and as an intermediate in the production of antioxidants, perfumes and catalysts. MEK is used by the hard wood pulping industry and in the production of smokeless powder. It is routinely used in printing inks, degreasing and cleaning fluids and as a component of the solvent system used in producing magnetic tape.

1.3 Manufacturing Process

Typically, MEK is manufactured in a totally enclosed continuous process that converts butenes into MEK. A mixed butenes stream is contacted with a circulating sulfuric acid-water mixture. Sufficient water is added to the olefin-acid-water mixture to form Secondary Butyl Alcohol (SBA). The SBA is heated to reaction temperature in a furnace where it is dehydrogenated to MEK and hydrogen. The MEK is then purified to remove water and some heavy ketones. MEK can also be produced via an acetic acid by-product route.

1.4 Distribution

Marine vessels, tank cars (rail cars), and tank trucks are used for shipment to domestic clients. In plant distribution is via pipeline and tank truck.

1.5 Fugitive Emissions

The U.S. Toxic Release Inventory (TRI) reports for MEK were filed by 2,389 facilities in 1995 (reporting emissions data for 1994). The average quantities released to air, water, and land by facilities reporting releases of at least 1 pound were 33,415 pounds, 46 pounds, and 22 pounds, respectively. Air dispersion modeling results for many of the highest emitters

confirm that average annual airborne concentrations beyond facility boundaries typically are below 0.5 ppm. For most facilities, fence line concentrations are expected to be well below that level. Releases to the environment from end use products are mainly to the air as a result of solvent evaporation from coated surfaces.

1.6 Workplace Monitoring

MEK manufacturing plants are continuous, enclosed processes with minimal occupational exposures. Potential exposures can occur during such operations as sample collection, maintenance of equipment, and loading of trucks and/or rail cars. Since MEK is highly volatile, the primary route of occupational exposure is expected to be by inhalation.

Typical 8-hour time weighted average (TWA) exposures to workers in an MEK manufacturing plant are shown below (Table 1). These values will serve as the Estimated Human Exposure (EHE) values for workers.

Table. 1 Typical 8-hour TWA Exposure Data from MEK Manufacturing Plant

Work Group	Geometric Mean
Maintenance	<0.3 ppm
Operations Personnel	0.3 - 1.4 ppm
Loaders	1.7 - 2.0 ppm

The concentrations of MEK to which maintenance workers, operations personnel, and loaders are exposed to, are well below the OSHA and ACGIH 8-hour TWA of 200 parts of contaminant per million parts of air (ppm). Modeling conducted to estimate typical task exposure levels under moderate ventilation indicted a probable average level of around 13 ppm MEK which is well below the OSHA and ACGIH Short-term (15 minute) Exposure Limit (STEL) of 300 ppm for MEK.

The EHE for the work group receiving the greatest exposure level (loaders) is 2.0 ppm. This value is several orders of magnitude below the NOEL's of 5000 ppm for repeated inhalation toxicity and 1000 ppm for maternal and developmental toxicity. Based on MEK's low order of toxicity and low predicted exposure concentrations, MEK can be considered to present a low potential for risk to workers.

2.0 Summary of Environmental Fate and Effects

2.1 Environmental Fate

Methyl ethyl ketone (MEK) is expected to partition primarily to the air (58.7%) and aquatic (41.3%) compartments, based on a level 1 fugacity model. MEK has been shown to biodegrade rapidly in aerobic, aqueous biodegradation tests and therefore, would not be

expected to persist in aquatic habitats. MEK is also not expected to persist in surface soils due to rapid evaporation to the air. In the air, physical degradation will occur due to hydroxyl radical (OH^-) attack.

MEK is expected to volatilize at a moderate rate from water based on a calculated Henry's Law constant of 5.60×10^{-5} atm·m³/mole at 25°C. The calculated half-life for the volatilization of MEK from surface water (1-meter depth) is predicted to range from 16 hours (from a river) to 7.4 days (from a lake). Hydrolysis is not considered a significant degradation process for MEK. However, aerobic biodegradation of MEK has been shown to occur rapidly under non-acclimated conditions, based on a result of 83% biodegradation from a 5-day BOD test. Additional biodegradation data developed using standardized test methods show that MEK is readily biodegradable in both freshwater and saltwater media (69 to 89% biodegradation in 20 days).

MEK will evaporate quickly from soil due to its high vapor pressure (110 hPa at 24°C), and is not expected to partition to the soil, based on a calculated soil adsorption coefficient ($\log K_{oc}$) of 0.58. MEK has the potential to leach through the soil due to its low soil adsorption.

In the air, methyl ethyl ketone is subject to oxidation predominantly by hydroxyl radical attack. The room temperature rate constants determined by several investigators are in good agreement for the reaction of MEK with hydroxyl radicals. The atmospheric half-life is expected to be 128 hours, based on a measured degradation rate of 1.0×10^{-12} cm³/molecule-sec at 27°C, and an OH^- concentration of 1.5×10^6 molecule/cm³, which is a commonly used default value for calculating atmospheric half-lives. Using OH^- concentrations representative of polluted (3×10^6) and pristine (3×10^5) air, the atmospheric half-life of MEK would range from 64 to 642 hours, respectively. Direct photolysis is not expected to be an important transformation process for the degradation of MEK.

2.2 Toxicity to Aquatic Organisms

Although MEK is calculated to partition substantially to the aquatic compartment, it is not expected to present a significant hazard because of its low aquatic toxicity and biodegradable nature. Overall, MEK presents a low potential hazard to aquatic biota.

MEK exhibits low acute and chronic aquatic toxicity based on data from quantitative structure-activity relationships (QSAR). This is confirmed by measured data for several aquatic organisms including fish, invertebrates, algae, and bacteria. Acute toxicity data calculated using the US EPA QSAR computer program, ECOSAR, generally are >1000 mg/l for fresh- and saltwater organisms with the exception of a saltwater fish endpoint of 217 mg/l (Table 2). Results from 24- to 96-hour toxicity studies range from 1,950 to more than 10,000 mg/L for freshwater and saltwater fish and invertebrates.

Table. 2 Calculated Environmental Effect Data

Organism	Duration (days)	Endpoint	Predicted Concentration (mg/l)
Green Algae	4	EC50	> 1,000
	> 4	ChV	43
Daphnid	2	LC50	> 1,000
	16	EC50	50
Fish (freshwater)	4	LC50	> 1,000
	14	LC50	> 1,000
	> 14	ChV	212
Mysid	4	LC50	> 1,000
Fish (saltwater)	4	LC50	217
Worm (terrestrial)	14	LC50	> 1,000

ChV - Chronic Value

Calculated chronic aquatic toxicity for a freshwater fish, invertebrate, and alga using the EPA ECOSAR model are in the range of 43 to 212 mg/l (Table 2). In addition, 16-hour to 7-day toxicity threshold levels (equivalent to 3% inhibition in cell growth) ranging from 190 to 4,300 mg/l have been reported for selected bacteria, algae, and protozoa.

The bioconcentration potential of MEK in aquatic organisms is expected to be low, based on a calculated bioconcentration factor of 0.7 for a freshwater fish, and the low probability of constant, long-term exposures.

2.3 Toxicity to Plants

Toxicity of MEK to aquatic plants is expected to be low based on a 7-day toxicity threshold value of 4,300 mg/L for a freshwater algae (Bringmann and Kühn. 1980).

2.4 Toxicity to Terrestrial Organisms

Although no measured data exist for terrestrial organisms, a calculated endpoint for an earthworm, 14-day LC50, suggests that MEK would exhibit low toxicity to soil dwelling organisms (Table 2).

3.0 Summary of Health Effects

3.1 Acute Toxicity and Primary Irritancy

MEK has a low order of toxicity following single oral, dermal, or inhalation exposure. MEK produces eye irritation and slight skin irritation following contact. MEK has not been shown to produce skin sensitization in animal studies or humans. MEK was ranked as “slightly toxic” based upon a summary of acute lethality studies conducted by the oral and pulmonary

routes (Kennedy and Graepel, 1991). MEK has excellent warning properties with an odor threshold of about 5 ppm (Amoore and Hautala, 1983).

3.2 Effects Resulting from Repeated Exposure

A 90-day inhalation study in rats at 0, 1250, 2500, or 5000 ppm MEK vapor for 6 hr/day, 5 days/week, resulted in no adverse effect on the clinical health or growth of male or female rats except for a depression of mean body weight in the 5000 ppm exposure group with slight but significant increases in liver weight, liver wt./body wt. ratio, and liver wt./brain wt. ratio at necropsy. The liver weight changes are considered to be adaptive changes and do not indicate toxic effects. Special neuropathological and routine pathological studies including examination of reproductive organs did not reveal any lesions that could be attributed to MEK exposure. No toxic effects were observed at 5000 ppm (Cavender et al, 1983).

3.3 Effects on Reproductive Capabilities

A reproductive toxicity study has been conducted on 2-butanol, which can be used as a surrogate for MEK. It has been shown that 2-butanol can be metabolized to MEK, which is subsequently metabolized further.

A single generation reproductive toxicity study with teratology screen of 2-butanol, a metabolite of MEK, was conducted in rats at concentrations of 0.3, 1.0, and 3.0% in drinking water. These animals were treated for eight weeks before mating. The pups were weaned at 21 days. Toxicity was observed in the first generation (F_0) parent rats at 3.0%. Therefore, 2.0% was selected as the highest dose for the second generation study (F_1). Thirty pups per sex per treatment group were selected as the F_1 generation. These rats were treated with either 0.3, 1.0, or 2.0% 2-butanol in the drinking water, since some signs of toxicity were seen in the parental animals at 3.0% 2-butanol. At both the 0.3% and 1.0% level 2-butanol was not toxic in terms of growth and reproduction efficiency; however, at 2.0%, 2-butanol caused a significant depression in growth of weanling rats. The F_1 generation were raised to maturity, mated to produce one set of litters, and sacrificed for gross and microscopic evaluation. Gross and microscopic pathologic findings were negative for the two lower dose levels, being limited to those frequently seen in untreated rat colonies. The 2.0% level resulted in a series of mild changes in the rat kidney which, while not suggestive of overt toxicity, appeared to represent responses to stress. No other findings of note were seen. 2-butanol produced no effects when administered to rats in the drinking water up to the level of 1% (equivalent to approximately 1500 mg/kg/day). The 2% dose level caused effects suggesting mild toxicity and/or stress reactions. There was no observed reproductive toxicity in parental animals. The 2.0% group offspring had a significant depression in growth of weanling rats. 2-Butanol was somewhat fetotoxic at the 2.0% dose level, as shown by decreased mean pup weights. This was a minimal response as shown by the fact that none of the other parameters (nidation, early or late fetal deaths) were detectably affected. Skeletal abnormalities seen in the 2-butanol groups were consistent in type and frequency with the spontaneous incidence observed in this rat colony. There were no significant soft tissue findings in the 2% treated group. All findings with 2-butanol at both 0.3 and 1.0% were negative with respect to signs of toxicity in terms of growth, gross and microscopic

pathological evaluations, and reproductive efficiency. However, at 2.0%, 2-butanol caused a significant depression in the growth of weaning rats. On the basis of this study, 2-butanol produced no effects when administered to rats in the drinking water at concentrations up to 1.0% (approximately 1500 mg/kg/day). The NOEL in this study was 1.0%. The administration of 2.0% 2-butanol produced effects which were suggestive of mild toxicity and/or stress reactions (LOEL = 2.0%). (FDRL, 1975, unpublished report).

3.4 Effects on Developmental Toxicity

Several studies conducted in laboratory animals have investigated the effects of MEK or 2-butanol on fetal development. The overall conclusion from these studies is that MEK produces a low level of developmental delay at maternally toxic levels but is not selectively teratogenic in laboratory animals. MEK was slightly fetotoxic in rats and mice following inhalation exposure of pregnant rats and mice to 3000 ppm.

The developmental toxicity studies were conducted by exposing rats or mice to MEK for 7 hours/day on days 6-15 of gestation (Schwetz et al, 1974; Deacon et al, 1981; Schwetz et al, 1991) and exposing rats to 2-butanol by inhalation to 3500, 5000, or 7000 ppm for 7 hours/day on days 1-19 of gestation (Brightwell et al, 1987).

The first study (Schwetz et al, 1974), conducted in Sprague-Dawley rats exposed to 1000 or 3000 ppm MEK, found no gross, soft tissue, or specific skeletal anomalies which occurred at a significantly increased incidence among litters of dams exposed to 1000 ppm MEK. The total number of litters with fetuses showing skeletal anomalies was significantly increased following exposure to 1000 ppm but not at the 3000 ppm exposure level. There was a statistically significant increase in the total number of gross and soft tissue abnormalities at 3000 ppm. The authors concluded that MEK was embryotoxic, fetotoxic, and potentially teratogenic to rats. No signs of maternal toxicity were seen. However, the incidence of major malformations was low enough to regard the teratogenic effects as questionable.

In a follow-up study to confirm the results seen in the first study, rats were again exposed to MEK by inhalation at concentrations of 400, 1000, or 3000 ppm. A significant decrease in maternal body weight gain was observed in the animals exposed to 3000 ppm MEK. Unlike the initial study, there were no gross or soft tissue malformations at any exposure level; however, the 3000 ppm exposure caused a significant increase in the incidence of delayed skeletal ossifications and an increase in the incidence of extra lumbar ribs. However, the skeletal abnormalities seen in the previous study were not seen in this study. The authors concluded that MEK was not embryotoxic or teratogenic and only slightly fetotoxic in the rat at exposure concentrations of 3000 ppm (Deacon et al, 1981). This study did not confirm the effects observed at the mid-dose only in the earlier study. The maternal and developmental NOELs from this study were 1000 ppm.

A third study reported on the developmental effects of MEK in Swiss mice. Groups of pregnant and nonpregnant mice were exposed to MEK vapor concentrations of 400, 1000, or 3000 ppm for 7 hr/day for 10 consecutive days. There were no differences in sensitivity to MEK exposure between the pregnant and nonpregnant mice. There was indication of

maternal toxicity shown by a concentration-related increase in relative liver and kidney weight, significant in the 3000 ppm dams. A mild concentration-related decrease in fetal body weight was observed for both male and females; however, this was statistically significant only for males at 3000 ppm. There were no statistically significant increases in the number of malformed fetuses per litter, although there were several atypical malformations not often found in control litters. There was a significant trend of increased incidence of misaligned sternebrae at 3000 ppm, a skeletal variation. No developmental or maternal effects were observed at vapor concentrations of 1000 ppm or less. After considering the results from the present study together with results obtained in rats, the authors concluded that MEK vapors caused developmental toxicity and a low incidence of malformations at concentrations that caused maternal toxicity (i.e., 3000 ppm). No maternal or developmental toxicity was observed at concentrations of 1000 ppm MEK or below (Schwetz et al, 1991).

The developmental toxicity of 2-butanol, a known metabolite of MEK was investigated in Sprague-Dawley rats exposed by inhalation to 3500, 5000, or 7000 ppm of 2-butanol. At the highest concentration, maternal toxicity was shown by a reduction of body weight and food consumption. A reduction in mean fetal body weight was observed at the 7000 ppm concentration. There was no increase in the incidence of fetal malformations at any concentration (Brightwell et al, 1987).

The effects of MEK and n-hexane vapors at exposure concentrations of 800 ppm, 1000 to 1500 ppm, and in a 300 ppm MEK:1200 n-hexane mixture were investigated in Wistar rats exposed for 23 hr/day throughout gestation and postnatal development. The pregnancy rate decreased and the number of resorptions increased in a concentration-related manner following exposure to MEK, n-hexane, and the mixture. All treatment groups exposed to the high concentrations had a resorption rate of 50%, and newborn pups in these groups displayed reductions in body weight and increases in the brain-to-body weight ratio that became more severe as the exposures continued during postnatal development relative to control animals. The decrease in body weight was greater for the animals exposed to the MEK:n-hexane mixture than for those exposed to n-hexane alone. Pups exposed for 3 weeks during gestation and 3 weeks postnatally to the MEK:n-hexane mixture failed to show any clinical or histopathological evidence of neurological damage. In contrast, the dams showed distinct evidence of peripheral neuropathy when exposed to the mixture for the same 6 weeks. The adult animals appeared more sensitive to the neurotoxic effects of the MEK:n-hexane mixture than the immature animals. The authors concluded that all of the exposures caused some embryotoxicity and fetotoxicity in the rat; however, there were no teratogenic effects in any of the offspring of exposed animals (Stoltenburg-Didinger et al, 1990).

3.5 Genotoxic Effects

The genotoxic effects of MEK have been examined using several different test systems. With the exception of inducing aneuploidy in yeast, MEK has been consistently negative in genotoxicity studies, both in vitro and in vivo.

MEK and the metabolically related 2-butanol were not mutagenic to the bacteria, *Salmonella typhimurium* and *Escherichia coli*, with or without metabolic activation. They did not induce mitotic gene conversion in the yeast, *Saccharomyces cerevisiae* or cause chromosome damage in mammalian cells (cultured rat liver cells) (Brooks et al, 1988).

MEK, at a concentration of 3.54%, induced chromosomal malsegregation, characterized aneuploidy, in *Saccharomyces cerevisiae* but did not induce mitotic recombinations or point mutations (Zimmermann et al, 1985). However, the protocol involved cold storage on ice for periods up to 17 hours after treatment for 4 hours, and aneuploidy was only observed after incubation on ice. This storage at ice-cold temperature may have been involved in the response. A number of chemicals have been shown to induce aneuploidy, many of which do not induce other detectable genetic effects (e.g., mutation or recombination). Thus, chemically induced chromosomal malsegregation might be the result of damage or alteration to different targets from those leading to mutation (i.e., the primary targets were not DNA or the DNA-metabolizing systems). Microtubules are candidate targets for aneuploidy induction.

Other investigators have reported negative genotoxicity studies of MEK in bacteria (Shimizu et al, 1985; Zeiger et al, 1992).

The clastogenicity of MEK was investigated in the in vivo micronucleus assay by administering 10 mL/kg of MEK to male and female Chinese hamsters (i.p.) and failed to show any mutagenic effect (Basler, 1986).

MEK had no effect in the *Salmonella*/microsome assay, mouse lymphoma assay, BALB/3T3 mouse embryo cell transformation assay, unscheduled DNA synthesis in rat primary hepatocytes, and in the in vivo mouse micronucleus assay (O'Donoghue et al, 1988).

3.6 Neurotoxic Effects

Five studies have assessed the neurotoxic potential of MEK. In four of these studies, MEK was administered by inhalation to rats; in the fifth, MEK was administered by injection to cats. None of these studies indicated that MEK produced nervous system damage.

Several studies assessed the neurotoxic potential of MEK administered to rats by inhalation (Cavender et al, 1983; Altenkirch et al, 1978; Saida et al, 1976; Egan et al, 1980). None of these studies provided any evidence that MEK produced nervous system damage. A study of MEK injected into cats also was negative for neurological effects (Spencer and Schaumburg, 1976).

Rats exposed to either 200 ppm of methyl n-butyl ketone (MnBK) or 2200 ppm of an MEK:MnBK mixture (10:1) for 6 weeks at 8 hr/day, 5 days/week by inhalation suffered clinical and histological evidence of neurological damage (i.e., muscular weakness and histopathological axonal hypertrophy and degeneration in the sciatic nerve, respectively) in both treatment groups (Duckett et al, 1974). This finding led to the hypothesis that MEK may

potentiate the neurotoxicity of other chemicals, including other ketones. Subsequent studies with n-hexane and MnBK support this hypothesis.

Sprague-Dawley rats were simultaneously exposed for 24 hr/day for up to 5 months to concentrations of 1125 ppm MEK, 400 ppm MnBK, or a mixture of 1125 ppm MEK and 225 ppm MnBK. No peripheral neuropathy occurred in the animals treated with MEK alone. Co-exposure to MEK:MnBK caused hind-limb paralysis after 25 days of exposure, compared to 42 days with MnBK alone (Saida et al, 1976).

Male Wistar rats were exposed to either 6,000 ppm MEK, 10,000 ppm of n-hexane, or 10,000 ppm of an MEK:n-hexane mixture (1.1:8.9 ratio) for 8 hr/day, 7 days/week for 15 weeks. The animals exposed to MEK all died of bronchopneumonia during the seventh week, but showed no signs of peripheral neuropathy. The rats co-exposed to MEK and n-hexane developed severe hind limb paralysis after about 5 weeks of exposure, compared to about 9 weeks for those exposed to n-hexane alone (Altenkirch et al, 1978 and 1979). Subsequent studies by the same investigators explored the concentration-response relationship for the MEK-potentiation of n-hexane neuropathy by exposing male Wistar rats to a 500 ppm or 700 ppm mixture of MEK:n-hexane blended at several different ratios. Two continuous exposure regimens were employed: 22 hr/day, 7 days/week for up to 9 weeks, and 8 hr/day, 7 days/week for 40 weeks. All of the animals exposed for 9 weeks survived the treatment. Severe hindlimb paralysis occurred about 1 week earlier in animals co-exposed to the 500 ppm MEK:n-hexane mixture (1:4 and 2:3 ratios) than in animals receiving a 500 ppm n-hexane exposure. The rats exposed to a 700 ppm mixture for 22 hr/day, in contrast, showed no difference in the time to onset relative to n-hexane alone. Rats exposed to the 700 ppm combinations for 8 hr/day failed to show any overt clinical signs of neurotoxicity during the 40 week study (Altenkirch et al, 1982).

Monthly neurophysiological evaluations were performed on rats exposed by inhalation to MEK (200 ppm), n-hexane (100 ppm), and a MEK:n-hexane mixture (300 ppm, 2:1 ratio) for 12 hr/day, 7 days/week for 6 months (Takeuchi et al, 1983). Statistically significant decreases in the motor nerve conduction velocity and mixed nerve conduction velocity were observed after 5 and 6 months of exposure to the MEK:n-hexane mixture. On termination of the study, there were no histopathological abnormalities in the proximal or distal nerves of the tail from any of the solvent-exposed animals. Using previously reported experimental results, the authors reported a concentration-related decrease in the motor nerve conduction velocity occurred with subchronic n-hexane exposures of 100, 200 and 500 ppm and that the effects for the MEK:n-hexane treated rats were more severe than in those rats exposed to 200 ppm of n-hexane.

Although the effects of acute exposures to ketones are well recognized, the effects of chronic exposure are less well understood. Metabolic studies have helped identify the toxic effects of several ketones and explain the lack of effects (e.g., neurotoxicity) of others. When absorbed into the bloodstream ketones may be eliminated unchanged in the expired air, or metabolized by a variety of metabolic pathways (i.e., carbonyl reduction, and -1 oxidation, decarboxylation, and transamination) to secondary alcohols, hydroxy ketones, diketones, and carbon dioxide (Topping et al, 1994). The -diketone metabolite is necessary for the

induction of delayed neuropathy (Spencer and Schaumburg, 1985). MEK is oxidized to 3-hydroxy-2-butanone, and to a lesser extent undergoes reduction to 2-butanol. MEK is also metabolized to 2,3-butanediol. The parent compound and its metabolites are rapidly cleared from the serum within 16 hours (DiVincenzo et al, 1976; Deitz et al, 1981). Although MEK does not form the -diketone metabolite, the potentiation of neurotoxicity induced by other ketones through co-exposure to MEK has been investigated. Under certain circumstances, MEK may also potentiate the liver and renal toxicity of haloalkanes. The mechanism responsible for the MEK-induced potentiation of -diketone neuropathy was studied by examining the toxicity, total neural tissue accumulation, and pharmacokinetics of 2,5-hexanedione following co-administration with MEK to male Fischer 344 rats (Ralston et al, 1985). When MEK and 2,5-hexanedione was given by gavage in a 1:1 ratio 5 days/week for up to 85 days, there was a reduction in time necessary to observe neurobehavioral performance decrements in sensorimotor tasks. This decrement was found to be correlated with higher blood values for 2,5-hexanedione when co-administered with MEK. The reduced blood clearance of 2,5-hexanedione led the authors to conclude that MEK acted by competitively inhibiting 2,5-hexanedione metabolism.

Studies performed in male Wistar rats found that a single 8-hr co-exposure to MEK:n-hexane at concentrations of 2200 ppm (1:10 ratio), 2630 ppm (1:3.2 ratio), or 4000 ppm (1:1 ratio) reduced the urinary excretion of n-hexane metabolites when compared to an exposure to n-hexane alone (Shibata et al, 1990).

Administration of 1.87 mL/kg/day of MEK by oral gavage to male Fischer 344 rats for 1 to 7 days resulted in an increase in total cytochrome P450 content and 7-ethoxycoumarin O-deethylase activity after only a single treatment (Robertson et al, 1989). When the MEK was administered orally for 4 days prior to a single 6 hr inhalation exposure to 1000 ppm n-hexane, there was an increase in the concentration of the metabolites 2,5-hexanedione and 2,5-dimethylfuran in the blood, sciatic nerve, and testis relative to the animals exposed to n-hexane alone. The authors concluded that MEK potentiated the neurotoxicity of n-hexane by inducing the enzymes responsible for the metabolic activation of n-hexane.

O'Donoghue et al (1984) found evidence of metabolic induction and chemical potentiation in male Sprague-Dawley rats administered MEK together with ethyl n-butyl ketone (EnBK) by either the oral or the pulmonary route. The urinary levels of the EnBK metabolites 2,5-heptanedione and 2,4-hexanedione were increased in the animals given 1 g/kg EnBK together with 1.5 g/kg MEK relative to animals given 1 g/kg of EnBK alone. A similar increase in EnBK metabolites was observed in the plasma of rats following inhalation exposure to 1400 or 2100 ppm of the MEK:EnBK mixture (1:1 and 2:1 ratios, respectively) relative to the animals exposed to 700 ppm EnBK. The authors concluded that MEK was capable of potentiating EnBK-induced neurotoxicity by inducing its metabolism to toxicologically active metabolites.

MEK fails to induce a peripheral neuropathy in exposed animals similar to that induced by n-hexane since it does not form -diketone metabolites, such as 2,5-hexanedione (Topping et al, 1994; Spencer and Schaumburg, 1985). Since MEK does not have any direct neurotoxic

effects the NOAEL is determined from the study with the highest concentration which investigated neurotoxicity endpoints (Cavendar et al, 1983), and is 5,000 ppm.

3.7 Carcinogenicity

A one-year dermal application of 50 mg of a 17% MEK solution applied twice per week resulted in no skin tumors in male mice (Horton et al, 1965). No other data are available.

3.8 Human Studies

MEK is readily absorbed and excreted either unchanged in expired air or as glucuronic acid conjugates in the urine. Humans absorbed approximately 75% of inhaled MEK. MEK is reduced to 2-butanol and oxidized to 3-hydroxy-2-butanone, which is reduced to 2,3-butanediol.

A recent study investigated the neurobehavioral effects of acute exposures of human volunteers to MEK, MIBK, or both solvents. Subjects were exposed to 200 ppm MEK, 100 ppm MIBK, or 100 ppm MEK and 50 ppm MIBK for four hours. No effects that could be attributed to chemical exposure were observed in any treatment group in psychomotor tests, sensorimotor tests, or a test of mood states. The authors concluded that exposures to MEK and/or MIBK at these concentrations produced minor sensory and irritant effects only.

4.0 Conclusions

MEK is a high production volume chemical primarily used in commercial and industrial settings and is rarely found in commercial products. The major use of MEK is as a solvent and chemical intermediate. As a solvent, MEK is used in surface coatings, adhesives, inks, traffic marking paints, cleaning fluids, and dewaxing agents. Manufacture of MEK takes place in an enclosed process and transport of the material occurs through enclosed systems or bulk carrier. This condition significantly limits exposure during manufacture and handling. Fence line concentrations are also expected to be negligible.

Based on physical and chemical properties, MEK is an unlikely environmental contaminant. Methyl ethyl ketone is not expected to persist in the environment. Aerobic biodegradation of methyl ethyl ketone occurs rapidly. MEK is not expected to persist in soil due to low soil adsorption and rapid evaporation to air. In the air, methyl ethyl ketone is subject to oxidation by hydroxyl radical attack. MEK has a low order of toxicity to aquatic organisms and plants, and bioconcentration in aquatic organisms is not expected to occur. It undergoes degradation in the atmosphere and in aqueous environments and has a low degree of toxicity to environmental species. MEK may contribute to the formation of photochemical smog.

MEK has been shown to be of a low order of toxicity following acute oral, dermal, and inhalation exposure. Contact with the eyes may produce irritation. MEK has not been shown to produce skin sensitization. No significant signs of toxicity were seen following

repeated inhalation exposure of rats to MEK at high concentrations. MEK and its metabolic surrogate, 2-butanol, do not appear to present significant risk of adverse reproductive or developmental effects. MEK has not been shown to have any neurotoxic potential. Human volunteers exposed to relatively high levels of MEK did not demonstrate significant effects, other than minor irritation and sensory effects.

The information obtained from this database allows for the characterization of toxicity hazard of MEK for both human/mammalian and environmental effects. Taken together, these considerations support the conclusion that MEK is a low priority for further work.

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