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Methyl ethyl ketone (MEK) (CASRN 78-93-3)

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Methyl ethyl ketone (MEK); CASRN 78-93-3

Health assessment information on a chemical substance is included in IRIS only after a comprehensive review of chronic toxicity data by U.S. EPA health scientists from several Program Offices and the Office of Research and Development. The summaries presented in Sections I and II represent a consensus reached in the review process. Background information and explanations of the methods used to derive the values given in IRIS are provided in the Background Documents.

STATUS OF DATA FOR MEK

File First On-Line 01/31/1987

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	on-line	05/01/1993
Inhalation RfC Assessment (I.B.)	on-line	07/01/1992
Carcinogenicity Assessment (II.)	on-line	12/01/1989

_I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

_I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name -- Substance Name -- Methyl ethyl ketone (MEK)
CASRN -- 78-93-3
Last Revised -- 05/01/1993

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg-day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of substances that are also carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

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__I.A.1. Oral RfD Summary

Critical Effect	Experimental Doses*	UF	MF	RfD
Decreased fetal birth weight	NOAEL: 1771 mg/kg-day (1% 2-butanol solution)	3000	1	6E-1 mg/kg-day
Multigeneration/ Developmental Rat Feeding Study	LOAEL: 3122 mg/kg-day (2% 2-butanol solution)			

Cox et al., 1975

*Conversion Factors and Assumptions: Based on actual consumption data for the NOAEL and regression analysis for the LOAEL of exposure to 2-butanol, a metabolic intermediate of methyl ethyl ketone.

__I.A.2. Principal and Supporting Studies (Oral RfD)

Cox, G.E., D.E. Bailey and K. Morgareidge. 1975. Toxicity studies in rats with 2-butanol including growth, reproduction and teratologic observations. Food and Drug Research Laboratories, Inc., Waverly, NY, Report No. 91MR R 1673.

The identification of the critical effect for methyl ethyl ketone (MEK), also referred to as 2-butanone, is based on its metabolic intermediate, 2- butanol. A detailed rationale for use of this intermediate of MEK can be found in Additional Comments/Studies.

Weanling FDRL-Wistar stock rats (30/sex/group) were given 2-butanol in drinking water at 0, 0.3, 1.0, or 3.0% solutions and a standard laboratory ration ad libitum. Weekly feed, fluid intakes and body weights were recorded to determine the efficiency of food utilization and to calculate the average daily intake of 2-butanol. The average daily intake of 2-butanol for males was 0, 538, 1644, and 5089 mg/kg-day and for females was 0, 594, 1771, and 4571 mg/kg-day for the 0, 0.3, 1.0, and 3.0% solutions, respectively. At the highest exposure level (3.0%), net weight gain was reduced compared with controls both in males (229 g vs. 269 g in controls) and females (130 g vs. 154 g in controls) during the 8 weeks of initial monitoring. However, no differences were found in the efficiency of food utilization.

After 9 weeks of exposure, parental matings were made with one male and one female from each of the respective treatment groups (P generation). Following birth of the first litter (F1A) of the parental generation, various reproduction and lactation responses were measured. This study design incorporated a multigeneration protocol with measurement of developmental toxicity endpoints. Significant effects were noted in the litters from the 3.0% 2-butanol dose group vs. the control group, including the number of pups/litter cast alive (8.46 vs. 10.3), the number of pups/litter alive at 4 days before culling (8.12 vs. 10.3), the number of pups/litter alive at 21 days (6.85 vs. 7.68), the mean body weight/pup after culling at 4 days (8.2 g vs. 10.3 g) and the mean body weight/pup at 21 days (28.4 g vs. 49.5 g).

Based on results found in the 3.0% (high-dose) 2-butanol F1A generation, the treatment of all high-dose parents and offspring was reduced to 2.0% 2- butanol for the remainder of the experimental protocol. Following a 2-week interim adaptation period to allow the F1A generation animals to attain a more normal weight, the P generation was subsequently remated to produce a second litter (F1B), and the F1A generation selected for an F2 mating. Therefore, a new high dose of 2.0% 2-butanol was calculated to be equivalent to 3384 mg/kg- day in males and 3122 mg/kg-day in females based on regression analysis of the 8 week water intake data. The F1B litters receiving 2.0% 2-butanol showed a slight reduction in average fetal weight compared with controls (3.74 g vs. 4.14 g in controls). Nidation, early fetal deaths, and late fetal deaths were not detectably affected. Skeletal findings also were reported for the F1B generation. The 2.0% group showed apparent increases in missing sternebrae, wavy ribs, and incomplete vertebrae ossification when compared with both the 0.3 and 1.0% groups. However, because of the rather high incidence in the control group for these

findings, these effects could not be determined to be compound-related. The 2.0% group also showed a reduction in the mean body weight per pup at day 4 following culling (9.48 g vs. 10.0 g in the control) and in the mean body weight at 21 days (34.9 vs. 41.1 g in the control). Although these reductions were not as great in the high dose (3.0%) F1A generation, the percent body weight reduction in the F1B high dose (2.0%) was doubled at 21 days (reductions of 5% at 4 days and 11% at 21 days). This generation showed the same doubling trend in fetal weight reduction as was reported in the F1A group exposed to 3.0% 2-butanol throughout (reductions of 21% at 4 days and 43% at 21 days). These results are also presented in abstract form by Gallo et al. (1977).

At the 2.0% level of the F2 generation, there were a number of histopathologic changes noted in the kidney of the male rats only. These changes were characterized by nonreactive tubular degeneration in the outer medullary zone, tubular cast formation, foci of tubular degeneration and regeneration, microcysts in the renal papilla, glomerular fibrosis, and focal epithelial calcification. These findings are consistent with the pattern of early stages of alpha 2u-globulin-associated rat nephrotoxicity as set forth by the Risk Assessment Forum (U.S. EPA, 1991). As per the Agency's guidance, it is not appropriate to use these specie-and sex-specific renal effects to establish a critical effect.

Administration of 2-butanol resulted in the occurrence of developmental effects. Decreased pup survivability and fetal weight were seen in the 3.0% group, and in the F1 offspring (F1A and F1B, whose parents received 3.05 and 2.0% 2-butanol, respectively). The decrease in fetal weight continued to be demonstrated in the F2 generation at the 2.0% level. Therefore, based on these developmental toxicologic endpoints, a LOAEL of 3122 mg/kg-day (2.0% solution) and a NOAEL of 1771 mg/kg-day (1.0% solution) are identified.

__I.A.3. Uncertainty and Modifying Factors (Oral RfD)

UF -- Four uncertainty factors of 10 each were applied, one to account for interspecies extrapolation and intraspecies variability (extrapolation to sensitive human populations); one to adjust for subchronic to chronic extrapolation since long-term effects in the dams during the exposure period were not reported in the principal study; one for incompleteness of the data base, including a lack of both subchronic and chronic oral exposure studies for MEK; and one to account for the absence of data for a second rodent specie for either MEK or 2-butanol. As is usual practice, the application of four full areas of uncertainty generally results in a total uncertainty factor of 3000, given the interrelationship among and overlap between the various areas of uncertainty described above.

MF -- None

__I.A.4. Additional Studies/Comments (Oral RfD)

Data on toxic effects in humans or laboratory animals following oral exposure to MEK are restricted to a limited number of acute studies. Oral LD50 values for MEK include 5522 and 2737 mg/kg in rats (Smyth et al., 1962 and Kimura et al., 1971, respectively) and 4,044 mg/kg in mice (Tanii et al., 1986). Single gavage doses of 15 mmol/kg MEK in corn oil (1082 mg/kg) produced no deaths or histological alterations in the livers of male Fischer 344 rats, but produced tubular necrosis in kidneys (Brown and Hewitt, 1984). Pre-administration of single gavage doses of MEK (or other ketonic solvents) enhanced the liver and kidney damage produced by a 0.5 mL/kg intraperitoneal dose of carbon tetrachloride (Brown and Hewitt, 1984). This MEK potentiation of carbon tetrachloride hepatotoxicity was also observed in similar experiments with male Sprague-Dawley rats (Dietz and Traiger, 1979).

At present there are insufficient oral exposure data of MEK from which to derive an oral RfD. Availability of oral exposure data of a metabolic intermediate of MEK, i.e., 2-butanol, was used to derive the RfD of MEK. The following is an explanation of the rationale for using the oral data of 2- butanol rather than attempting a route-to-route extrapolation of the available inhalation data for MEK.

Traiger and Bruckner (1976) have estimated that approximately 96% of an administered dose of 2-butanol is oxidized in vivo to MEK. The data from the Dietz et al. (1981) study support this estimation. Administration of 1776 mg/kg 2-butanol by gavage shows peak blood 2-butanol concentrations (0.59 mg/mL) within 2 hours; the compound is barely detectable after 16 hours. As the blood concentrations of 2-butanol fall, the peak concentrations of MEK (0.78 mg/mL) and 2,3-butanediol (0.21 mg/mL) occurred at 8 and 18 hours respectively. Ultimately, 2-butanol and MEK are metabolized through the same intermediates.

Additional metabolism of the ketone occurs by oxidation to hydroxylated intermediates such as 2,3-butanediol, all of which can be eliminated in the urine (DiVincenzo et al., 1977). DiVincenzo et al. (1976) have previously identified MEK, 2-butanol, and other oxidative metabolites of MEK in the serum of guinea pigs following administration of MEK.

A pharmacokinetic model was presented by Dietz et al. (1981) to describe the biotransformation of 2-butanol and MEK in rats when given a dose calculated to produce an equivalent calculated adjusted urinary concentration. When MEK is administered by gavage at a dose of 1690 mg/kg, the detection of the formation of 2-butanol and the oxidative metabolites corresponds to that previously reported in the guinea pig. By 18 hours post administration, MEK is barely detectable in the blood (peak concentration of 0.95 mg/mL at 4 hours), but a peak blood concentration (0.26 mg/mL) of the oxidative metabolite 2,3-butanediol can be detected. Peak blood concentrations of 2- butanol (0.033 mg/mL) occurred after 6 hours.

Although it is not known if the effects reported by Cox et al. (1975) are due to either 2-butanol directly or indirectly through another common metabolite, the weight of evidence of the available data argues for using the butanol data as a surrogate approach to the development of the RfD for MEK. It is assumed in this surrogate approach that 2-butanol is not the active metabolite causing the effects reported by Cox, given the profile of metabolism for both 2-butanol and MEK. Therefore, it is appropriate to utilize data from the oral administration of 2-butanol in order to derive an RfD for MEK in lieu of appropriate oral data for MEK.

Decreased fetal body weight was also reported in pregnant mice exposed by inhalation to 0, 398, 1010, or 3020 ppm MEK (0, 1174, 2978, or 8906 mg/cu.m, respectively, assuming 25 C and 760 mm Hg) 7 hours/day during gestational days 6-15 (Schwetz et al., 1991; Mast et al., 1989). The only maternal effect observed was a concentration-related increase in relative liver and kidney weight. The difference was statistically significant in the dams exposed to 3020 ppm MEK. The biologic significance of this increase has not been ascertained. The decrease in fetal body weight was observed in the 3020-ppm group, however the difference was statistically significant only in the males. There was a statistically significant ($p<0.05$) trend with increasing concentration in the incidence of fetuses with misaligned sternebrae, but this trend was not apparent in the incidence of litters with misaligned sternebrae. Although increased incidence of fetuses and litters with malformations were observed in exposed groups compared with controls, the increases were not statistically significant. The observed fetal malformations (cleft palate, fused ribs, missing vertebrae and syndactyly) present in the exposed groups were not observed in concurrent or contemporary control groups of the same strain of mice. The Schwetz et al. (1991) study identified a NOAEL of 1126 ppm and a LOAEL of 3020 ppm for the occurrence of significant, developmental effects in mice including a decrease in fetal body weight, thereby corroborating the effects observed by Cox et al. (1975).

Sprague-Dawley rats were exposed to 0, 1126, or 2618 ppm MEK (0, 3320, or 7720 mg/cu.m, respectively, assuming 25 C and 760 mm Hg) 7 hours/day during gestational days 6-15 (Schwetz et al., 1974). The following endpoints were used to assess exposure-related effects: maternal (body weight, food intake, liver weight, SGOT levels, number of implantations/litter size) and fetal (examination for anomalies, incidence of fetal resorptions, fetal body measurements). No maternal effects or effect on the incidence of fetal resorptions were observed. A decrease in fetal body weight and crown-rump length were observed in the 1126 ppm offspring, however, these effects were not observed in the offspring of the rats exposed to 2618 ppm. There were no gross, soft tissue, or specific skeletal anomalies that occurred at a significantly increased incidence among litters of dams exposed to 1126 ppm MEK. However, the

total number of litters containing fetuses with anomalous skeletons was significantly increased compared with controls. In the fetuses of the 2618-ppm group, there was a significantly increased number of fetuses and litters having gross anomalies (two acaudate fetuses with an imperforate anus and 2 brachygnathous fetuses). No single soft tissue anomaly occurred at a statistically significant increased incidence, but the total number of litters containing fetuses with soft tissue anomalies was significantly greater than in controls.

Groups of 25 pregnant Sprague-Dawley rats were exposed to 0, 412, 1002, or 3005 ppm MEK (0, 1215, 2956, or 8861 mg/cu.m, respectively, assuming 25 C and 760 mm Hg) 7 hours/day during gestational days 6-15 (Deacon et al., 1981). Decreased maternal body weight gain and increased water consumption were observed in the 3005 ppm group. No other maternal effects were noted. No statistically significant differences in the incidence of external or soft- tissue alterations were observed among exposed fetuses. A significant decrease in the incidence of delayed ossification of interparietal bones of the skull and an increase in the incidence of extra lumbar ribs and in the occurrence of delayed ossification of cervical centra were noted at the 3005-ppm exposure level.

Data for humans and rats support the assumption that approximately 50% of inhaled MEK is absorbed. From measurements of environmental and exhaled air concentrations, Perbellini et al. (1984) calculated pulmonary retentions of about 70% in workers exposed to concentrations less than 300 ppm for 4 hours (most of the measurements were made at environmental concentrations at or below 100 ppm). From similar measurements, Liira et al. (1988) calculated a pulmonary retention of about 53% for male human volunteers exposed to 200 ppm for 4 hours. Kessler et al. (1988) reported a pulmonary retention of 40% for rats exposed to concentrations less than or equal to 180 ppm for up to about 14 hours.

Although a route-to-route extrapolation could be attempted from the inhalation data, a number of assumptions would need to be made with regard to the inhalation and oral absorption efficiencies making a route-to-route extrapolation limited at best. The developmental effects of MEK inhalation exposure are consistent with the developmental effects seen following oral exposure to 2-butanol and therefore make such an exercise plausible. However, the calculation of an inhalation absorption efficiency for MEK is problematic. The pulmonary retention values discussed above are calculated for exposures of 200 ppm (Liira et al., 1988) and 300 ppm (Perbellini et al., 1984) for a limited 4-hour exposure in humans. The pulmonary retention data of Kessler et al. (1988) using rats, although for a longer period of time (14 hours), was at a maximum concentration of 180 ppm. The calculation of the 40% pulmonary retention value is dependent upon a low concentration that is not limited by metabolic capacity but by transport to the metabolizing enzymes. This retention value, therefore, is valid only if related to normal physiologic processes. Inhalation effects of MEK are seen at concentrations an order of magnitude greater than was used to calculate the rat pulmonary retention value. The toxicity of MEK may be a result of challenges made to a saturable enzymatic detoxification mechanism. Therefore, it cannot be assumed that the pulmonary retention value will be the same at exposures of less than 180 ppm or at greater than 1800 ppm. For this reason, it is inappropriate to estimate the pulmonary retention value at these effect levels, thereby precluding derivation of an oral RfD based upon extrapolation from inhalation effects.

__I.A.5. Confidence in the Oral RfD

Study -- Low
Database -- Low
RfD -- Low

Confidence in the principal study is low. The multigeneration/ developmental study for 2-butanol defined a critical effect that is corroborated by inhalation exposure data. Although the study employed an adequate number of animals and examined appropriate endpoints, lowering the high-dose group from 3.0 to 2.0% confounded determination of the critical effect. Confidence in the data base is low. This RfD is based on a multigeneration developmental study for a compound that is nearly completely converted to MEK in a short period of time. This compound exhibits similar developmental effects as seen by inhalation exposure to MEK. However, the lack of oral data for MEK itself and the absence of data in a second specie precludes

any higher level for data base confidence. This assessment for MEK is based upon the strength of data supporting the use of the 2-butanol multigeneration study and the concurrence of developmental effects for inhalation exposure to MEK and assumes that 2-butanol was not responsible for the fetal toxicity. There is a lack of data on the metabolism of 2-butanol and MEK over time thereby decreasing the confidence in the use of this surrogate approach. Therefore, confidence in the RfD is low.

__I.A.6. EPA Documentation and Review of the Oral RfD

Source Document -- This risk assessment is not presented in any existing U.S. EPA document.

Other EPA Documentation -- U.S. EPA, 1984, 1985

Agency Work Group Review -- 06/24/1985, 07/08/1985, 05/16/1990, 07/17/1991, 09/23/1992, 11/05/1992

Verification Date -- 11/05/1992

__I.A.7. EPA Contacts (Oral RfD)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (301)345-2870 (phone), (301)345-2876 (FAX) or Hotline.IRIS@epamail.epa.gov (internet address).

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_I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name -- Methyl ethyl ketone (MEK)
CASRN -- 78-93-3
Last Revised -- 07/01/1992

The inhalation Reference Concentration (RfC) is analogous to the oral RfD and is likewise based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. The inhalation RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extrarespiratory effects). It is expressed in units of mg/cu.m. In general, the RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily inhalation exposure of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Inhalation RfCs were derived according to the Interim Methods for Development of Inhalation Reference Doses (EPA/600/8-88/066F August 1989) and subsequently, according to Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (EPA/600/8-90/066F October 1994). RfCs can also be derived for the noncarcinogenic health effects of substances that are carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

__I.B.1. Inhalation RfC Summary

Critical Effect	Exposures*	UF	MF	RfC
Decreased fetal birth weight Mouse Developmental Study	NOAEL: 2978 mg/cu.m (1010 ppm, nominal) NOAEL(ADJ): 2978 mg/cu.m NOAEL(HEC): 2978 mg/cu.m LOAEL: 8906 mg/cu.m (3020 ppm, nominal)	1000	3	1E+0 mg/cu.m

Schwetz et al., 1991;	LOAEL(ADJ): 8906 mg/cu.m
Mast et al., 1989	LOAEL(HEC): 8906 mg/cu.m

*Conversion Factors: MW = 72.1 Assuming 25 C and 760 mm Hg. NOAEL (mg/cu.m) = 1010 ppm x 72.1/24.45 = 2978 mg/cu.m. Currently, the approach for dose- response analysis of developmental endpoints does not duration-adjust exposure concentrations. NOAEL(ADJ) = NOAEL = 2978 mg/cu.m. The NOAEL(HEC) was calculated for a gas:extrarespiratory effect assuming periodicity was attained. Since the b:a lambda values are unknown for the experimental animal species (a) and human (h), a default value of 1.0 is used for this ratio. NOAEL(HEC) = NOAEL(ADJ) x (b:a lambda(a)/b:a lambda(h)) = 2978 mg/cu.m.

__I.B.2. Principal and Supporting Studies (Inhalation RfC)

Schwetz, B.A., T.J. Mast, R.J. Weigel, J.A. Dill and R.E. Morrissey. 1991. Developmental toxicity of inhaled methyl ethyl ketone in mice. Fund. Appl. Toxicol. 16: 742-748.

Mast, T.J., J.A. Dill, J.J. Evanoff, R.L. Rommereim, R.J. Weigel and R.B. Westerberg. 1989. Inhalation developmental toxicology studies: Teratology study of methyl ethyl ketone in mice. Final Report. Prepared by Pacific Northwest Laboratory, Battelle Memorial Institute, for the National Toxicology Program, Washington, DC. PNL-6833 UC-408.

Pregnant Swiss mice were exposed to 0, 398, 1010 or 3020 ppm methyl ethyl ketone (0, 1174, 2978 or 8906 mg/cu.m, respectively, assuming 25 C and 760 mm Hg) 7 hours/day during gestational days 6-15. The Schwetz et al. (1991) and the Mast et al. (1989) reports are the same developmental mouse study presented in different formats and are hence considered as one single study. The number of dams exposed to methyl ethyl ketone ranged from 23-28 mice depending upon exposure group. The dams were killed on gestational day 18. The only maternal effect observed was a concentration-related increase in relative liver and kidney weight. The difference was statistically significant only in the dams exposed to 3020 ppm methyl ethyl ketone. The biological significance of this increase has not been ascertained. A decrease in fetal body weight was also observed in the 3020 ppm exposed group; however, the difference was significant only in the males. There was a significant ($p<0.05$) trend in the incidence of misaligned sternebrae present in fetuses but not reflected in a similar analysis of litters of the animals exposed to 3020 ppm. Additionally, although no significant increase of any single malformation was found, there were several malformations (cleft palate, fused ribs, missing vertebrae and syndactyly) present at low incidences in exposed groups.

Neither maternal nor developmental toxicity was observed at exposures at or less than 1010 ppm (2978 mg/cu.m). At 3020 ppm (8906 mg/cu.m), an equivocal maternal effect was reported; however, mild developmental effects (decreased fetal body weight and misaligned sternebrae) were found. Based on the absence of both maternal and developmental toxic effects, a NOAEL of 1126 ppm (HEC=2978 mg/cu.m) is established. The LOAEL is established at 3020 ppm (HEC=8906 mg/cu.m) based on the appearance of mild, but significant developmental effects.

Groups of 21-23 pregnant Sprague-Dawley rats were exposed to 0, 1126 or 2618 ppm methyl ethyl ketone (0, 3320 or 7720 mg/cu.m, respectively, assuming 25 C and 760 mm Hg) 7 hours/day during gestational days 6-15 (Schwetz et al., 1974). The following endpoints were used to assess exposure-related effects: maternal body weight, food intake, liver weight, SGOT levels, and number of implantations/litter size; and fetal anomalies, incidence of resorptions, and fetal body measurements.

No maternal effects or effects on the incidence of fetal resorptions were observed. A decrease in fetal body weight and crown-to-rump length was observed in the offspring exposed to 1126 ppm; however, these effects were not observed in the offspring of the rats exposed to 2618 ppm There were no gross, soft tissue or specific skeletal anomalies that occurred at a significantly increased incidence among litters of dams exposed to 1126 ppm methyl ethyl ketone. However, the total number of litters containing fetuses with anomalous skeletons was increased significantly compared to controls. In the fetuses exposed to 2618 ppm methyl ethyl ketone, there was a significantly increased number of fetuses and litters having gross anomalies (two

acaudate fetuses with an imperforate anus and two brachygnathous fetuses) compared to the incidence among controls. No single soft tissue anomaly occurred at a statistically significant increased incidence, but the total number of litters containing fetuses with soft tissue anomalies was significantly greater than in controls.

The study by Deacon et al. (1981) was conducted to determine the repeatability of the fetotoxic effects observed in the Schwetz et al. (1974) study. Groups of 25 pregnant Sprague-Dawley rats were exposed to 0, 412, 1002 or 3005 ppm methyl ethyl ketone (0, 1215, 2955 or 8861 mg/cu.m, respectively, assuming 25 C and 760 mm Hg) 7 hours/day during gestational days 6-15. Decreased maternal body weight gain and increased water consumption were observed in the group exposed to 3005 ppm. No other maternal effects were noted. No statistically significant differences in the incidence of external or soft-tissue alterations were observed among exposed fetuses. A significant decrease in the incidence of delayed ossification of interparietal bones of the skull and an increase in the incidence of extra lumbar ribs and in the occurrence of delayed ossification of cervical centra were noted at the 3005 ppm exposure level.

__I.B.3. Uncertainty and Modifying Factors (Inhalation RfC)

UF -- An uncertainty factor of 1000 reflects factors of 10 to account for interspecies extrapolation, sensitive individuals, and incomplete data base including a lack of chronic and reproductive toxicity studies.

MF -- A modifying factor of 3 was used to address the lack of unequivocal data for respiratory tract (portal-of-entry) effects.

__I.B.4. Additional Studies/Comments (Inhalation RfC)

Slight nose and throat irritation was observed in 10 human volunteers exposed to 100 ppm methyl ethyl ketone (HEC=295 mg/cu.m) for 5 minutes. Exposure to 300 ppm (HEC=885 mg/cu.m) was judged to be intolerable by the subjects (Nelson et al., 1943).

Male and female volunteers (12-13/sex) were exposed to 186 ppm (HEC=549 mg/cu.m, assuming 25 C and 760 mm Hg) for 4 hours. No statistically significant changes in neurobehavioral performance were observed (Dick et al., 1988).

Groups of male and female Fischer 344 rats (n=15) were exposed to 0, 1254, 2518 or 5041 ppm methyl ethyl ketone (0, 3698, 7425 or 14,865 mg/cu.m, respectively, assuming 25 C and 760 mm Hg) 6 hours/day, 5 days/week for 90 days (Cavender et al., 1983; Toxigenics, 1981). For each exposure group, 10 animals were used for general histopathology and 5 animals for neuropathologic examination. Tissues examined included nasal cavity, trachea and bronchi, lung, liver and kidney. The prevalence of chronic respiratory disease in the pulmonary region was 100% across control and all exposure groups. There were also high prevalences of nasal inflammation, including submucosal lymphocytic infiltration and lumenal exudate, across control and all exposure groups. These latter lesions, however, varied slightly across the nasal cavity section examined and with exposure level tested. Although the authors suggest that the pulmonary lesions are secondary to mycoplasma infection, no infectious agent was cultured. In other investigations utilizing a model for Mycoplasma pulmonis, pulmonary lesions showed a concentration-response indicative of upper airway irritation (Broderson et al., 1976). The high prevalences of both the nasal and pulmonary lesions in this study preclude unequivocal interpretation regarding respiratory effects. No histopathologic alterations of other major tissues or of neuropathology were observed. An increase in absolute and relative liver weight and relative kidney weight was observed in the animals of both sexes exposed to 5041 ppm. An increase in serum alkaline phosphatase levels was also observed in the female rats exposed to 5041 ppm methyl ethyl ketone. At the highest concentration, females were found to have decreased absolute and increased relative brain weight, however, no pathological changes were observed in the medulla oblongata or the sciatic and tibial nerves. No functional tests (pulmonary or neurologic) were performed in these studies. Based on toxicity remote to the respiratory tract described above, this study provisionally identifies a NOAEL of 2518 ppm (HEC=1326 mg/cu.m) and a LOAEL of 5041 ppm (HEC=2654 mg/cu.m).

Groups of 5 male Wistar rats were exposed to 10,000 ppm methyl ethyl ketone (29,489 mg/cu.m, assuming 25 C and 760 mm Hg) 8 hours/day, 7 days/week for 15 weeks. Because of severe upper respiratory tract irritation, the concentration was lowered to 6000 ppm (17,693 mg/cu.m). The exposed rats died after 7 weeks of exposure; the cause of death was bronchopneumonia. Severe hindlimb weakness was observed in all animals given a methyl ethyl ketone/n- hexane mixture by the 9th week of exposure, which progressed to severe paresis. These effects were observed again when the experiment was repeated. However, these effects were not observed when methyl ethyl ketone was administered alone (Altenkirch et al., 1978).

A group of 25 adult rats (strain not given) was exposed to 235 ppm (693 mg/cu.m) 7 hours/day, 5 days/week for 12 weeks (LaBelle and Brieger, 1955). The dose duration-adjusted concentration is equivalent to 144 mg/cu.m. A control group was included, but the number of animals was not given. At the end of the study, 15 rats were examined microscopically (organs not given) and hematologically (hemoglobin, erythrocyte, leukocyte, neutrophil, lymphocyte, and monocyte counts). The remaining 10 rats were reserved for growth studies. No adverse effects were observed, but only a few critical parameters were measured for a single exposure concentration. Similarly, 15 guinea pigs were exposed to methyl ethyl ketone at the same concentration as were the rats. No adverse effects were reported for the exposed guinea pigs. However, this information is only presented qualitatively in the report. Furthermore, it was reported that the guinea pigs experienced a vitamin deficiency possibly contributing to two deaths during the exposure period.

Male Wistar rats (8/group) were exposed to 0 or 200 ppm methyl ethyl ketone (0 or 590 mg/cu.m, assuming 25 C and 760 mm Hg) 12 hours/day, 7 days/week for 24 weeks. A slight increase in motor nerve conduction velocity and mixed nerve conduction velocity and a decrease in distal motor latency were observed at 4 weeks of exposure. However, no difference was observed after 4 weeks [NOEL(HEC)=295 mg/cu.m] (Takeuchi et al., 1983).

Groups of 12 Sprague-Dawley rats were continuously exposed to 1125 ppm methyl ethyl ketone (3318 mg/cu.m, assuming 25 C and 760 mm Hg) for 16-55 days. Pathological examination of the sciatic nerve and intrinsic foot muscles revealed no peripheral neuropathy [NOEL(HEC)=3318 mg/cu.m] (Saida et al., 1976).

Four baboons were exposed to 100 ppm methyl ethyl ketone (295 mg/cu.m, assuming 25 C and 760 mm Hg) continuously for 7 days. Operant conditioning behavior conducted during exposure was compared to pre-exposure test scores. The operant behavior selected was a match-to-sample discrimination task and the experimental protocol allowed the performance of each baboon during exposure to be compared to his performances during a clean air exposure in the same chamber immediately prior to each exposure. There was no significant effect on accuracy; however, there was a decrease in mean response time and response during delay (Geller et al., 1979). The authors (Geller et al., 1979) suggested that this could be an early manifestation of the incoordination and narcosis observed in guinea pigs after acute exposure to 10,000 ppm methyl ethyl ketone (29,489 mg/cu.m, assuming 25 C and 760 mm Hg) (Patty et al., 1935). However, it should be pointed out that each baboon in this study was exposed to four different chemicals of which methyl ethyl ketone was given second.

Swiss mice were exposed to various levels of methyl ethyl ketone. A decrease in the immobility developed in a behavioral despair swimming test was observed. A 50% decrease in immobility (ID50) was observed at 2065 ppm (6089 mg/cu.m, assuming 25 C and 760 mm Hg) (DeCeaurriz et al., 1983).

Although the role of methyl ethyl ketone in potentiating peripheral neuropathies caused by potent neurotoxins such as hexane and methyl n- butylketone is documented (Altenkirch et al., 1978; Saida et al., 1976), current experimental data indicate that, by itself, methyl ethyl ketone has little if any neurotoxic potential. Several studies examining neurotoxicity of methyl ethyl ketone have employed neurohistopathology to evaluate toxicity. No peripheral neurohistopathological changes were noted in rats exposed continuously to 1125 ppm methyl ethyl ketone for up to 5 months (Saida et al., 1976). No treatment-related central or peripheral neurohistopathology was observed in rats exposed for 90 days (6 hours/day, 5 days/week) to methyl ethyl

ketone concentrations up to 5041 ppm (Toxigenics, 1981; also reported in Cavender et al., 1983). In a study combining experiments of methyl ethyl ketone and n-hexane, Altenkirch et al. (1978) reported that all 10 male rats exposed to 6000 ppm methyl ethyl ketone (8 hours/day, 7 days/week) died in the 7th week without neurological symptoms or pathology although central and extensive peripheral neurohistopathology was observed in animals concurrently exposed to n-hexane. The authors also reported that animals in all exposure groups (both methyl ethyl ketone and hexane) were somnolent during exposure. A few studies have attempted to examine neurological deficits through functional testing in addition to histopathology. Takeuchi et al. (1983) reported an alteration in nerve conduction velocities but only in the 4th week of a 24-week exposure to 200 ppm methyl ethyl ketone; the alteration was not corroborated by histopathology and was in the opposite direction to that predicted by peripheral neurotoxins such as n-hexane. Results from other functional-deficit studies in humans (Dick et al., 1988) have been negative and in baboons (Geller et al., 1979), inconclusive, perhaps due to experimental design problems. At present, there is no convincing experimental evidence that methyl ethyl ketone, by itself, is neurotoxic to either experimental animals or humans other than possibly inducing CNS depression at high exposure levels.

__I.B.5. Confidence in the Inhalation RfC

Study -- Medium
Database -- Low
RfC -- Low

Confidence in the principal study is medium. This and other developmental studies were well-designed and tested several exposure concentrations and several endpoints of toxicity. Although the principal and supporting studies corroborate an effect level for developmental toxicity endpoints, there are insufficient data presented for possible respiratory effects. Confidence in the data base is low. There are no multigenerational studies and only one subchronic study. Furthermore, these studies do not adequately address portal-of-entry effects given that short-term exposure to higher concentrations than that established for the LOAEL cause nasal and throat irritation in both human and experimental animal species. Reflecting medium confidence in the principal study and low confidence in the data base, confidence in the RfC is low.

__I.B.6. EPA Documentation and Review of the Inhalation RfC

Source Document -- This is not presented in any existing U.S. EPA document

Other EPA Documentation -- None

Agency Work Group Review -- 04/21/1988, 05/26/1988, 03/22/1990, 05/16/1990, 07/17/1991

Verification Date -- 07/17/1991

__I.B.7. EPA Contacts (Inhalation RfC)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (301)345-2870 (phone), (301)345-2876 (FAX) or Hotline.IRIS@epamail.epa.gov (internet address).

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_II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name -- Methyl ethyl ketone (MEK)
CASRN -- 78-93-3
Last Revised -- 12/01/1989

Section II provides information on three aspects of the carcinogenic assessment for the substance in question; the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure and from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in The Risk Assessment Guidelines of 1986 (EPA/600/8-87/045) and in the IRIS Background Document. IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment also utilize those Guidelines where indicated (Federal Register 61(79):17960-18011, April 23, 1996). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

_II.A. Evidence for Human Carcinogenicity

__II.A.1. Weight-of-Evidence Characterization

Classification -- D; not classifiable as to human carcinogenicity

Basis -- Based on no human carcinogenicity data and inadequate animal data.

__II.A.2. Human Carcinogenicity Data

None.

__II.A.3. Animal Carcinogenicity Data

Inadequate. No data were available to assess the carcinogenic potential of methyl ethyl ketone by the oral or inhalation routes. In a skin carcinogenesis study, two groups of 10 male C3H/He mice received dermal applications of 50 mg of a solution containing 25 or 29% methyl ethyl ketone in 70% dodecylbenzene twice a week for 1 year. No skin tumors developed in the group of mice treated with 25% methyl ethyl ketone. After 27 weeks, a single skin tumor developed in 1 of 10 mice receiving 29% methyl ethyl ketone (Horton et al., 1965).

__II.A.4. Supporting Data for Carcinogenicity

Methyl ethyl ketone was not mutagenic for Salmonella typhimurium strains TA98, TA100, TA1535, or TA1537 with or without rat hepatic homogenates (Florin et al., 1980; Douglas et al., 1980). Methyl ethyl ketone induced aneuploidy in the diploid D61, M strain of Saccharomyces cerevisiae (Zimmermann et al., 1985). Low levels of methyl ethyl ketone combined with low levels of nocodazole (another inducer of aneuploidy), also produced significantly elevated levels of aneuploidy in the system (Mayer and Goin, 1987).

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_II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure

None.

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_II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation

Exposure

None.

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_II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)

__II.D.1. EPA Documentation

U.S. EPA. 1985. Health and Environmental Effects Profile for Methyl Ethyl Ketone. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1988. Updated Health Effects Assessment for Methyl Ethyl Ketone. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC.

The 1988 Updated Health Effects Assessment for Methyl Ethyl Ketone has received Agency review.

__II.D.2. EPA Review (Carcinogenicity Assessment)

Agency Work Group Review -- 05/30/1989

Verification Date -- 05/30/1989

__II.D.3. EPA Contacts (Carcinogenicity Assessment)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (301)345-2870 (phone), (301)345-2876 (FAX) or Hotline.IRIS@epamail.epa.gov (internet address).

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_III. [reserved]
_IV. [reserved]
_V. [reserved]

_VI. Bibliography

Substance Name -- Methyl ethyl ketone (MEK)
CASRN -- 78-93-3
Last Revised -- 06/01/1993

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_VII. Revision History

Substance Name -- Methyl ethyl ketone (MEK)
CASRN -- 78-93-3

Date	Section	Description
03/31/1987	I.A.6.	Documentation corrected
03/01/1988	I.A.2.	Paragraph 2 clarified
07/01/1989	II.	Carcinogen assessment now under review
07/01/1989	VI.	Bibliography on-line
12/01/1989	II.	Carcinogen assessment on-line
12/01/1989	VI.C.	Carcinogen references added
04/01/1990	I.B.	Inhalation RfC now under review
06/01/1990	I.A.	Oral RfD summary noted as pending change
06/01/1990	IV.F.1.	EPA contact changed
08/01/1991	I.A.	Withdrawn pending further review
08/01/1991	VI.A.	Oral RfD references withdrawn
01/01/1992	IV.	Regulatory Action section on-line
07/01/1992	I.B.	Inhalation RfC on-line
07/01/1992	VI.B.	Inhalation RfC references on-line
08/01/1992	VI.B.	Inhalation RfC references clarified
10/01/1992	I.A.	Work group review date added
12/01/1992	I.A.	Work group review date added
05/01/1993	I.A.	Oral RfD summary replaced; RfD changed
05/01/1993	VI.A.	Oral RfD references replaced
06/01/1993	VI.C.	Minor correction
04/01/1997	III., IV., V.	Drinking Water Health Advisories, EPA Regulatory Actions, and Supplementary Data were removed from IRIS on or before April 1997. IRIS users were directed to the appropriate EPA Program Offices for this information.
01/09/2002	I., II.	This chemical is being reassessed under the IRIS Program.

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_VIII. Synonyms

Substance Name -- Methyl ethyl ketone (MEK)
CASRN -- 78-93-3
Last Revised -- 01/31/1987

78-93-3
aethylmethylketon
2-butanone
butanone-2
ethyl methyl cetone
ethylmethylketon
ethyl methyl ketone
ketone, ethyl methyl
meetco
MEK
methyl acetone
Methyl Ethyl Ketone
metiletilchetone
metyloetyloketon
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