# IRIS SUMMARY

0071
Methyl ethyl ketone (MEK); CASRN 78-93-3; 00/00/00

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, Regional 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 METHYL ETHYL KETONE (MEK)

File First On-Line 01/31/1987

| Category (section) | Status | Last Revised |
|---|---|---|
| Oral RfD Assessment (I.A.) | On-Line | 00/00/0000 |
| Inhalation RfC Assessment (I.B.) | On-Line | 00/00/0000 |
| Carcinogenicity Assessment (II.) | On-Line | 00/00/0000 |

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## _I. CHRONIC HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

## __I.A. REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)

Methyl ethyl ketone (MEK)
CASRN – 78-93-3
Last Revised -- 00/00/0000

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.

This RfD replaces the previous RfD of 0.6 mg/kg-day entered on IRIS 5/01/1993. The new RfD is based on application of a newer methodology.

## ___I.A.1. ORAL RfD SUMMARY

| Critical Effect | Experimental Doses* | UF | MF | RfD |
|---|---|---|---|---|
| Decreased pup body weight | NOAEL: 594 mg/kg-day (0.3% 2-butanol solution) | 1000 | 1 | 0.7 mg/kg-day |
| Multigeneration reproductive developmental rat drinking water study | LOAEL: 1771 mg/kg-day (1% 2-butanol solution)<br>$LED_{05}$: 657 mg/kg-day | | | |

Cox et al., 1975

*Conversion Factors and Assumptions -- Average intakes reported by study authors based on water intake and body weight data. F1A, F1B, and F2 body weights were analyzed by benchmark dose modeling. The lower 95% confidence interval on the effective dose associated with a 5% decrease in F1A body weight on postnatal day 21 ($LED_{05}$) was selected as the point of departure for the RfD.

## ___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 precursor, 2-butanol. A detailed rationale for use of 2-butanol as a surrogate for MEK can be found in Section I.A.4 ADDITIONAL STUDIES/COMMENTS.

Cox et al. (1975) conducted a multigeneration reproductive and developmental toxicity study of 2-butanol. The study did not include statistical analyses of the results, but all collected data were fully reported. The study results are also presented in abstract form by Gallo et al. (1977). Weanling FDRL-Wistar stock rats (30/sex/group) were given 2-butanol in drinking water at 0, 0.3, 1, or 3%

solutions and a standard laboratory ration *ad libitum*. Weekly food consumption, fluid intakes, and body weights were examined to determine the efficiency of food utilization and to calculate the average daily intake of 2-butanol. The average daily intake of 2-butanol as reported by the authors for the initial 8 weeks of the study (intake was not reported for subsequent weeks) was 0, 538, 1644, and 5089 mg/kg-day (males) and 0, 594, 1771, and 4571 mg/kg-day (females) for the 0, 0.3, 1, and 3% solutions, respectively. After 9 weeks of initial exposure, males and females from each exposure group were mated to produce F1A litters, which were delivered naturally and nursed through 21 days of lactation. Because increased mortality and decreased body weight occurred in the F1A at the 3% dose level, all high-dose parents and F1A offspring were given drinking water without 2-butanol between days 10 and 21 of lactation and then 2% 2-butanol for the remainder of the experimental protocol. Pup and dam weights were recorded on days 4 and 21 after birth. The 2% 2-butanol exposure level is estimated to have produced average daily intakes of 3384 mg/kg-day in males and 3122 mg/kg-day in females based on a linear regression analysis of the reported average intakes for males and females in the 0, 0.3, 1, and 2% groups.

After a 2-week post-lactation period, the F0 females were remated with males of their respective exposure groups to produce F1B litters. The F1B pregnancies of 20 pregnant rats per group were terminated on gestation day 20.

Selected male and female F1A rats (30 of each sex per exposure group) were continued on their respective treatment protocols (0, 0.3, 1, or 2% 2-butanol) and mated at 12 weeks of age to produce F2 litters that were delivered and nursed through day 21 of lactation. F2 pup weights were assessed at days 4 and 21. At day 21, adult F1A rats were sacrificed and selected tissues were examined histologically.

At the highest exposure level (3%), net parental (F0) body weight gain was reduced compared with controls during the 8 weeks of initial exposure. As compared to the control group, marked litter effects on pup survival and body weight were noted in the litters (F1A) from the high-dose group (3%). The high-dose mean F1A body weights at 4 and 21 days represent 22% and 39% decreases, respectively, compared with control values. The body weight decreases relative to control at days 4 and 21 were 5% and 4% for the 0.3% group, and 7% and 10% for the 1% group, respectively (see Table 1). The change in body weight at day 21 in the 1% group is considered to be biologically significant.

During the second pregnancy, the high-dose F0 dams receiving 2% 2-butanol exhibited reduced weight gain compared to control, 0.3% or 1% dams. Average weight of F1B fetuses was reduced in the 2% group compared with controls (3.74±1.01 g vs. 4.14±1.45 g, respectively), with log-likelihood ratio tests indicating that mean body weights significantly decreased with increasing dose levels.

F2 pups from the high-dose group (2%) showed a reduction in the mean pup body weight at postnatal days 4 (9.5 vs. 10.0 g in the control) and 21 (35 vs. 40 g in the control). Mean body weights

of F2 pups in the 0.3% and 1% groups were similar to controls at 4 days (9.7 and 9.6 g) and 21 days (39 and 39 g). Although the body weight reductions in the high-dose F2 pups were not as great as those observed in the high-dose F1A pups, a continued decrease in body weight occurred in the pups at days 4 and 21 (reductions of 5% at 4 days and 13% at 21 days compared with F2 controls) (see Table 1).

No toxicologically significant exposure-related changes in organ weights or increased incidences of lesions were found in the adult F1A rats sacrificed 21 days after the F2 birth.

In summary, the results of the Cox et al. (1975) study show that administration of 2-butanol in drinking water at concentrations as high as 3% did not affect reproductive performance variables in rats, but produced maternal toxicity accompanied by developmental effects at the highest exposure level. Decreased F0 parental weight gain prior to mating, decreased F1A pup survival, and decreased F1A pup weights among survivors at postnatal days 4 and 21 were seen in the groups exposed to 3% 2-butanol in the drinking water. At the 2% level (*i.e.*, the adjusted high-dose level administered following F1A postnatal day 21), the following effects were noted: decreased maternal body weight gain during the second pregnancy of the F0 dams; decreased F1B fetal body weights when pregnancy was terminated at gestation day 20; and decreased F2 pup weights at postnatal days 4 and 21. At the next lower dose level (1%), only reduced F1A pup weight was observed. Developmental endpoints were not affected at the 0.3% 2-butanol exposure levels in any of the generations.

2-Butanol treatment did not increase the incidence of relevant neoplastic or non-neoplastic lesions in F1A generation rats that were exposed from gestation and continuing through 12 weeks after birth, mating, and gestation and lactation of the F2 generation. No indications of reproductive toxicity were noted at the highest dose level (3% or 4571 mg/kg-day).

Table 1. Body weight (litter means and standard deviation) for F1A and F2 neonatal rats and F1B fetuses exposed to 2-butanol (Cox et al., 1975).

| **Endpoint (generation)** | **Control** | **0.3% (594 mg/kg-day[a])** | **1% (1771 mg/kg-day[a])** | **2% (3122 mg/kg-day[b])** |
|---|---|---|---|---|
| F1A pup body weight, day 4 | 10.7±1.1 | 10.2±1.3 | 9.97±1.3 | 8.3±1.8[c] |
| F1A pup body weight, day 21 | 49±3.8 | 47±3.9 | 44±4.8 | 30±11.9[c] |
| F1B fetal body weight, gestation day 20 | 4.14±1.5 | 4.16±0.7 | 4.38±1.0 | 3.74±1.0 |
| F2 pup body weight, day 4 | 10.0±1.4 | 9.7±1.6 | 9.6±2.3 | 9.5±1.6 |
| F2 pup body weight, day 21 | 40±6.1 | 39±7.8 | 39±9.4 | 35±4.7 |

[a] Average daily intake of 2-butanol as reported by the authors.
[b] Calculated based on a linear regression analysis of the reported average intakes and drinking water concentrations of 2-butanol.
[c] Means for F1A pups exposed to 3% 2-butanol (4571 mg/kg-day). These were not included in the modeling due to possibly confounding mortality.

The fetal body weight data from the F1B generation and the day 4 and day 21 pup weights from the F1A and F2 generations were analyzed by benchmark dose modeling. Decreased F1A pup survival observed in the highest dose group (*i.e.*, 3% solution) is likely to have confounded the effects on body weight. Therefore, these data were not included in the modeling. Models for continuous data (linear, polynomial, or power), either with a constant variance or with variance as a power function of the mean value (using an additional model parameter), were fit to the data using U.S. EPA Benchmark Dose Software (version 1.3.1). This software was used to calculate potential points of departure for deriving the RfD, by estimating the effective dose at a specified level of response ($ED_x$), and its 95% lower bound ($LED_x$). In the case of pup or fetal body weight, there is no specific decrement that is generally regarded as indicative of an adverse response. Consequently, for each generation, a 5% decrease in the mean pup or fetus body weight per litter (compared with the control mean) was selected as the benchmark response because it was a response rate that fell within the range of experimental dose levels used in the Cox *et al.* study. The $ED_{05}$ and $LED_{05}$ values calculated from the various data sets from Cox et al. (1975) are summarized in Table 2.

Table 2. Benchmark doses for developmental effects in rats from various generations of Cox et al. (1975) and potential points of departure for the MEK RfD.

| **Endpoint** | **$ED_{05}$ [a] (mg/kg-day)** | **$LED_{05}$ [a] (mg/kg-day)** |
|---|---|---|
| F1A pup body weight, day 4[b] | 1387 | 803 |
| F1A pup body weight, day 21[b] | 878 | 657 |
| F1B fetal body weight, gestation day 20 | 2198 | 1046 |
| F2 pup body weight, day 4 | 3471 | 1347 |
| F2 pup body weight, day 21 | 2056 | 901 |

[a] $ED_{05}$ = Benchmark dose associated with a 5% decrease in litter mean pup or fetus body weight (compared with control mean).
$LED_{05}$ = 95% lower confidence limit on the $ED_{05}$.
[b] The data for the high-dose group (3%) were not included in the modeling.

The $LED_{05}$ values from these data sets are within 2-fold of each other; therefore, all the modeling results are equally plausible. The lowest point of departure, based on the decreased pup body weight at postnatal day 21 in the F1A generation ($LEL_{05}$ = 657 mg/kg-day), was selected for derivation of the RfD as the most health protective value.

## ___I.A.3. UNCERTAINTY AND MODIFYING FACTORS (ORAL RfD)

UF = 1000.

A 10-fold uncertainty factor was used to account for laboratory animal-to-human interspecies differences. No information is available on the toxicity of MEK in humans exposed by the oral route. No other information is available to assess possible differences between animals and humans in pharmacodynamic responses to MEK. Rat and human PBPK models for oral exposure to MEK could potentially be used to decrease pharmacokinetic uncertainty in extrapolating from rats to humans, but such models are not currently available.

A 10-fold uncertainty factor for intraspecies differences was used to account for potentially sensitive human subpopulations. Although the RfD is based on a potentially sensitive population (developing fetus and neonates), this uncertainty factor is appropriate because of the lack of human oral exposure information on the range of responses to MEK in human subpopulations.

A 10-fold uncertainty factor was used to account for deficiencies in the available MEK database. No oral data are available for MEK; however, the available pharmacokinetic and inhalation toxicity data support 2-butanol as an appropriate surrogate for MEK. Although no chronic studies are available, the database includes a two-generation reproductive and developmental toxicity assay wherein rats were exposed to 2-butanol for 14–18 weeks with observed effects limited to reductions in body weight. The absence of organ-specific toxicity following a 14-18 week exposure to 2-butanol reduces the uncertainty associated with the lack of chronic toxicity data for MEK or 2-butanol.

A 5% decrease in pup weight, relative to control, was selected to help identify the point of departure. Although dose-response data suggested a trend of decreased body weight with increasing dose, the 2-generation Cox *et al.* study provides no evidence that this effect was associated with permanent functional alterations. In this 2-generation study, reduction in offspring body weight (as high as 43% in F1A rats on postnatal day 21) was not associated with impairment of reproductive performance or other toxicologically relevant endpoints evaluated in the study. Further, the pup body weight reductions in the first set of offspring (F1A) in the low- and mid-dose groups were less apparent in the next generation (F2). In the F2 generation on postnatal day 21, the only group of pups with body weights not similar to the control was the high-dose group; these offspring were born to dams with body weights 13% lower than the control. Since there were no other effects in the range of the $LED_{05}$ of 657 mg/kg-day, no further adjustments were considered for identifying a level of oral exposure to MEK associated with a minimal level of risk.

Consistent with EPA practice (U.S. EPA, 1991b), an uncertainty factor was not used to account for extrapolation from less than chronic results because developmental toxicity (decreased neonatal body weight following in utero and neonatal exposure) was used as the critical effect. The developmental period is recognized as an obligate and sensitive lifestage where exposure during certain time windows of development are more relevant to induction of developmental effects than lifetime exposure.

MF = 1.

## ___I.A.4. ADDITIONAL STUDIES/COMMENTS (ORAL RfD)

No studies examining the subchronic or chronic effects of oral exposure to MEK in humans or experimental animals were identified. The repeat-dose oral toxicity database is limited to data for 2-butanol, a metabolic precursor, and 3-hydroxy-2-butanone, a metabolite.

The 2-butanol data consist of the 2-generation reproductive and developmental toxicity study in the rat (Cox et al., 1975) that was selected as the principal study used in deriving the MEK RfD. For 3-hydroxy-2-butanone a 13-week drinking water study in rats is available (Gaunt et al., 1972). No *in vivo* toxicity studies of repeat exposure (by any route) to 2,3-butanediol (the other main metabolite of MEK) are available. The finding of developmental toxicity in rats exposed orally to 2-butanol in the Cox et al. study is consistent with similar findings in inhalation developmental toxicity studies of MEK (Schwetz et al., 1974, 1991; Deacon et al., 1981) and 2-butanol (Nelson et al., 1989, 1990). Given these observations, it is plausible that the developmental effects produced by 2-butanol and MEK are caused by MEK or a subsequent metabolite common to both. The only other effect associated with long-term oral exposure to 2-butanol is nephrotoxicity in male rats (Cox et al., 1975) that can be characterized as $\alpha_{2u}$-globulin-mediated, which is not a relevant endpoint for human health risk assessment (U.S. EPA, 1991a).

Data from the 13-week drinking water study with 3-hydroxy-2-butanone in CFE rats (Gaunt et al., 1972) are suggestive of an adverse hematological effect (slight anemia, as indicated by decreased hemoglobin concentration and red blood cell count). This effect, however, is not consistent with the hematological findings in the studies of 2-butanol (oral and inhalation exposure) or MEK (inhalation exposure). This study of drinking water exposure to 3-hydroxy-2-butanone provides no information concerning the potential for developmental effects, which are the key effects seen with oral and inhalation exposure to 2-butanol and inhalation exposure to MEK. Thus, 3-hydroxy-2-butanone does not appear to be an appropriate surrogate for assessing toxicity of MEK.

Pharmacokinetic and toxicologic data support the use of 2-butanol as an appropriate surrogate for MEK. Pharmacokinetic findings in rats supporting the use of 2-butanol as a surrogate for MEK include: 1) orally administered 2-butanol was almost completely converted to MEK and its metabolites within 16 hours; 2) peak MEK blood concentrations occurred at similar times after administration of 1776 mg/kg 2-butanol (7–8 hours) or 1690 mg/kg MEK (4–5 hours); and 3) common metabolites (3-hydroxy-2-butanone and 2,3-butanediol) were formed and eliminated with similar kinetics after administration of 2-butanol or MEK (Traiger and Bruckner, 1976; Dietz et al., 1981). Comparable pharmacokinetic data for 2-butanol and MEK in humans are not available; however, evidence for conversion to 2-butanol in humans supports the assumption that rats and humans metabolize 2-butanol similarly. Toxicologic findings supporting the use of 2-butanol as a MEK surrogate include: 1) fetal body weight deficits were critical effects in studies of rats (Schwetz et al., 1974; Deacon et al., 1981) and mice (Schwetz et al., 1991) exposed to MEK by inhalation during gestation, and in a two-generation reproductive and developmental toxicity study in rats exposed to 2-butanol in drinking water

(Cox et al., 1975), and in a study of rats exposed by inhalation during gestation to 2-butanol (Nelson et al., 1989); and 2) the relationships between air concentrations and degree of fetal body weight changes were consistent for MEK and 2-butanol.

As an alternative to using 2-butanol data as a surrogate for MEK, consideration was given to route-to-route extrapolation to derive oral doses from existing inhalation data for development of a RfD for MEK. Unfortunately, deficiencies in absorption data preclude the application of these methods for MEK. See the Toxicological Review (U.S. EPA, 2003) for a detailed discussion of the relevant pharmacokinetic data.

## ___I.A.5. CONFIDENCE IN THE ORAL RfD

Study -- Medium to Low
Data Base -- Low
RfD -- Low

The overall confidence in this RfD assessment is low. Confidence in the principal study is medium to low. The multigeneration reproduction and developmental drinking water toxicity study for 2-butanol defined a critical effect that is corroborated by inhalation exposure developmental toxicity studies for MEK. The principal study examined appropriate reproductive, developmental, and systemic toxicity endpoints in an adequate number of rats exposed to control conditions or three dose levels and identified NOAELs and LOAELs for maternal and developmental toxicity and a NOAEL for reproductive toxicity. Lowering the drinking water concentration of 2-butanol in the high-dose group from 3% to 2%, however, confounds the ability to discern the dose level responsible for the observed developmental effects. Furthermore, the study was conducted prior to the implementation of good laboratory practices (GLPs), and certain parameters routinely evaluated in studies of more current design (e.g., estrous cyclicity, sperm parameters, and uterine weight) were not measured in Cox *et al*. Confidence in the database is low. The database lacks chronic exposure information for MEK by any route of exposure. Consequently, the RfD is based on toxicity data for 2-butanol, a compound that is rapidly metabolized to MEK in rats and shows a time-course profile of metabolites following oral administration that is similar to the profile for MEK. No pharmacokinetic data are available, however, to confirm that the rapid conversion of 2-butanol to MEK seen in rats also occurs in humans. Although similar developmental effects were reported following oral and inhalation exposure to 2-butanol and by inhalation exposure to MEK, the lack of oral data for MEK itself and the absence of data in a second species precludes any higher level of database confidence. Reflecting the medium to low confidence in the principal study and low confidence in the database, confidence in the RfD is low.

## ___I.A.6. EPA DOCUMENTATION AND REVIEW OF THE ORAL RfD

Source Document -- U.S. EPA, 2003.

This assessment was peer reviewed by external scientists. Their comments have been evaluated carefully and incorporated in finalization of this IRIS summary. A record of these comments is included as an appendix to U.S. EPA, 2003.

Agency Consensus Date -- __/__/__

## ___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 (email address).

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## __I.B. REFERENCE CONCENTRATION FOR CHRONIC INHALATION EXPOSURE (RfC)

Methyl ethyl ketone (MEK)
CASRN –78-93-3
Last Revised -- 00/00/0000

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 generally expressed in units of $mg/m^3$. 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.

This RfC replaces the previous RfC of 1 $mg/m^3$ entered on IRIS 7/01/1992. The new RfC is based on application of a newer methodology and consideration of new data.

## __I.B.1. INHALATION RfC SUMMARY

| Critical Effect | Experimental Doses* | UF | MF | RfC |
|---|---|---|---|---|
| Increased incidence of misaligned sternebrae | NOAEL: 2980 mg/m³ 100<br>LOAEL: 8909 mg/m³ | | 1 | 15 mg/m³ |
| Mouse developmental study | LEC: 5202 mg/m³<br>$LEC_{(ADJ)}$: 1517 mg/m³<br>$LEC_{(HEC)}$: 1517 mg/m³ | | | |

Schwetz et al., 1991

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*Conversion Factors and Assumptions – MW = 72.1. Assuming 25˚ C and 760 mm Hg., 1 ppm = 72.1/24.45 = 2.95 mg/m³. Duration adjustment of exposure concentrations was employed (7 h/day on days 6-15 of gestation): $LEL_{(ADJ)}$ = 5202 mg/m³ × 7 h/24 h = 1517 mg/m³. The $LEC_{(HEC)}$ was calculated for a gas:extrarespiratory effect assuming periodicity was attained. The blood:gas (air) partition coefficient ($H_{b/g}$) value for MEK in humans (H) was estimated to be 125 (Fiserova-Bergerova and Diaz, 1986), whereas in rats (A) this value ranged from 138 to 139 (Thrall et al., 2002). According to the RfC methodology, where the ratio of animal to human blood:air partition coefficients ($(H_{b/g})_A/(H_{b/g})_H$) is greater than one, a value of one is used for the ratio. Thus, $NOAEL_{(HEC)}$ = 1517 mg/m³ x ($(H_{b/g})_A/(H_{b/g})_H$) = 1517 mg/m³.

## ___I.B.2. PRINCIPAL AND SUPPORTING STUDIES (INHALATION RfC)

Deacon, M.M., M.D. Pilny, J.A. John, B.A. Schwetz, F.J. Murray, H.O. Yakel, and R.A. Kuna. (1981) Embryo- and fetotoxicity of inhaled methyl ethyl ketone in rats. Toxicol Appl Pharmacol 59:620-2.

Dow Chemical Corporation. (1979) Teratologic evaluation of inhaled methyl ethyl ketone in rats. OTS Fiche #0205871. Document No. 878211793.

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.

NTP (National Toxicology Program). (1990) Inhalation developmental toxicology studies: teratology

study of methyl ethyl ketone (CAS No. 78-93-3) in mice. NTP Study: TER88046. Research Triangle Park, NC.

Deacon et al. (1981) exposed groups of 26, 19, 19, and 18 Sprague-Dawley dams to nominal MEK concentrations of 0, 400, 1000, and 3000 ppm, respectively (7 hours/day on gestation days 6–15). Results from this study were also reported by Dow Chemical Corporation (1979). Average measured MEK concentrations during the experiment were 412, 1002, and 3005 ppm (1215, 2955, and 8865 mg/m$^3$). Dams exposed to 3005 ppm of MEK exhibited maternal toxicity: a slight decrease in weight gain (326 g for 3005 ppm group vs. 351 g for control; $p<0.05$ at gestation day 16) and increased water consumption on days 15–17 (82 mL/day for 3005 ppm group vs. 69 mL/day for control; $p<0.05$ at gestation day 16) (Dow Chemical Corporation, 1979). None of the exposure levels produced statistically significant effects on the incidences of pregnancy or resorption, the average number of implantations or live fetuses per dam, or fetal weight and length. No statistically significant differences in the incidences of external or soft-tissue alterations were observed in the exposed versus the control groups. Statistically significant differences in the incidences of litters with extra ribs was observed in the 3005-ppm exposure group compared with the controls. The incidence of extra ribs was 2/26 for control litters, compared with 0/19, 0/19, and 6/18 for 412-, 1002-, and 3005-ppm litters, respectively. Thus, this study found maternal toxicity (decreased weight gain) and fetal toxicity (increased incidence of skeletal variations) at 3005 ppm (7 hours/day on gestation days 6–15) (LOAEL), but not at 412 or 1002 ppm (NOAEL).

Schwetz et al. (1991) exposed groups of 10 virgin Swiss CD-1 mice and 33 sperm plug-positive (gestation day 0) females to mean MEK concentrations of 0, 398±9, 1010±28, and 3020±79 ppm (0, 1174±27, 2980±83, and 8909±233 mg/m$^3$) by inhalation for 7 hours/day on gestation days 6–15. Dams were then sacrificed on day 18 of gestation. Results from this study were also reported by Mast et al. (1989) and NTP (1990). At these exposure concentrations (0, 398, 1010, or 3020 ppm), the number of gravid/mated mice were 26/33, 23/33, 26/33, and 28/33, respectively. In the dams, a slight, concentration-related increase in liver-to-body-weight ratios was observed (increase of approximately 7% over control at 3020 ppm). Two statistically significant developmental effects were observed: 1) a decrease in mean fetal body weight (per litter) at 3020 ppm in males (5% decrease compared with controls) and for male and female fetuses combined (4% decrease compared with controls); and 2) a positive trend for increasing incidence of fetuses (total) with misaligned sternebrae with increasing exposure level (incidences were 31/310, 27/260, 49/291, and 58/323 for the control through 3020-ppm exposure groups). No increase in the incidence of intrauterine death was observed in any of the exposed groups. No statistically significant increases in the incidence of malformations occurred. Developmental and maternal effect levels were established at 3020 ppm (7 hours/day on gestation days 6–15) for a small, but statistically significant, decrease in fetal body weight among males, increased incidence of misaligned sternebrae, and an increase in maternal liver-to-body-weight ratio.

Data for these developmental effects in rats and mice were analyzed by benchmark dose analysis (see Table 3). In Sprague-Dawley rats, Deacon et al. (1981) reported a statistically significant

increase in the incidence of litters with fetuses with extra ribs. In CD-1 mice, Schwetz et al. (1991) identified two statistically significant developmental effects in fetuses exposed to MEK: decreased fetal weight per litter (continuous data) and a trend for increasing incidence of fetuses with misaligned sternebrae with increasing exposure level (dichotomous data).

Table 3. Developmental effect data for rodents exposed to MEK by inhalation.

| Endpoint | Approximate MEK Concentration (ppm) | | | |
|---|---|---|---|---|
| | 0 | 400 | 1000 | 3000 |
| Incidence of extra ribs (rats) (incidence of litters with any fetus with extra ribs/litters at each dose) (Deacon et al., 1981) | 2/26 | 0/19 | 0/19 | 6/18 |
| Fetal body weight (mice) (mean [g] ±standard deviation) (Schwetz et al., 1991) | 1.35±0.07 | 1.35±0.06 | 1.33 ±0.07 | 1.29 ±0.08 |
| Incidence of misaligned sternebrae (mice) (Incidence/number of fetuses) (Schwetz et al., 1991) | 31/310 | 27/260 | 49/291 | 58/323 |

All nested models for dichotomous variables available in the EPA Benchmark Dose Software (BMDS version 1.3.1) were fit to the incidence data for rat litters with extra ribs (Deacon et al., 1981) (see Table 3). A 5% increase in the incidence of extra ribs was selected as the benchmark response because it was a response rate that fell within the range of experimental dose levels used in the Deacon et al. study. All models – the nested logistic (NLogistic), the NCTR, and the Rai and vanRyzin models – provided similar fits to the data, based on the summary results reported in the BMDS output, and detailed examination of the graphs and goodness-of-fit statistics. Model fits were not improved by incorporation of litter size (as a litter-specific covariate) or by incorporation of intra-litter correlations, as determined by comparisons of AIC (Akaike's Information Criterion) values. The model-predicted effective concentration ($EC_{05}$) associated with a 5% extra risk of affected fetuses per litter using the NCTR model (fitting only slightly better than the other models) was 3317 ppm. The corresponding $LEC_{05}$ was 2993 ppm (see Table 4).

Models for continuous data (linear, polynomial, or power) in the EPA Benchmark Dose Software, either with a constant variance or with variance as a power function of the mean value (using an additional model parameter), were fit to the fetal mouse body weight data (Schwetz et al., 1991) (see Table 3). A decrease in the mean fetal body weight of 1 standard deviation of the control mean was selected as the benchmark response for this endpoint consistent with the recommendations of the Benchmark Dose Technical Guidance Document (U.S. EPA, 2000). This corresponds to a 5% decrease in the mean control group weight for this data set. A constant variance linear continuous-variable model (BMDS version 1.3.1) provided the best fit to the data (as indicated by the lowest AIC with a goodness-of-fit p value > 0.1). The model-predicted EC associated with a mean fetal body weight of 1 standard deviation below the control mean was 3339 ppm. The corresponding LEC was 2273 ppm (see Table 4).

The nested, dichotomous-variable models available in the EPA BMD software were fit to the individual litter data for fetuses with misaligned sternebrae (Mast et al., 1989, Schwetz et al., 1991) (see Table 3). All three nested models provided adequate fits to the data, based on the summary results reported in the BMDS output. Use of a non-linear model was found not to improve model fit. A 10% extra risk for misaligned sternebrae was selected as the benchmark response, since the model and the data are most consistent in this range of the data set. Also, the Benchmark Dose Technical Guidance Document recommends estimation of a 10% BMR for a point of consistent comparison across chemicals (U.S. EPA, 2000). Because the three model fits were very similar, an average of the $LEC_{10}$s was calculated as the point of departure. The respective $EC_{10}$ and $LEC_{10}$ associated with a 10% extra risk for misaligned sternebrae were 3214 and 1764 ppm, respectively (see Table 4).

Table 4. Benchmark concentrations for developmental effects in mice and rats and potential points of departure for the MEK RfC.

| Endpoint | Benchmark Response Level | EC, mg/m³ (ppm)[a] | LEC, mg/m³ (ppm)[a] |
|---|---|---|---|
| Increased incidence of extra ribs (rats) (Deacon et al., 1981) | 5% | 9781 (3317) | 8826 (2993) |
| Decreased fetal body weight (mice) (Schwetz et al., 1991) | 1 s.d. ≈ 5% | 9847 (3339) | 6705 (2273) |
| Increased incidence of misaligned sternebrae (mice) (Schwetz et al., 1991) | 10% | 9478 (3214) | 5202 (1764) |

[a]Sample calculation: (2452 ppm x 72.1 mg/mmol)/24.45 = 7231 mg/m³, assuming 25° C and 760 mm Hg.

As shown in Table 4, benchmark modeling of the data produced similar points of departure for the three developmental endpoints observed in the two species (within 2-fold). The lowest point of departure based on the incidence of misaligned sternebrae in CD-1 mice exposed to MEK 7 hours/day on days 6–15 of gestation ($LEC_{10}$ = 5202 mg/m³) was selected for derivation of the RfC as the most health protective value.

## ___I.B.3. UNCERTAINTY AND MODIFYING FACTORS (INHALATION RfC)

UF = 100.

A 3-fold uncertainty factor was used for interspecies extrapolation, since this factor embodies two areas of uncertainty: pharmacokinetics and pharmacodynamics. In this assessment, the pharmacokinetic component was addressed by the calculation of the human equivalent concentration (HEC) according to the procedures in the RfC Methodology (U.S. EPA, 1994). Accordingly, only the pharmacodynamic area of uncertainty remains as a partial factor for interspecies uncertainty ($10^{0.5}$ or

approximately 3).

A 10-fold uncertainty factor for intraspecies differences was used to account for potentially sensitive individuals within the human population. Although the RfC is based on a potentially sensitive population (developing offspring), this uncertainty factor is appropriate because of the lack of information on the range of responses in human subpopulations exposed to MEK.

A 3-fold uncertainty factor was used to account for database deficiencies. In this case, a partial factor was applied ($10^{0.5}$ or approximately 3). The minimum database requirements for derivation of an RfC are satisfied by the Cavender et al. (1983) study (see Section I.B.4). Data from an oral multigeneration reproductive and developmental toxicity study (Cox et al., 1975) with a metabolic precursor, 2-butanol, demonstrated no systemic toxicity or reproductive effects in rats dosed for 14–18 weeks and confirm developmental toxicity as the critical endpoint. Histological information available in the reproductive organs from the subchronic inhalation study (Cavender et al., 1983) gives additional indication that MEK is not likely to be a reproductive toxicant. Neurotoxicity is adequately addressed by the subchronic inhalation study of Cavender et al. (1983), in which animals were examined for both neurological function and for CNS lesions with special neuropathological procedures. The results from this study indicate that MEK has little, if any, neurotoxic potential itself when tested in laboratory animals under conditions of high-level repeated inhalation exposure. Consistent with this finding is a lack of mechanistic evidence for neurotoxicity. The developmental toxicity studies revealed no evidence of neurotoxicity potential in developing populations, although specific tests for neurological toxicity were not performed. Deficiencies with the data base covering portal-of-entry effects (e.g., irritation effects) are considered to be addressed by the human volunteer study of Dick et al. (1992).

Consistent with EPA practice (U.S. EPA, 1991b), an uncertainty factor was not used to account for extrapolation from less than chronic results because developmental toxicity (decreased pup body weight) was used as the critical effect. The developmental period is recognized as a sensitive lifestage where exposure during certain time windows of development are more relevant to induction of developmental effects than lifetime exposure.

MF = 1.

## ___I.B.4. ADDITIONAL STUDIES/COMMENTS (INHALATION RfC)

As with other small molecular weight, aliphatic or aromatic chemicals, acute exposure to high concentrations of MEK results in reversible CNS depression. Data from a series of studies involving acute, 4-hour exposures of volunteers (Dick et al., 1984, 1988, 1989, 1992) found no exposure-related changes in performance of psychomotor and mood tests or incidences of irritation. Evidence for neurotoxic effects in humans repeatedly exposed to MEK is limited to a few case reports of neurological impairment in workers (Welch et al., 1991; Seaton et al., 1992; Callender, 1995; Orti-Pareja et al., 1996).

The database of animal studies is fairly large (e.g., numerous neurological studies are available; see Section 4.2.2 of U.S. EPA, 2003), but it is lacking a chronic bioassay of MEK toxicity. A subchronic inhalation toxicity study in rats is available (Cavender et al., 1983). This study, however, is not used as the principal study due to the possible effect of a suspected infectious agent confounding the ability of the study to address portal-of-entry effects in the respiratory tract. Otherwise, it is high-quality study and thus satisfies the minimum database requirements necessary to derive an RfC for MEK (U.S. EPA, 1994).

Cavender et al. (1983) exposed male and female Fischer 344 rats (15/sex/group) in a whole body dynamic air flow chamber to MEK 6 hours/day, 5 days/week, for 90 days. The reported time-weighted average exposure concentrations (by gas-liquid chromatography) of MEK were 0, 1254, 2518, or 5041 ppm (0, 3700, 7430, or 14,870 mg/m$^3$). The results of this study are also reported in Toxigenics (1981). At the study termination, 10 animals/sex/group were subject to routine gross pathology and histopathology. Special neurohistopathological studies were conducted on the medulla and the sciatic and tibial nerves of the remaining five male and five female rats from each group.

Cavender et al. (1983) reported no deaths during the 90-day study. Transient, statistically significant depressions in body weight gain compared to the control were seen in high dose (5041 ppm) male and female rats early in the study. There were no treatment-related effects on food consumption or in the ophthalmological studies in any MEK-exposed rats. The evaluation of neurological function (*i.e.*, assessments of posture, gait, facial muscular tone or symmetry, and four neuromuscular reflexes) revealed no abnormalities (Toxigenics, 1981). At all exposure concentrations, female rats exhibited statistically significant ($p<0.05$), dose-dependent increases in absolute liver weight as compared to controls, which were unaccompanied by any histopathology. Other statistically significant differences in organ weights included decreased brain weights (absolute and relative) and spleen weights (absolute) in 5041 ppm females and increased relative kidney weights in 5041 ppm males and females. Differences in the serum chemistry values for the female rats in the 5041 ppm exposure group included significant increases in serum potassium, alkaline phosphatase, and glucose, and a significant decrease in SGPT activity compared to controls. No differences in serum chemistry between MEK-exposed males and control animals were observed. The only statistically significant differences in hematology parameters were significantly higher mean corpuscular hemoglobin in 5041 ppm male and female rats and mean corpuscular hemoglobin concentration in 5041 ppm females; this increase corresponded to a slight but not significant decrease in number of red blood cells. With the exception of larger urine quantity in 5041 ppm males, no urinalysis parameters were significantly different in MEK-exposed rats.

Routine gross and histopathological examinations and the special neuropathology studies revealed no lesions that could be attributed to MEK exposure (Cavender et al., 1983). Thus, while the increase in absolute liver weights and mildly altered serum enzyme activities in high-dose female rats only were indicative of possible liver damage, no histopathological lesions in the liver were observed. The authors stated that response may have been the result of a physiological adaptation mechanism. The decrease in brain weight in the 5041 ppm females (9% compared to controls) was an indication of possible effects of MEK on brain tissue; however, no histopathological lesions of the brain were

observed.

Minimal to mild lesions of the upper or lower respiratory tract were noted in all control and MEK-exposed rats. These lesions of the respiratory tract were coded as chronic respiratory disease and consisted of "multifocal accumulation of lymphoid cells in the bronchial wall and peribronchial tissues with occasional polymorphonuclear cells (eosinophils) in the perivascular areas of small veins" (Toxigenics, 1981). Because the bronchial epithelium remained intact and exudates were not present in bronchial lumens, the lesions were considered insignificant pathologically. In addition, the authors reported an increased prevalence of nasal inflammation (including submucosal lymphocytic infiltration and luminal exudate) across control and all exposure groups. There was no difference in the character or severity of lesions among the control and three treatment groups. The authors suggested that the pulmonary lesions were secondary to mycoplasma infection; unfortunately, no infectious agent was cultured to verify this etiology. While there is no indication that respiratory lesions are related to MEK exposure, these results confound the outcome of the study with regard to lesions of the upper respiratory tract.

A NOAEL of 2518 ppm and a LOAEL of 5041 ppm were identified from this study (Cavender et al., 1983) based on toxicity remote to the respiratory tract—*i.e.*, reduced body weight gain, increased relative liver weight, and decreased brain weight.

Animals studies provide no convincing evidence that exposure to MEK alone causes persistent neurotoxic effects. Saida *et al.* (1976) found no evidence of peripheral neuropathy (as indicated by paralysis) following continuous exposure of 12 Sprague-Dawley rats to 1125 ppm (3318 mg/m$^3$) of MEK for periods of 16 to 55 days. Cavender *et al.* (1983) found no neurological effects in special neuropathological studies of the medulla and sciatic and tibial nerves of rats exposed to MEK at concentrations up to 5041 ppm (14,870 mg/m$^3$) for 90 days. Takeuchi *et al.* (1983) exposed male Wistar rats (8 per group) to 200 ppm (590 mg/m$^3$) of MEK 12 hours/day for 24 weeks and found no evidence of a persistent effect on motor or mixed nerve conduction velocity, distal motor nerve latency, or histopathological lesions of tail nerves. Couri *et al.* (1974) exposed 4 cats, 4 rats, 5 mice, and an unknown number of chickens to 1500 ppm (4425 mg/m$^3$) MEK 24 hours/day, 7 days/week for 7–9 weeks with no apparent adverse neurologic effects.

The range of toxic effects in animals resulting from inhalation exposure to MEK indicates that developmental effects are the most sensitive, toxicologically relevant endpoint. Inhalation exposure of experimental animals to approximately 3000 ppm MEK (7 hours/day) during gestation resulted in developmental effects, with no evidence of neurological effects (Schwetz et al., 1974, 1991; Deacon et al., 1981).

### ___I.B.5. CONFIDENCE IN THE INHALATION RfC

Study -- High

Data Base -- Medium
RfC – Medium

The overall confidence in this RfC assessment is medium. Confidence in the principal study is high. The principal study was well-designed and tested several exposure concentrations over a reasonable range that included maximum tolerated doses for both dams and fetuses. Although the principal and supporting studies corroborate an effect level for developmental toxicity endpoints, confidence in the database is medium. The database is lacking chronic exposure toxicity information from any route of exposure, and no multigenerational reproductive and developmental toxicity studies are available for MEK itself. The subchronic inhalation study by Cavender et al. (1983) satisfies the minimum inhalation database requirements for derivation of an RfC and the neurological testing results figure prominently in the assessment. Evidence for neurotoxic effects in humans repeatedly exposed to MEK is limited to a few case reports of neurological impairment in workers and one study of problematic design reporting increased incidence of subjectively reported neurological symptoms in MEK-exposed workers. This evidence, however, is confounded by multiple chemical exposures and uncertainty in the exposure concentrations. Well-conducted studies in experimental animals, however, provide no convincing evidence that repeated inhalation exposure to MEK (at much higher exposure levels than those in the workplace) is capable of producing persistent neurological effects. Portal-of-entry effect concerns are addressed by the by finding of no net irritant effects in humans exposed to MEK at a concentration of 590 $mg/m^3$ for 4 hours (Dick *et al.*, 1992). Reflecting high confidence in the principal study and medium confidence in the database, confidence in the RfC is medium.

### ___I.B.6. EPA DOCUMENTATION AND REVIEW OF THE INHALATION RfC

Source Document -- U.S. EPA, 2003.

This assessment was peer reviewed by external scientists. Their comments have been evaluated carefully and incorporated in finalization of this IRIS summary. A record of these comments is included as an appendix to U.S. EPA, 2003.

Agency Consensus Date -- __/__/__

### ___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 (email address).

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## _II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Methyl ethyl ketone (MEK)
CASRN -- 78-93-3
Last Revised -- 00/00/0000

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 inhalation exposure. Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

The rationale and methods used to develop the carcinogenicity information in IRIS is described in the Draft Revised Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1999. Guidelines for carcinogen risk assessment. Review Draft, NCEA-F-0644, July. Risk Assessment Forum. http://www.epa.gov/ncea/raf/cancer.htm). The quantitative risk estimates result from application of a low-dose extrapolation procedure, and both the central estimate and upper bound estimate of risk per unit of exposure are presented. The quantitative risk estimates are presented in three ways to facilitate their use. The oral slope factor is the 95% upper bound on the estimate of risk per (mg/kg)/day of oral exposure. The unit risk is the 95% upper bound on the estimate of risk, either per µg/L drinking water or per µg/cu.m air breathed. The third form in which risk is presented is the 95% lower bound on the estimated concentration of the chemical in drinking water or air associated with cancer risks of 1 in 10,000, 1 in 100,000, or 1 in 1,000,000.

## __II.A. EVIDENCE FOR HUMAN CARCINOGENICITY

### ___II.A.1. WEIGHT-OF-EVIDENCE CHARACTERIZATION

Under the draft revised guidelines for carcinogen risk assessment (U.S. EPA, 1999), EPA concludes the *data are inadequate for an assessment of human carcinogenic potential* of MEK. Studies of humans chronically exposed to MEK are inconclusive, and MEK has not been tested for carcinogenicity in animals by the oral or inhalation routes.

### ___II.A.2. HUMAN CARCINOGENICITY DATA

Inadequate. The few available epidemiological studies of MEK-exposed workers are inadequate to discern an association between MEK exposure and an increased incidence of cancer (Alderson and Rattan, 1980; Wen et al., 1985; Spirtas et al., 1991; Blair et al., 1998). In these studies, the epidemiological evidence is based on a small number of site-specific deaths, and each is confounded by exposure to multiple chemicals. A case-control study examining the association between paternal exposures to several solvents, including MEK, and childhood leukemia is exploratory in nature and cannot be used to reliably support the existence of any such association.

## ___II.A.3. ANIMAL CARCINOGENICITY DATA

Inadequate. No cancer bioassay is available from which to assess the carcinogenic potential of MEK in experimental animals by the oral or inhalation routes. In a skin carcinogenesis study, groups of 10 male C3H/He mice received dermal applications of 50 mg of a solution containing 17, 25, or 29% MEK in dodecylbenzene (50, 70, or 70%, respectively) twice a week for 1 year (Horton et al., 1965). No skin tumors developed in the groups of mice treated with 17% MEK or 25% MEK with 5% benzyl disulfide (a weak accelerant for skin tumors in C3H mice). After 27 weeks, a single skin tumor developed in 1 of 10 mice treated with 29% MEK and 0.8% 2-phenylbenzothiophene. Horton et al. (1965) is an inadequate test of MEK carcinogenicity due to concomitant exposure to chemicals that are expected to accelerate the rate of skin tumor formation.

## ___II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

MEK has not exhibited mutagenic activity in a number of conventional short-term test systems. *In vitro* tests showed that MEK was not genotoxic in the Salmonella (Ames) assay with or without metabolic activation, the L5178/$TK^{+/-}$ mouse lymphoma assay, and the BALB/3T3 cell transformation assay, and did not induce unscheduled DNA synthesis in rat primary hepatocytes, chromosome aberrations, or sister chromatic exchange (Florin *et al.*, 1980; Douglas *et al.*, 1980; O'Donoghue *et al.*, 1988; NTP, undated; Zeiger *et al.*, 1992). No induction of micronuclei was found in the erythrocytes of mice (O'Donoghue *et al.*, 1988) or hamsters (WHO, 1992) after intraperitoneal injection with MEK. The only evidence of mutagenicity was mitotic chromosome loss at a high concentration in a study on aneuploidy in the diploid D61, M strain of the yeast *Saccharomyces cerevisiae* (Zimmerman *et al.*, 1985); the relevance of this positive result to humans is unknown. In general, studies of MEK yielded little or no evidence of mutagenicity. SAR analysis suggests that MEK is unlikely to be carcinogenic based on the absence of any structural alerts indicative of carcinogenic potential (Woo *et al.*, 2002).

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## __II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

Not applicable. Data are inadequate for derivation of an oral slope factor for MEK.

## __II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

Not applicable. Data are inadequate for derivation of inhalation unit risk for MEK

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## __II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)

### ___II.D.1. EPA DOCUMENTATION

Source Document -- U.S. EPA, 2003

This assessment was peer reviewed by external scientists. Their comments have been evaluated carefully and incorporated in finalization of this IRIS summary. A record of these comments is included as an appendix to U.S. EPA, 2003.

### ___II.D.2. EPA REVIEW (CARCINOGENICITY ASSESSMENT)

Agency Consensus Date -- __/__/__

### ___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 (email address).

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## _VI. BIBLIOGRAPHY

Methyl ethyl ketone (MEK)
CASRN – 78-93-3
Last Revised -- 00/00/0000

### __VI.A. ORAL RfD REFERENCES

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.

Deacon, M.M., M.D. Pilny, J.A. John et al. (1981) Embryo- and fetotoxicity of inhaled methyl ethyl ketone in rats. Toxicol Appl Pharmacol 59:620-622.

Dietz, F.K., M. Rodriguez-Giaxola, G.J. Traiger, V.J. Stella and K.J. Himmelstein. (1981) Pharmacokinetics of 2-butanol and its metabolites in the rat. J Pharmacokin Biopharmacol 9(5):553-576.

Gallo, M.A., B.L. Oser, G.E. Cox and D.E. Bailey. (1977) Studies on the long- term toxicity of 2-butanol. Toxicol Appl Pharmacol 41:135. (Abstract)

Gaunt, I.F., P.G. Brantom, I.S. Kiss, P. Grasso, and S.D. Gangolli. (1972) Short-term toxicity of acetoin (acetylmethylcarbinol) in rats. Food Cosmet Toxicol 10(2):131-41.

Nelson, B.K., W.S. Brightwell, A. Khan, et al. (1989) Lack of selective developmental toxicity of three butanol isomers administered by inhalation to rats. Fundam Appl Toxicol 12:469-79.

Nelson, B.K., W.S. Brightwell, and E.F. Krieg Jr. (1990) Developmental toxicology of industrial alcohols: a summary of 13 alcohols administered by inhalation to rats. Toxicol Ind Health 6(3-4):373-87.

Schwetz, B.A., B.K.J. Leong and P.J. Gehring. (1974) Embryo- and fetotoxicity of inhaled carbon tetrachloride, 1,1-dichloroethane and methyl ethyl ketone in rats. Toxicol Appl Pharmacol 28:452-464.

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 Swiss mice. Fund Appl Toxicol 16:742-748.

Traiger, G.J. and J.V. Bruckner. (1976) The participation of 2-butanone in 2- butanol-induced potentiation of carbon tetrachloride hepatotoxicity. J Pharmacol Exp Ther 196:493-500.

U.S. EPA (U.S. Environmental Protection Agency). (1991a) Alpha 2u-globulin: Association with chemically induced renal toxicity and neoplasia in the male rat. Risk Assessment Forum. Washington, DC. EPA/625/3-91/019F.

U.S. EPA. (1991b) Guidelines for developmental toxicity risk assessment. Federal Register 56:63798-63826.

U.S. EPA. (2000) Benchmark dose technical guidance document. External Review Draft. EPA/630/R-00/001.

U.S. EPA. (2003) Toxicological review of methyl ethyl ketone in support of summary information on the Integrated Risk information System (IRIS). National Center for Environmental Assessment, Washington, DC. Available on line from http://www.epa.gov/iris.

## __VI.B. INHALATION RfC REFERENCES


Callender, T.J. (1995) Neurotoxic impairment in a case of methyl ethyl ketone exposure. Arch Environ Health 50 (5):392.

Cavender, F.L., H.W. Casey, H. Salem, J.A. Swenberg and E.J. Gralla. (1983) A 90-day vapor inhalation toxicity study of methyl ethyl ketone. Fund Appl Toxicol 3(4):264-270.

Couri, D., L.B. Hetland, J.J. O'Neill, et al. (1974) Comments on a plastics industry neurotoxicity in relationship to methylbutyl ketone. In: Proceedings of the 5th Annual Conference on Environmental Toxicology, Fairborn, Ohio. Wright Patterson Air Force Base, Ohio, Aerospace Medical Research Laboratory. AMRL Technical Report No. 74-125. pp. 109-120.

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.

Deacon, M.M., M.D. Pilny, J.A. John, et al. (1981) Embryo- and fetotoxicity of inhaled methyl ethyl ketone in rats. Toxicol Appl Pharmacol 59:620-622.

Dick, R.B., J.V. Seizer, R. Wait, et al. (1984) Effects of acute exposure of toluene and methyl ethyl ketone on psychomotor performance. Int Arch Occup Environ Health 54:91-109.

Dick, R.B., W.D. Brown, J.V. Seizer, et al. (1988) Effects of short duration exposures to acetone and methyl ethyl ketone. Toxicol Lett 43:31-49.

Dick, R.B., J. Seizer, B. Taylor, et al. (1989) Neurobehavioral effects of short duration exposures to acetone and methyl ethyl ketone. Br J Ind Med 46:111-21.

Dick, R.B., E.F. Krieg Jr., J. Seizer, B. Taylor. (1992) Neurobehavioral effects from acute exposures to methyl isobutyl ketone and methyl ethyl ketone. Fundam Appl Toxicol 19(3):453-73.

Dow Chemical Corporation. (1979) Teratologic evaluation of inhaled methyl ethyl ketone in rats. OTS Fiche #0205871. Document No. 878211793. (These data are the same as Deacon et al., 1981.)

Fiserova-Bergerova, V., and M.L. Diaz. (1986) Determination and prediction of tissue-gas partition coefficients. Int Arch Occup Environ Health 58:75-87.

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.

NTP (National Toxicology Program). (1990) Inhalation developmental toxicology studies: teratology study of methyl ethyl ketone (CAS No. 78-93-3) in mice NTP study: TER88046. Research Triangle Park, NC. (These data are the same as Mast et al., 1989.)

Orti-Pareja, M., F.J. Jimenez-Jimenez, J. Miquel, et al. (1996) Reversible myoclonus, tremor, and ataxia in a patient exposed to methyl ethyl ketone. Neurol 46(1):272.

Saida, K., J.R. Mendell and H.S. Weiss. (1976) Peripheral nerve changes induced by methyl n-butyl ketone and potentiation by methyl ethyl ketone. J Neuropath Exp Neurol 35(3):205-225.

Schwetz, B.A., B.K.J. Leong and P.J. Gehring. (1974) Embryo-/and fetotoxicity of inhaled carbon tetrachloride, 1,1-dichloroethane and methyl ethyl ketone in rats. Toxicol Appl Pharmacol 28:452-464.

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

Seaton, A., E.H. Jellinek, and P. Kennedy. (1992) Major neurological disease and occupational exposure to organic solvents. Quart J Med 84(305):707-12.

Takeuchi, Y., Y. Ono, N. Hisanaga et al. (1983) An experimental study of the combined effects of n-hexane and methyl ethyl ketone. Br J Ind Med 40:199-203.

Thrall, KD., J.J. Soelberg, K.K. Weitz, and A.D. Woodstock. (2002) Development of a physiologically based pharmacokinetic model for methyl ethyl ketone in F344 rats. J Toxicol Environ Health 65(13):881-96.

Toxigenics. (1981) 90-Day vapor inhalation toxicity study of methyl ethyl ketone in albino rats. Submitted to Chemical Industry Institute of Toxicology, Research Triangle Park, NC. Doc. ID 878212064, Microfiche No. 205953.

U.S. EPA (U.S. Environmental Protection Agency). (1991b) Guidelines for developmental toxicity risk assessment. Federal Register 56:63798-63826.

U.S. EPA. (1994) Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry. EPA/600/8-90/066F.

U.S. EPA. (2000) Benchmark dose technical guidance document. External Review Draft. EPA/630/R-00/001.

U.S. EPA. (2003) Toxicological review of methyl ethyl ketone in support of summary information on the Integrated Risk information System (IRIS). National Center for Environmental Assessment, Washington, DC. Available on line from http://www.epa.gov/iris.

Welch, L., H. Kirshner, A. Heath, et al. (1991) Chronic neuropsychological and neurological impairment following acute exposure to a solvent mixture of toluene and methyl ethyl ketone (MEK). J Toxicol Clin Toxicol 29(4):435-45.

---

## __VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

Alderson, M. and N. Rattan. (1980) Mortality of workers on the isopropyl plant and two MEK dewaxing plants. Br J Ind Med 37:85-9.

Blair, A., P. Hartge, P.A. Stewart, et al. (1998) Mortality and cancer incidence of aircraft maintenance workers exposed to trichloroethylene and other organic solvents and chemicals: Extended follow up. Occup Environ Med 55(3):161-71.

Douglas, G.R., E.R. Nestmann, J.L. Betts, et al. (1980) Mutagenic activity in pulp mill effluents. Water chlorination: Environ Impact Health Effects 3:865-880.

Florin, I., L. Rutberg, M. Curvall and C.R. Enzell. (1980) Screening of tobacco smoke constituents for mutagenicity using the Ames test. Toxicology 18:219-232.

Horton, A.W., E.L. Bingham, M.J.G. Burton and R. Tye. (1965) Carcinogenesis of the skin. III. The contribution of elemental sulfur and of organic sulfur compounds. Cancer Res 25:1759-1763.

O'Donoghue, J.L., S.R. Haworth, R.D. Curren, et al. (1988) Mutagenicity studies on ketone solvents: methyl ethyl ketone, methyl isobutyl ketone, and isophorone. Mutat Res 206(2):149-61.

Spirtas, R., P.A. Stewart, J.S. Lee, et al. (1991) Retrospective cohort mortality study of workers at an aircraft maintenance facility: I. Epidemiological results. II. Exposures and their assessment. Br J Ind Med 48(8):515-37.

U.S. EPA (U.S. Environmental Protection Agency). (1999) Guidelines for carcinogen risk assessment. Preliminary draft. October 2000. U.S. Environmental Protection Agency, National Center for Environmental Assessment. NCEA-F-0644.

U.S. EPA. (2003) Toxicological review of methyl ethyl ketone in support of summary information on the Integrated Risk information System (IRIS). National Center for Environmental Assessment, Washington, DC. Available on line from http://www.epa.gov/iris.

Wen, C.P., S.P. Tsai,, N.S. Weiss, et al. (1985) Long-term mortality study of oil refinery workers. IV. Exposure to the lubricating-dewaxing process. J Natl Cancer Inst 74:11-8.

Woo, Y-T., D. Lai, J.L. McLain, et al. (2002) Use of mechanism-based structure-activity relationships analysis in carcinogenic potential ranking for drinking water disinfection by-products. Environ Health Persp 110 (Suppl. 1):75-87.

WHO (World Health Organization). (1992) Methyl ethyl ketone. Environmental health criteria. Volume 143.

Zeiger, E., B. Anderson, S. Haworth, et al. (1992) Salmonella mutagenicity tests: V. Results from the testing of 311 chemicals. Environ Mol Mutagen 19(Suppl 21):2-141.

Zimmermann, F.K., V.M. Mayer, I. Scheel and M.A. Resnick. (1985) Acetone, methyl ethyl ketone, ethyl acetate, acetonitrile and other polar aprotic solvents are strong inducers of aneuploidy in Saccharomyces cerevisiae. Mutat Res 149(3):339-351.

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## _VII. REVISION HISTORY

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. |
| 00/00/0000 | I., II., VI. | RfD, RfC, and cancer sections updated |

## _VIII. SYNONYMS

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
RCRA waste number U159
UN 1193
UN 1232