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

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the IRIS assessment development process. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website.

STATUS OF DATA FOR METHYL ETHYL KETONE (MEK)

File First On-Line 01/31/1987

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	09/26/2003
Inhalation RfC (I.B.)	yes	09/26/2003
Carcinogenicity Assessment (II.)	yes	09/26/2003

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

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

Substance Name — Methyl ethyl ketone (MEK)
CASRN — 78-93-3
Last Revised — 09/26/2003

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.

While the current RfD of 0.6 mg/kg-day remains the same as the previous RfD that was entered on IRIS 5/01/1993 (see Section VII. Revision History), the latest RfD is based on the application of newer risk assessment methodology.

I.A.1. Oral RfD Summary

Critical Effect	Experimental Doses*	UF	MF	RfD
Decreased pup body weight **Multigeneration reproductive developmental rat drinking water study** **(Cox et al., 1975)**	NOAEL: 594 mg/kg-day (0.3% 2-butanol solution) LOAEL: 1,771 mg/kg-day (1% 2-butanol solution) LED_{05}: 639 mg/kg-day	1,000	1	0.6 mg/kg-day

* 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. A molar adjustment of the LED_{05} was performed to account for differences in the molecular weights of 2-butanol and MEK: 657 mg 2-butanol/kg-day x (72.1066 g MEK/mol ÷ 74.1224 g 2-butanol/mol) = 639 mg MEK/kg-day.

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

Cox, GE; Bailey, DE; Morgareidge, K. (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.

Identification of the critical effect for MEK (also known as 2-butanone) is based on its metabolic precursor, 2-butanol. The available pharmacokinetic and toxicologic data support

the use of 2-butanol as an appropriate surrogate for MEK. Rationale for using 2-butanol as a surrogate for MEK can be found in Section I.A.4., Additional Studies/Comments (Oral RfD).

Cox et al. (1975) conducted a multigeneration reproductive and developmental toxicity study of 2-butanol. While the study did not include statistical analyses of the results, all collected data were fully reported. The study results are also summarized in abstract form by Gallo et al. (1977) and more fully in the Toxicological Review of MEK (U.S. EPA, 2003). An EPA-sponsored peer review of this study was conducted in 2003 (U.S. EPA, 2003, Appendix A).

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 measured 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, 1,644, and 5,089 mg/kg-day (males) and 0, 594, 1,771, and 4,571 mg/kg-day (females) for the 0, 0.3, 1, and 3% solutions, respectively. After 8 weeks of initial exposure, F0 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 2% 2-butanol for the remainder of the experimental protocol. Pup and dam weights were recorded on days 4 and 21 after birth. The intake (in mg/kg-day) at the 2% 2-butanol exposure level was not reported by the study authors, but was estimated to correspond to average daily intakes of 3,384 mg/kg-day in males and 3,122 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 3% groups.

After a 2-week post-lactation period, the F0 females were remated with males from their respective exposure group 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/sex/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% 2-butanol), net parental (F0) body weight gain was reduced compared with controls during the initial 8-week exposure period. The study authors reported no effect on F0 reproductive parameters. However, an increase in the incidence of F0 male rats that failed to copulate with F0 females was noted at the highest dose (0% - 1/30; 0.3% - 2/30; 1% - 0/30; 3% - 6/30). The biological significance of this finding is uncertain. When

compared to the control group, marked litter effects on pup survival and body weight were noted in the F1A litters 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 to 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 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 at days 4 and 21 in the 0.3% group (9.7 and 9.6 g, respectively) and 1% group (39 and 39 g, respectively) were similar to controls. Although 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 day 4 and 13% at day 21 compared with F2 controls) (see Table 1).

Adult F1A rats were sacrificed 21 days after the F2 birth and examined histopathologically. Kidney lesions were observed in high-dose male rats only and were consistent with the pattern of early stages of alpha$_{2u}$-globulin-associated rat nephropathy as described by the Risk Assessment Forum (U.S. EPA, 1991a). Testing was not conducted, however, to demonstrate the presence of the protein alpha$_{2u}$, and thus the biological significance of this finding to humans is uncertain. No other toxicologically significant exposure-related changes in organ weights or increased incidences of lesions were found.

In summary, the results of the Cox et al. (1975) study demonstrate that the administration of 2-butanol in drinking water to rats at a concentration of 3% produced maternal toxicity accompanied by developmental effects, but did not affect reproductive performance (with the possible exception of effects on male rat copulatory success). 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 observed in the groups exposed to 3% 2-butanol in the drinking water. At the 2% level (adjusted 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 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%), reduced F1A pup weight was observed, but the reduction was not observed in subsequent

generations at the same exposure level. Developmental endpoints were not affected at the 0.3% exposure levels in any of the generations.

2-Butanol increased the incidence of kidney lesions in F1A generation rats that were exposed from gestation continuing through 12 weeks after birth, mating, and gestation and lactation of the F2 generation. No other treatment-related histopathology was observed.

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

Endpoint (generation)	Control	0.3% (594 mg/kg-day[a])	1% (1,771 mg/kg-day[a])	2% (3,122 mg/kg-day[b])
F1A pup body weight, day 4	10.7±1.1	10.2±1.3	10.0±1.3	8.3±1.8[c]
F1A pup body weight, day 21	49.0±3.8	47.0±3.9	44.0±4.8	30.0±11.9[c]
F1B fetal weight, gestation day 20	4.1±1.5	4.2±0.7	4.4±1.0	3.7±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	40.0±6.1	39.0±7.8	39.0±9.4	35.0±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] Mean weights for F1A pups exposed to 3% 2-butanol (4,571 mg/kg-day). These were not included in the modeling due to possibly confounding mortality.
Source: Cox et al. (1975).

Fetal weight data from the F1B generation and day 4 and 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, the 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 EPA's Benchmark Dose Software (BMDS version 1.3.1). The 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. (1975) study. The ED_{05} and LED_{05} values calculated from the various data sets from the study are summarized in Table 2.

Table 2. Benchmark doses for developmental effects in various generations of rats exposed to 2-butanol 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]	1,387	803
F1A pup body weight, day 21[b]	878	657
F1B fetal weight, gestation day 20	2,198	1,046
F2 pup body weight, day 4	3,471	1,347
F2 pup body weight, day 21	2,056	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.
Source: Cox et al. (1975).

LED_{05} values from the data sets are within 2-fold of each other, suggesting that 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 (LED_{05} = 657 mg/kg-day), was selected for deriving the RfD as the most health protective value.

A molar adjustment of the LED_{05} accounted for differences in the molecular weights of 2-butanol and MEK:

LED_{05} = 657 mg/kg-day 2-butanol x
72.1066 g/mol MEK

74.1224 g/mol 2-butanol

 = 639 mg/kg-day MEK

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 susceptible human subpopulations. In the absence of information on the variability in response of humans to MEK exposure, the default value of 10 was used.

A 10-fold uncertainty factor was used to account for deficiencies in the available MEK database. While no oral data are available for MEK, the available pharmacokinetic and inhalation toxicity data support 2-butanol as an appropriate surrogate for MEK. Nonetheless, the use of 2-butanol data to estimate the toxicity associated with MEK exposure introduces some uncertainty in the assessment. 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 and histopathologic changes in the kidney of male rats only. The absence of any other

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.

An uncertainty factor for extrapolation from a LOAEL to a NOAEL was not necessary because BMD modeling was used to determine the point of departure. The dose corresponding to a 5% decrease in pup weight, relative to control, was selected as the point of departure. There is no specific decrement in fetal/pup weight that is generally recognized as indicative of an adverse effect. Further, there were no other effects in the range of the LED_{05} of 657 mg/kg-day. Therefore, 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, 1991a), an uncertainty factor was not used to account for extrapolation from less than chronic results because developmental toxicity (decreased pup body weight following in utero and neonatal exposure) was used as the critical effect. The developmental period is recognized as a susceptible lifestage where exposure during certain time windows are more relevant to the 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.

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 to derive the RfD for MEK. 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. (1975) study is consistent with 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). While the finding is consistent with the pattern of early stages of alpha$_{2u}$-globulin-mediated rat nephropathy as described by the Risk Assessment Forum (U.S. EPA, 1991a), the biological significance of this finding to

humans is uncertain. Testing was not conducted to demonstrate the presence of the protein alpha$_{2u}$.

Data from the 13-week drinking water study with 3-hydroxy-2-butanone in CFE rats (Gaunt et al., 1972) suggest a possible 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 studies of 2-butanol (oral and inhalation exposure) or MEK (inhalation exposure). The Gaunt et al. (1972) study provides no information concerning the potential for developmental effects that have been identified as the key effects observed 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 the toxicity of MEK.

Pharmacokinetic and toxicologic data support the use of 2-butanol as an appropriate surrogate for MEK. Supporting pharmacokinetic findings in rats include: (1) orally administered 2-butanol was almost completely (96%) converted to MEK and its metabolites within 16 hours, (2) peak MEK blood concentrations occurred at similar times after the administration of 1,776 mg/kg 2-butanol (7-8 hours) and 1,690 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 the 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 of MEK 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 surrogate for MEK include: (1) fetal 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 to 2-butanol by inhalation during gestation (Nelson et al., 1989), and (2) the relationships between air concentrations and the degree of fetal weight changes were consistent for MEK and 2-butanol.

As an alternative to using 2-butanol data as a surrogate for MEK, the use of route-to-route extrapolation to derive oral doses from existing inhalation data was considered for developing an RfD for MEK. However, deficiencies in absorption data preclude the application of this method for MEK. See the Toxicological Review (U.S. EPA, 2003) for a detailed discussion of the relevant pharmacokinetic data.

For more detail on Susceptible Populations, exit to [the toxicological review, Section 4.7](#) (PDF).

I.A.5. Confidence in the Oral RfD

Study — Medium to Low
Database — 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, 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. (1975). 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.

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF).

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 EPA's Toxicological Review of Methyl Ethyl Ketone (U.S. EPA, 2003). *To review this appendix, exit to the toxicological review, Appendix A: Summary of External Peer Review and Public Comments and Disposition (PDF)*

Date of Agency Consensus — 09/10/2003

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

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (fax), or hotline.iris@epa.gov (email address).

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

Substance Name — Methyl ethyl ketone (MEK)
CASRN — 78-93-3
Last Revised — 09/26/2003

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.

The current RfC of 5 mg/m^3 replaces an earlier RfC of 1 mg/m^3 that was entered on IRIS 7/01/1992 (see Section VII. Revision History). The new RfC is based on the application of a newer methodology and consideration of new data.

I.B.1. Inhalation RfC Summary

Critical Effect	Experimental Doses*	UF	MF	RfC
Developmental toxicity (skeletal variations) **Mouse developmental study** **(Schwetz et al., 1991)**	LEC: 5,202 mg/m^3 LEC$_{(ADJ)}$: 1,517 mg/m^3 LEC$_{(HEC)}$: 1,517 mg/m^3	300	1	5 mg/m^3

*Conversion Factors and Assumptions: MW = 72.1. Assuming 25ºC and 760 mm Hg, 1 ppm = 72.1/24.45 = 2.95 mg/m^3. Duration adjustment of exposure concentrations was employed (7 h/day on days 6-15 of gestation): LEC$_{(ADJ)}$ = 5,202 mg/m^3 × 7 h/24 h = 1,517 mg/m^3. 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, LEC$_{(HEC)}$ = 1,517 mg/m^3 x ((H$_{b/g}$)$_A$/(H$_{b/g}$)$_H$) = 1,517 mg/m^3.

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

Deacon, MM; Pilny, MD; John, J.A; et al. (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, BA; Mast, TJ; Weigel, R.J; et al. (1991) Developmental toxicity of inhaled methyl ethyl ketone in mice. Fund Appl Toxicol 16:742-748.

Mast, TJ; Dill, JA; Evanoff, JJ; et al. (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, 1,000, or 3,000 ppm, respectively (7 hours/day on gestation days 6-15). Results from the study were also reported by Dow Chemical Corporation (1979). Average measured MEK concentrations were 412, 1,002, and 3,005 ppm (1,215, 2,955, and 8,865 mg/m^3). Dams exposed to 3,005 ppm MEK exhibited maternal toxicity that was demonstrated by a slight decrease in weight gain (326 g for 3,005 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 3,005 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 incidence 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 groups when compared with the control. Statistically significant differences in the incidence of litters with extra ribs was observed in the 3,005 ppm exposure group when compared with the controls. The incidence of extra ribs was 2/26 for control litters versus 0/19, 0/19, and 6/18 for 412, 1,002, and 3,005 ppm litters, respectively. Thus, this study found maternal toxicity (decreased weight gain) and fetal toxicity (increased incidence of skeletal variations) at 3,005 ppm (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, 1,010±28, or 3,020±79 ppm (0, 1,174±27, 2,980±83, or 8,909±233 mg/m^3) by inhalation for 7 hours/day on gestation days 6-15. Dams were then sacrificed on gestation day 18. Results from this study were also reported by Mast et al. (1989) and NTP (1990). At these exposure concentrations (0, 398, 1,010, or 3,020 ppm), the number of gravid/mated mice were 26/33, 23/33, 26/33, and 28/33, respectively. A slight concentration-related increase in liver-to-body-weight ratio (approximately 7% over control at 3,020 ppm) was observed in the dams. Two statistically significant developmental effects were observed: (1) a decrease in mean fetal weight (per litter) at 3,020 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 the 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 3,020 ppm exposure groups). No increase in the incidence of intrauterine death was observed in any of the exposed groups, and no statistically significant increases in the incidence of malformations occurred. Developmental and maternal effect levels were established at 3,020 ppm for a small,

but statistically significant, decrease in fetal weight among males, increased incidence of misaligned sternebrae, and an increase in maternal liver-to-body-weight ratio.

Data for the developmental effects described above in rats (Deacon et al., 1981) and mice (Schwetz et al., 1991) were analyzed by benchmark dose modeling (see Table 3).

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

Endpoint	Approximate MEK Concentration (ppm)			
	0	**400**	**1,000**	**3,000**
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 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/# of fetuses) **(Schwetz et al., 1991)**	31/310	27/260	49/291	58/323

All nested models for dichotomous variables available in EPA's 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. (1981) study. All models - the nested logistic (NLogistic), the NCTR, and the Rai and vanRyzin models - provided similar fits to the data. Model fits were 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 incorporating litter size (as a litter-specific covariate) or intralitter 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) is 3,317 ppm, and the corresponding LEC_{05} is 2,993 ppm (see Table 4).

Models for continuous data (linear, polynomial, or power) in EPA's Benchmark Dose Software (BMDS version 1.3.1), 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) (Table 3). A decrease in the mean fetal weight of 1 standard deviation of the control mean was selected as the benchmark response (BMR) for this endpoint consistent with the recommendations in EPA's Benchmark Dose Technical Guidance Document (U.S. EPA, 2000). This BMR corresponds to a 5% decrease in the mean control group weight for this data set. A constant variance linear continuous-variable model 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 weight of 1 standard deviation below the control mean is 3,339 ppm, and the corresponding LEC is 2,273 ppm (Table 4).

The nested, dichotomous-variable models available in the BMDS version 1.3.1 were fit to 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. The use of a non-linear model did not 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 within this range of the data set. Also, the Benchmark Dose Technical Guidance Document recommends estimating a 10% benchmark response (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} was calculated as the point of departure. The respective EC_{10} and LEC_{10} associated with a 10% extra risk for misaligned sternebrae were 3,214 and 1,764 ppm, respectively (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/m^3 (ppm)[a]	LEC, mg/m^3 (ppm)[a]
Increased incidence of extra ribs (rats) (Deacon et al., 1981)	5%	9,781 (3,317)	8,826 (2,993)
Decreased fetal body weight (mice)	1 s.d. (approx.	9,847	6,703

Endpoint	Benchmark Response Level	EC, mg/m^3 (ppm)[a]	LEC, mg/m^3 (ppm)[a]
(Schwetz et al., 1991)	5%)	(3,339)	(2,273)
Increased incidence of misaligned sternebrae (mice) (Schwetz et al., 1991)	10%	9,478 (3,214)	5,202 (1,764)

[a]Sample calculation: (2452 ppm x 72.1 mg/mmol)/24.45 = 7231 mg/m^3, assuming 25ºC and 760 mm Hg.

As shown in Table 4, benchmark modeling produced similar points of departure for the three developmental endpoints observed in the two species (within 2-fold). The lowest point of departure was based on the incidence of misaligned sternebrae in CD-1 mice exposed to MEK 7 hours/day on days 6-15 of gestation (LEC$_{10}$ = 5,202 mg/m^3) and was selected for deriving the RfC as the most health protective value.

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

UF = 300.

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 is 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 susceptible individuals within the human population. In the absence of information on the variability in response of humans to MEK exposure, the default value of 10 was used.

Consistent with EPA practice (U.S. EPA, 1991b), an uncertainty factor was not used to account for the extrapolation from less than chronic results because developmental toxicity

resulting from a narrow period of exposure (gestation days 6-15) was used as the critical effect. The developmental period is recognized as a susceptible lifestage when exposure during certain time windows of development are more relevant to the induction of developmental effects than lifetime exposure.

A 10-fold uncertainty factor was used to account for database deficiencies. As noted earlier, the minimum database requirements for deriving an RfC are satisfied by the Cavender et al. (1983) study. Inhalation developmental toxicity studies are available in two species (Deacon et al., 1981; Schwetz et al., 1991). The database lacks a chronic inhalation toxicity study and multigeneration reproductive toxicity study. 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 central nervous system lesions with special neuropathological procedures. The results from this study indicate that MEK has little, if any, neurotoxic potential by itself when tested in adult laboratory animals under conditions of high-level repeated inhalation exposure. Consistent with this finding is a lack of mechanistic evidence for neurotoxicity. The MEK database does not, however, specifically include a developmental neurotoxicity study.

A UF for extrapolation from a LOAEL to a NOAEL was not necessary because BMD modeling was used to determine the point of departure. The exposure concentration corresponding to a 10% extra risk of misaligned sternebrae in CD-1 mice (Schwetz et al., 1991) was selected as the point of departure. There is no specific level of extra risk for a skeletal variant that is generally regarded as indicative of an adverse effect. Further, there were no effects in the range of the LEC_{HEC} of 1,517 mg/m^3 other than those that appeared to be related to a general delay in growth. Therefore, no further adjustments were considered for identifying a level of inhalation exposure to MEK associated with a minimal level of risk.

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 central nervous system depression. Data from a series of NIOSH-sponsored 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 and numerous neurological studies are available (see Section 4.2.2. of U.S. EPA, 2003), but it lacks a chronic bioassay of MEK toxicity. While a subchronic inhalation toxicity study in rats is available (Cavender et al., 1983), it is not used as the principal study due to the potential 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 a high-quality study that 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, 1,254, 2,518, or 5,041 ppm (0, 3,700, 7,430, or 14,870 mg/m^3). Results of the 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 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 (5,041 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 when 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 5,041 ppm females and increased relative kidney weights in 5,041 ppm males and females. Differences in the serum chemistry values for female rats in the 5,041 ppm exposure group included significant increases in serum potassium, alkaline phosphatase, and glucose, and a significant decrease in SGPT activity when 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 higher mean corpuscular hemoglobin in 5,041 ppm male and female rats and higher mean corpuscular hemoglobin concentration in 5,041 ppm females. The findings corresponded to a slight but not significant decrease in number of red blood cells. With the exception of larger urine quantity in 5,041 ppm males, no urinalysis parameters were significantly different in MEK-exposed ratswhen compared with controls.

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 indicated possible liver damage, no histopathological lesions in the liver were observed. The authors stated that the response may have been the result of a physiological adaptation mechanism. While the decrease in brain weight in the 5,041 ppm females (9% compared to controls) indicated possible effects of MEK on brain tissue, no histopathological lesions of the brain were observed.

Minimal to mild lesions in the upper or lower respiratory tract were noted in all control and MEK-exposed rats and were coded as chronic respiratory disease consisting 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. While the authors suggested that the pulmonary lesions were secondary to mycoplasma infection, no infectious agent was cultured to verify this etiology. Since there is no indication that respiratory lesions are related to MEK exposure, the results confound the outcome of the study with regard to lesions of the upper respiratory tract.

In summary, review of the Cavender et al. (1983) findings reveals effects remote to the respiratory tract in the 5,041 ppm animals that are of uncertain biological significance, including: reduced body weight gain, statistically significant increases in relative liver weight (males and females) and altered serum liver enzymes (females), and decreased brain weight (females). As noted previously, reported liver effects are more likely indicative of a physiological adaptive response than toxicity. The finding of decreased brain weight observed in female rats raises concerns, but is difficult to interpret. Generally, with a brain weight reduction of 5%, one might expect evidence of corresponding pathology; however, no treatment-related brain pathology was observed in this study. The reduction in brain weight relative to controls observed in only one sex also raises questions about the relevance of the finding. Thus, while the reduction in brain weight at 5,041 ppm is noteworthy, its biological significance is uncertain.

Animal 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 1,125 ppm (3,318 mg/m^3) MEK for 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 5,041 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) 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 1,500 ppm (4,425 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 3,000 ppm MEK (7 hours/day) during gestation resulted in developmental effects (Schwetz et al., 1974, 1991; Deacon et al., 1981).

For more detail on Susceptible Populations, exit to [the toxicological review, Section 4.7](#) (PDF).

I.B.5. Confidence in the Inhalation RfC

Study — High
Database — 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 lacks 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 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.

For more detail on Characterization of Hazard and Dose Response, exit to [the toxicological review, Section 6](#) (PDF)

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 EPA's Toxicological Review of Methyl Ethyl Ketone (U.S. EPA, 2003). ***[To review this appendix, exit to the toxicological review, Appendix A: Summary of External Peer Review and Public Comments and Disposition (PDF)](#)***

Date of Agency Consensus — 09/10/2003

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

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (fax), or hotline.iris@epa.gov (email address).

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Methyl ethyl ketone (MEK)
CASRN — 78-93-3
Last Revised — 09/26/2003

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/cancerguidelines/draft-guidelines-carcinogen-ra-1999.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/m^3 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.

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF).

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.7 (PDF).

II.A.2. Human Carcinogenicity Data

Inadequate.

The small number of available epidemiological studies concerning 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 (Lowengart et al., 1987) 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 and one or more other solvents (dodecylbenzene, benzyl disulfide, phenylbenzothiophene, and/or decalin) twice a week for 1 year (Horton et al., 1965). A single skin tumor developed in 1 of 10 mice treated for 27 weeks with the solution containing 29% MEK, and in 1 of 15 mice treated with the solution containing 17% MEK. The study is an inadequate test of MEK carcinogenicity because of 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* (Zimmermann 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).

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

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

II.B.1. Summary of Risk Estimates

Not applicable.

II.B.2. Dose-Response Data (Carcinogenicity, Oral Exposure)

Not applicable.

II.B.3. Additional Comments (Carcinogenicity, Oral Exposure)

Not applicable.

II.B.4. Discussion of Confidence (Carcinogenicity, Oral Exposure)

Not applicable.

II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

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

II.C.1. Summary of Risk Estimates

Not applicable.

II.C.2. Dose-Response Data for Carcinogenicity, Inhalation Exposure

Not applicable.

II.C.3. Additional Comments (Carcinogenicity, Inhalation Exposure)

Not applicable.

II.C.4. Discussion of Confidence (Carcinogenicity, Inhalation Exposure

Not applicable.

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

II.D.1. EPA Documentation

Source Documents -- 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 EPA's Toxicological Review of Methyl Ethyl Ketone (U.S. EPA, 2003). *To review this appendix, exit to the toxicological review, Appendix A: Summary of External Peer Review and Public Comments and Disposition (PDF)*.

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

Agency Consensus Date — 09/10/2003

II.D.3. EPA Contacts (Carcinogenicity Assessment

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (fax), or hotline.iris@epa.gov (email address).

III. [reserved]
IV. [reserved]
V. [reserved]

VI. Bibliography

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

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VII. Revision History

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

Date	Section	Description
12/01/1989	II.	Carcinogen assessment on-line
08/01/1991	I.A.	RfD withdrawn pending further review
07/01/1992	I.B.	Inhalation RfC on-line
05/01/1993	I.A.	Oral RfD summary replaced; RfD changed
09/26/2003	I., II., VI.	RfD, RfC, and cancer sections updated

VIII. Synonyms

Substance Name — Methyl ethyl ketone (MEK)
CASRN — 78-93-3
Last Revised — 09/26/2003

- aethylmethylketon
- 2-butanone
- butanone-2
- ethyl methyl cetone
- ethylmethylketon
- ethyl methyl ketone
- ketone, ethyl methyl
- meetco
- MEK
- methyl acetone

- metiletilchetone
- metyloetyloketon
- RCRA waste number U159
- UN 1193
- UN 1232