Methyl Isobutyl Ketone (MIBK); CASRN 108-10-1;

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 Isobutyl Ketone

File First On-Line 03/31/1987

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	Withdrawn, qualitative discussion	04/25/2003
Inhalation RfC (I.B.)	yes	04/25/2003
Carcinogenicity Assessment (II.)	yes	04/25/2003

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

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

Substance Name — Methyl Isobutyl Ketone (MIBK)
CASRN — 108-10-1
Last Revised — 04/25/2003

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.

An oral RfD for methyl isobutyl ketone (MIBK) was withdrawn on 03/01/91. The health effects data for MIBK were reviewed by EPA at that time and determined to be inadequate for derivation of an oral RfD.

I.A.1. Oral RfD Summary

Not applicable. No oral RfD was developed for MIBK because no critical effect was identified after subchronic exposure. As no chronic oral studies were available, it is uncertain whether chronic exposure at the same exposure levels would have induced biologically significant adverse effects. The database was limited to two subchronic oral exposure studies: one 13-week gavage exposure study (Microbiological Associates, Inc., 1986) and one 90-day *ad libitum* drinking water study (Carnegie-Mellon Institute, 1977a, b). Effects that may be associated with changes in the liver or kidney occurred at approximately 1000 mg/kg-day in both studies and at 250 mg/kg-day in the gavage study, but the effects were not considered to be clearly adverse for reasons discussed in section 4.5.1 of the Toxicological Review (U.S. EPA, 2003).

Transient lethargy, a clear adverse effect, was also reported at 1000 mg/kg-day in the subchronic gavage study, but severity and prevalence data by dose level were not provided, so it was not clear whether the effect was significantly elevated from control levels. In addition, the lethargy was rated as only minimal to mild to moderate, and it was only observed in close association with the gavage exposures but not with drinking water exposure. Thus, acute lethargy may have been an artifact of the bolus method of administration that probably resulted in repeated, temporarily high blood levels of MIBK (or metabolites). The relevance of bolus oral exposures to likely chronic oral exposure scenarios in humans is uncertain. Thus, no quantitative risk assessment was conducted for the transient lethargy endpoint.

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

Not applicable.

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

Not applicable.

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

Not applicable.

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

I.A.5. Confidence in the Oral RfD

Not applicable.

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 U.S. EPA (2003). ***To review this appendix, exit to the toxicological review, Appendix A, Summary of and Response to External Peer Review Comments (PDF).***

Agency Consensus Date — 04/02/2003

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 Isobutyl Ketone (MIBK)
CASRN — 108-10-1
Last Revised — 04/25/2003

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/cu.m. In general, the RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily inhalation exposure of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Inhalation RfCs were derived according to the Interim Methods for Development of Inhalation Reference Doses (EPA/600/8-88/066F August 1989) and subsequently, according to Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (EPA/600/8-90/066F October 1994). RfCs can also be derived for the noncarcinogenic health effects of substances that are carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

I.B.1. Inhalation RfC Summary

Critical Effect	Exposures*	UF	MF	RfC
Reduced fetal body weight, skeletal variations, and increased fetal death in mice, and skeletal variations in rats (Tyl et al., 1987).	$NOAEL_{HEC}$ = 1026 mg/m^3 $LOAEL_{HEC}$ = 3073 mg/m^3	300	1	3 mg/m^3

* Conversion Factors and Assumptions — HECs were calculated according to EPA guidance (U.S. EPA, 1994) for category 3 gases by adjusting intermittent exposure levels to a continuous exposure basis and multiplying the result by a ratio of the animal blood gas partition coefficient ($NOAEL_{HEC}(mg/m^3) = NOAEL_{ADJ}(mg/m^3) \times (H_{b/g})_A/(H_{b/g})_H$). EPA guidance (U.S. EPA, 1994) indicates that the default value of the $(H_{b/g})_A/(H_{b/g})_H$ ratio should be set equal to 1 if blood:air partition coefficient data are not available for either humans or animals. As no animal blood:air partition coefficients were located, the $LOAEL_{HEC}$ and $NOAEL_{HEC}$ values for MIBK were set equal to the continuous duration-adjusted exposure concentrations in all cases.

In the Tyl et al. (1987) study, the daily exposure cycle was comprised of 6 hours of exposure followed by 18 hours of no exposure. Therefore, experimental concentrations in Tyl et al. (1987) were duration-adjusted (by a factor of 6/24) to provide estimated equivalent continuous exposure concentrations, consistent with U.S. EPA (2002).

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

Tyl, R.W., K.A. France, L.C. Fisher, I.M. Pritts, T.R. Tyler, R.D. Phillips, and E.J. Moran. (1987) Developmental toxicity evaluation of inhaled methyl isobutyl ketone in Fischer 344 rats and CD-1 mice. Fundam Appl Toxicol 8:310-327.

WIL Research Laboratories. (2000) An inhalation two-generation reproductive toxicity study of methyl isobutyl ketone (MIBK) in rats. (Revised audited draft of only the first of 9 volumes). Sponsored by the Chemical Manufacturers Association. Lab Study No. WIL-186007; Sponsor Study No. KET-14.0-MIBK-WIL.

The Tyl et al. (1987) developmental toxicity study was identified as the principal study and is described below; the WIL Research Laboratories (2000) reproductive toxicity study is presented to support the principal study.

The NOAEL-LOAEL approach was used to identify the critical effect from inhalation exposure in animals. The method used to review the entire data array to decide on the critical effect was to convert all inhalation effect levels to HEC exposure levels following EPA guidance (U.S. EPA, 1994) and identify the lowest HEC exposure level associated with clearly adverse effects. By this method of comparison, the lowest HEC adverse effect level was identified as 3073 mg/m^3 in the Tyl et al. (1987) study, and among the effects observed at that exposure level, the critical effects were skeletal variations in mice and rats and reduced fetal body weight and increased fetal death in mice. The corresponding $NOAEL_{HEC}$ was 1026 mg/m^3. Several additional effects observed at 3073 mg/m^3 (but not at 1026 mg/m^3) in the Tyl et al. (1987) study included hypoactivity, ataxia, and lacrimation in mouse and rat dams and reduced maternal body weight and body weight gain in rats. In a two-generation reproductive toxicity assay in rats (WIL Research Laboratories, 2000), no neonatal developmental effects (number of offspring with gross external malformations at birth, number of stillbirths, number of live births, body weight on post-natal day 1, or survival to post-natal day 4) were seen in either generation of rats exposed to air concentrations of MIBK up to 8219 mg/m^3 (2055 mg/m^3 HEC) for 6 hrs/day for 70 days prior to mating, throughout mating, and during most of gestation and lactation.

Tyl et al. (1987):
Developmental and maternal toxicity were evaluated in groups of 35 pregnant Fischer 344 rats

and 30 pregnant CD-1 mice exposed by inhalation to 0, 300, 1000, or 3000 ppm (0, 307, 1026, 3073 mg/m^3) MIBK for 6 hrs/day on gestation days 6 through 15 (Bushy Run Research Center, 1984; Tyl et al., 1987). Animals were sacrificed on gestation day 21 (rats) or 18 (mice). Dams were evaluated for exposure-related changes in clinical signs, body weight, food consumption, organ weights (kidney, liver, and gravid uterus), and reproductive parameters; fetuses were evaluated for exposure-related changes in body weight and viability and for external, skeletal, and thoracic and peritoneal visceral alterations.

Maternal mean body weight, weight gain, and food consumption were significantly decreased in rats exposed to 3073 mg/m^3 (but not to <=1026 mg/m^3) MIBK during the exposure period, but they had recovered to control levels by the day of sacrifice; maternal body weight was not affected in mice. Maternal clinical signs observed in rats or mice included coordination loss, hindlimb weakness, paresis, irregular gait, hypoactivity, ataxia, unkempt fur, negative tail or toe pinch, piloerection, lacrimation, or red perioral encrustation; these clinical signs were observed only during the exposure period and only at 3073 mg/m^3. Three maternal deaths (12% of the animals in the group) occurred in mice exposed to 3073 mg/m^3 after the first exposure on gestation day 6; no further deaths occurred in that group, and no exposure-related deaths occurred in the other mouse or rat exposure groups.

No exposure-related effects were observed in rats or mice with respect to numbers of corpora lutea, total implants, percent implantation loss, live fetuses per litter, non-viable implants per litter, percent live fetuses, and sex ratio. In mice, there was an increased mean number of dead fetuses per litter at 3073 mg/m^3 (0.6 per litter as compared to 0.1 in controls). Fetal body weights (litter weight, male weight per litter, and female weight per litter) were significantly reduced in rats exposed to 307 (the mean by 3%) and 3073 mg/m^3 (the mean by 6%) (not at 1026 mg/m^3), and in mice at 3073 mg/m^3 (the mean by 13%) (not at <=1026 mg/m^3). The authors indicated that the reduced fetal body weight in rats at 307 mg/m^3 was confounded by litter size and was apparently not treatment-related.

No exposure-related change in the incidence of malformations of any type were observed in rat and mouse fetuses. The number of litters with observations indicating retarded skeletal ossification was significantly increased to various degrees in both rats and mice at 3073 mg/m^3 relative to controls for a variety of skeletal endpoints, with scattered increases in litters with retarded ossification at lower exposure levels that were not considered by the authors to be exposure-related. The numbers of individuals with various manifestations of retarded skeletal ossification were also apparently increased in rats and mice at 3073 mg/m^3 relative to controls, but no results of statistical comparisons were indicated in the study report.

WIL Research Laboratories (2000):
Reproductive toxicity of MIBK was evaluated in a two-generation inhalation study in

Crl:CD®(SD)BR rats (WIL Research Laboratories, 2000). Groups of 30 male and 30 female F_0 rats were exposed whole-body to MIBK vapors at mean measured concentrations of 0, 491, 999, and 1996 ppm (0, 2012, 4093, and 8178 mg/m^3) for 6 hrs/day for 70 consecutive days prior to mating and throughout mating. F_0 females were further exposed until gestation day 20 and again during lactation days 5 to 21; pups were not directly exposed during lactation. Litters were culled to four per sex on lactation day 4. At weaning on lactation day 21, groups of 30 male and 30 female F_1 rats at each exposure level were randomly selected, including at least one male and one female from each viable litter. Beginning at 7 days after weaning, selected F_1 rats were exposed (using the same exposure schedule that was used for the F_0 rats) to mean measured concentrations of 0, 506, 1002, and 2006 ppm (0, 2073, 4105, and 8219 mg/m^3).

F_0 and F_1 parental rats were evaluated for reproductive endpoints (estrous cycle regularity and duration, sperm count, production rate, motility, and morphology, mating and fertility indices, number of days between pairing and coitus, gestation length, parturition, litter size, pup sex ratio, and ovarian follicle counts and corpora lutea in control and high-exposure females), survival, clinical signs, startle response, food consumption, body weight, organ weights, comprehensive gross pathology, and histopathology of major organ systems and all gross lesions (10/sex in control and high-exposure groups and all rats that died prior to terminal sacrifice).

F_1 and F_2 pups were evaluated for developmental endpoints, including post-natal survival (both before and after resumption of maternal exposures during lactation), clinical signs, body weight, and external anatomical integrity (skeletal examinations were conducted in pups with abnormal external changes). F_1 pups were also evaluated for balanopreputial separation in males and vaginal perforation in females. Complete gross pathology evaluations were performed in F_1 pups that were not selected for mating and in all F_2 pups. The report did not mention any examination of hematology, blood chemistry, and urine chemistry in parental groups or offspring of either generation.

Parental survival in both generations was unaffected by exposure. Only transient deviations of body weight from control levels were observed in F_0 rats. High-exposure F_1 parental female body weights were depressed through mating but not throughout gestation and lactation. F_1 parental males showed transient depressed body weight at 2073 and 4105 mg/m^3 and consistently depressed body weight at 8219 mg/m^3, in spite of elevated food consumption (g food consumed/kg bw/day) in the 8219 mg/m^3 exposure group. No exposure-related effect on body weight gain was seen in parental rats of either generation. Among F_0 rats, increased relative liver weights (males and females at 8178 mg/m^3) and increased relative kidney weights (males at >=2012 mg/m^3; females at >=4093 mg/m^3) were observed. Significantly increased relative adrenal and ovary weights were also observed in F_0 females at 8178 mg/m^3.

In the F_1 parental groups, significant increases in relative liver weight (males at >=4105 mg/m^3; females at 8219 mg/m^3) and relative kidney weight (males at >=2073 mg/m^3; females at 8219 mg/m^3) were observed, and significantly increased relative seminal vesicle, right testis, left cauda epididymis, and adrenal glands were seen in F_1 parental males at 8219 mg/m^3.

The incidence of rats with centrilobular hepatocellular hypertrophy (considered by the authors to be an adaptive response) was significantly increased in F_0 males at >=4093 mg/m^3 and in F_1 parental males at >=4105 mg/m^3. The prevalence of nephropathy characterized by inflamed and thickened basophilic tubule membranes was significantly increased in F_0 males exposed to 8178 mg/m^3 and in F_1 parental males at >=4105 mg/m^3. F_1 parental males also showed increased prevalence of acidophilic spherical inclusions/droplets in the renal cortical tubular epithelium at >=4105 mg/m^3, but the authors reported that there was no evidence of fully developed $alpha_{2u}$-globulin-related renal tubular lesions. No other exposure-related gross or microscopic tissue changes were observed in F_0 or F_1 parental groups.

Signs suggestive of CNS depression were observed in mid- and high-exposure parental groups in both generations. Reduced startle response during exposure was observed in F_0 males and females at >=4093 mg/m^3, in F_1 parental males at >=4105 mg/m^3, and in F_1 parental females at 8219 mg/m^3. Transient unsteady gait and prostration were observed among F_1 parental males and females approximately 1 hour following exposure to 8219 mg/m^3 on several days prior to mating, but the effect attenuated with repeated exposures; similar neurological symptoms were not reported in F_0 rats.

The only effect reported in offspring was significantly depressed body weights on day 14 post-partum in F_1 and F_2 male and female pups in mid- and high-exposure groups; however, pup body weights were not different from those of controls on days 7 and 21 post-partum. No other exposure-related changes were observed in any reproductive or developmental endpoint in either generation, including an absence of anatomical changes in F_0 and parental F_1 reproductive organs.

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

UF = 300.

An uncertainty factor of 3 was used for interspecies extrapolation. A factor of 10 was not used because EPA guidance (U.S. EPA, 1994) was followed for animal-to-human dosimetric adjustment of exposure levels. A factor of 10 was used for intraspecies variability. An additional uncertainty factor of 10 for database deficiency was also applied, based on the lack of developmental neurotoxicity data and definitive neurotoxicity data in general, and based on the lack of any chronic toxicity data. A two-year bioassay that is currently being conducted by

the National Toxicology Program but was not available for inclusion at the time of this assessment; this study might have permitted further consideration of the liver, kidney, and CNS effects reported in numerous subchronic inhalation studies. Because critical developmental stages may occur within brief time windows during gestation, exposure concentration may be more important than total exposure period duration for inducing developmental effects during gestational exposures. Therefore, an uncertainty factor for extrapolation from subchronic to lifetime exposure duration was not applied, following EPA guidance (U.S. EPA, 1991a).

MF = 1.

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

No studies were available that provided reliable MIBK exposure-response data in humans from chronic or subchronic inhalation exposures. Studies of workers exposed repeatedly to mixtures of solvents that include MIBK have associated various neuropathies and decrements in neurobehavioral performance tests with exposure (AuBuchon et al., 1979; Tsai et al., 1997; Valciukas et al., 1985). However, the results are not sufficient for establishing causality or for characterizing an inhalation exposure-response relationship in humans, as exposure levels for individual solvents were not reported and/or the degree to which MIBK contributed to the observed effects is uncertain.

No chronic duration inhalation exposure studies in animals were available.

The available inhalation data in the substantial database of subchronic MIBK inhalation studies in animals indicate that developmental effects were the most clearly adverse effects. The following discussion provides an evaluation of effects that may be associated with adverse changes to the liver, kidney, and CNS that were reported in animals at exposure levels comparable to those associated with developmental effects. Because these effects did not show a clear, toxicological continuum of severity and/or marked progression of response with increasing dose or any treatment-related corroborative gross pathologies or histopathological lesions, they were not considered to be clearly adverse and were therefore considered to be of uncertain relevance to effects in humans after chronic exposures.

Evidence indicating that an MIBK-induced increase in serum cholesterol occurred in animals after subchronic inhalation exposure is relatively strong, but the increases were not dramatic and the effect was not sufficiently adverse to be considered the critical effect in the absence of a continuum of increasingly severe, related effects, such as liver lesions, at higher exposure levels. Moreover, it is uncertain if the increases in serum cholesterol in rats following exposure to MIBK have any relevance to humans for more severe effects, like cardiovascular

toxicity, since it is generally acknowledged that the rat model is not considered a good species for predicting cardiovascular effects in humans and because the rat, like the mouse, is relatively resistant to hyperlipidemia and atherosclerosis (Sipes et al., 1997; Loeb and Quimby, 1999). The HEC exposure level of 185 mg/m^3 was associated with increased serum cholesterol in 26-week-old male Fischer 344 rats after a 13-week intermittent inhalation exposure (Phillips et al., 1987). The observed mean serum cholesterol levels of 59 and 65 mg/dL at 185 and 737 mg/m^3 HEC exposures, respectively, were elevated not only as compared to the study control group (Phillips et al., 1987), but also as compared to other relevant reference values.

Although adverse gross or histopathological liver lesions were not observed in any animal inhalation study, Duguay and Plaa (1997) provided evidence that increased *de novo* hepatocellular synthesis of cholesterol occurred in male rats after acute inhalation exposure to 200 and 600 ppm MIBK (819 and 2458 mg/m^3; 4 hrs/day for 3 days) but not after acute exposure to 100 ppm (410 mg/m^3). They found that MIBK-induced accumulation of newly synthesized cholesterol in the bile canalicular membrane apparently altered the membrane lipid dynamics, possibly potentiating cholestasis that was induced by other chemicals.

Interference with cholesterol metabolism in other parts of the body cannot be ruled out as a possible contributing mechanism of hypercholesterolemia. In spite of relatively strong evidence indicating that hypercholesterolemia occurs in rats after subchronic repeated inhalation exposures to MIBK, in the absence of histopathological changes in the liver the effect was not considered to be clearly adverse. The available database does not provide sufficient information to indicate whether chronic inhalation exposures would cause more severe liver effects in animals.

Hepatomegaly in mice was also associated with the HEC exposure levels of >=185 mg/m^3 (Phillips et al., 1987), but there was no evidence of any other hepatic effect in mice at any exposure level; thus, the mouse hepatomegaly may be considered simply an adaptive response to prolonged hepatic metabolism of MIBK.

Increased urinary glucose occurred in male rats at 185 mg/m^3 and in both sexes at a higher exposure level (Phillips et al., 1987), suggesting that the ability of the kidney proximal tubule to resorb sugars was impaired, particulary since blood sugar levels were unaffected at the same exposure levels. In this study, alpha$_{2u}$-globulin hyaline droplet formation but no other renal lesions was observed in male rats at the same exposure levels that induced glucosuria. However, renal hyaline droplet formation is not considered by EPA to be relevant to humans for the purposes of risk assessment, because alpha$_{2u}$-globulin is produced in male rats to much greater degrees than in female rats or humans (U.S. EPA, 1991b). The impaired renal function indicated by glucosuria may be attributable to the hyaline droplet lesions in male rats (Phillips

et al., 1987). Glucosuria observed in high-exposure females may be indicative of nascent adverse kidney changes but are not corroborated by observations of kidney histopathologies. Glucosuria occurred at exposure concentrations lower than those associated with the kidney weight increases observed in several studies.

Effects associated with adverse changes in the liver and kidney generally occurred at lower concentrations than neurological effects in repeated exposure animal studies. The principal effects associated with neurological impairment in animals were behavioral changes (e.g., hypoactivity, ataxia, and unsteady gait) that were only observed during exposure events in repeated exposure studies. The lowest HEC exposure level at which neurological effects were observed in animals was 549 mg/m^3 for reduced activity in rats that only occurred during the daily 6-hour exposure events (David et al., 1999). Because the neurological symptoms are acute effects that occur during exposure events, it may not be appropriate to adjust exposure concentrations in repeated exposure experiments to continuous exposure equivalents for these effects. Indeed, neurological symptoms were observed during exposure events in rats at the exposure duration-adjusted concentration of 549 mg/m^3 (actually repeated exposure to 3073 mg/m^3) (David et al., 1999), but no neurological effects were seen in rats, dogs, and monkeys that were exposed continuously to an exposure level (410 mg/m^3) comparable to the duration-adjusted level (MacEwen et al., 1971; MacKenzie, 1971; Vernot et al., 1971).

Neurological clinical signs attenuated with repeated exposure over 13 weeks (David et al., 1999), possibly reflecting an adaptive increase in the capacity for hepatic metabolism of MIBK. Repeated exposures at higher MIBK concentrations induced more severe symptoms, such as ataxia, coordination loss, hindlimb weakness, paresis, and irregular gait (Bushy Run Research Center, 1984; Tyl et al., 1987; WIL Research Laboratories, 2000). However, the database of subchronic inhalation animal studies-including one comprehensive histological evaluation of central and peripheral nervous system tissues (Spencer et al., 1975)-includes no reports of MIBK-induced adverse effects in gross and histological examinations of nervous system tissues (Carnegie-Mellon Institute of Research, 1977a,b; David et al., 1999; Hazleton Laboratories, Inc., 1966, 1968; MacEwen et al., 1971; MacKenzie, 1971; Phillips et al., 1987; Vernot et al., 1971) or in batteries of neurobehavioral task performance tests (David et al., 1999; Garcia et al., 1978; Geller et al., 1978).

MIBK may induce the observed neurological symptoms by causing transient nerve membrane changes. On the basis of experiments in isolated mouse synaptosomes, Huang et al. (1993) proposed that monoketones, including MIBK, may disrupt the function of embedded enzymes and receptor proteins in nerve cell membranes by increasing the fluidity of the membrane. The transient nature of observed neurological symptoms corresponds with the observation that blood levels of MIBK increase during exposure but rapidly drop off after cessation of an exposure event (Hjelm et al., 1990) because MIBK is rapidly metabolized (Granvil et al.,

1994). MIBK levels peaked quickly in the brain, and then MIBK was rapidly eliminated from brain tissue in mice administered a single intraperitoneal injection, whereas the brain levels of a principal MIBK metabolite, 4-hydroxy-4-methyl-2-pentanone, continued to increase throughout a 90-minute post-exposure period (Granvil et al., 1994). No studies were located that evaluated the ability of MIBK metabolites to induce neurological effects.

In summary, reduced fetal body weight, delayed ossification, and increased fetal death in mice and skeletal variations in rats were identified as the critical effects in a substantial database of subchronic inhalation studies; the $LOAEL_{HEC}$ for developmental effects was 3073 mg/m^3 and the corresponding $NOAEL_{HEC}$ was 1026 mg/m^3 (Tyl et al., 1987). In a two-generation inhalation reproductive toxicity assay in rats (WIL Research Laboratories, 2000), no developmental effects were observed in neonates at exposure levels up to 8219 mg/m^3 (2055 mg/m^3 HEC). Effects that may be associated with adverse changes to the liver, kidney, and CNS were also reported in numerous subchronic inhalation studies at comparable exposure levels, but in the absence of effects data from chronic exposure studies, they were not considered to be clearly adverse and therefore were considered to be of uncertain relevance to effects in humans from chronic exposures.

Benchmark dose methodology was explored for estimating an RfC for MIBK, but was not considered an appropriate method of dose-response analysis for the developmental toxicity endpoints selected as the critical effect (see Toxicological Review, U.S. EPA, 2003). A more traditional approach based on NOAEL/LOAEL perspective was applied.

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

I.B.5. Confidence in the Inhalation RfC

Study — medium
Database — low to medium
RfC -- low to medium

Confidence in the principal inhalation study is medium because it uses an adequate number of study animals and exposure levels to evaluate a comprehensive set of developmental endpoints. Confidence in the inhalation toxicity database is low to medium because the database comprises a number of well-designed subchronic toxicity, neurotoxicity, and reproductive/developmental toxicity animal bioassays, but no data were available for lifetime exposures that would be useful for definitive evaluation of the biological significance of observed liver, kidney, and CNS effects. No studies have evaluated immunotoxicity in laboratory animals, although existing bioassays provide no suggestion that immune effects are

expected to occur in association with MIBK exposure. Confidence in the selection of the critical effects of reduced fetal body weight, skeletal variations, and increased fetal death in mice and skeletal variations in rats is medium because the developmental effects are clearly adverse and indicate a clear threshold for developmental effects. A constellation of effects from subchronic inhalation assays, however, are suggestive of adverse changes in the kidney, liver, and CNS and occurred at similar exposure levels. The kidney, liver, and CNS effects are collectively suggestive of adverse changes but individually are not sufficiently adverse to be considered critical effects in the absence of clearly adverse changes such as gross or histopathological lesions. Overall confidence in the RfC is low to medium, reflecting a lack of information concerning liver, kidney, and CNS effects after chronic exposure and a lack of data regarding health effects from chronic duration inhalation exposure in humans or animals.

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 U.S. EPA (2003).***To review this appendix, exit to the toxicological review, Appendix A, Summary of and Response to External Peer Review Comments (PDF)***.

Agency Consensus Date — 04/02/2003

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 Isobutyl Ketone (MIBK)
CASRN — 108-10-01
Last Revised — 04/25/2003

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/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 cancer guidelines (U.S. EPA, 1999), the data for MIBK are inadequate for an assessment of human carcinogenic potential. No data were located regarding the existence of an association between cancer and MIBK exposure in humans, but studies of the in vivo and in vitro genotoxicity of MIBK overwhelmingly provided negative responses (Brooks et al., 1988; Goodyear Tire and Rubber Company, 1982; Litton Bionetics, Inc., 1978; Microbiological Associates, 1984a, b, c, d, e, f; O'Donoghue et al., 1988; Shell Oil Company, 1982).

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

No cancer epidemiology studies were located for this assessment.

II.A.3. Animal Carcinogenicity Data

No carcinogenicity assays in animals were located for this assessment.

II.A.4. Supporting Data for Carcinogenicity

Not applicable.

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

No quantitative estimate of carcinogenic risk from oral exposure was derived because no cancer epidemiology studies in humans and no carcinogenicity assays in animals were located.

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

No quantitative estimate of carcinogenic risk from inhalation exposure was derived because no cancer epidemiology studies in humans and no carcinogenicity assays in animals were located.

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).***To review this appendix, exit to the toxicological review, Appendix A, Summary of and Response to External Peer Review Comments (PDF)***.

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

Agency Consensus Date — 04/02/2003

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 (enternet address).

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

VI. Bibliography

Substance Name — Methyl Isobutyl Ketone (MIBK)
CASRN — 108-10-1

VI.A. Oral RfD References

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VII. Revision History

Substance Name — Methyl isobutyl ketone
CASRN — 108-10-1

Date	Section	Description
03/01/1991	I.A.	Oral RfD withdrawn pending additional review
04/25/2003	I., II, VI.	RfD, RfC and cancer sections updated

VIII. Synonyms

Methyl isobutyl ketone (MIBK)
CASRN — 108-10-1
Last Revised — 04/25/2003

- 108-10-1
- HEXON
- HEXONE
- ISOBUTYL-METHYLKETON
- ISOBUTYL METHYL KETONE
- ISOPROPYLACETONE
- KETONE, ISOBUTYL METHYL
- METHYL-ISOBUTYL-CETONE
- METHYLISOBUTYLKETON
- Methyl Isobutyl Ketone
- 4-METHYL-PENTAN-2-ON
- 2-METHYL-4-PENTANONE
- 4-METHYL-2-PENTANONE
- METILISOBUTILCHETONE
- 4-METILPENTAN-2-ONE
- METYLOIZOBUTYLOKETON
- MIBK
- MIK
- 2-PENTANONE, 4-METHYL-
- RCRA WASTE NUMBER U161

- SHELL MIBK
- UN 1245