Methyl tert-butyl ether (MTBE); CASRN 1634-04-4

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 MTBE

File First On-Line 12/01/1991

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	not evaluated	
Inhalation RfC (I.B.)	yes	09/01/1993
Carcinogenicity Assessment (II.)	not evaluated	

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

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

Substance Name — Methyl tert-butyl ether (MTBE)
CASRN — 1634-04-4

Not available at this time.

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

Substance Name — Methyl tert-butyl ether (MTBE)
CASRN — 1634-04-4
Last Revised — 09/01/1993

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

I.B.1. Inhalation RfC Summary

Critical Effect	Exposures*	UF	MF	RfC
Increased absolute and relative liver and kidney weights and increased severity of spontaneous renal lesions (females), increased prostration (females), and swollen periocular tissue (males and females) **Chronic Rat 24-Month Inhalation Study** **Chun et al., 1992**	NOAEL: 1453 mg/cu.m (403 ppm) NOAEL(ADJ): 259 mg/cu.m NOAEL(HEC): 259 mg/cu.m LOAEL: 10899 mg/cu.m (3023 ppm) LOAEL(ADJ): 1946 mg/cu.m LOAEL(HEC): 1946 mg/cu.m	100	1	3E+0 mg/cu.m

*Conversion Factors and Assumptions — MW = 88.15. Assuming 25 C and 760 mmHg, NOAEL(mg/cu.m) = 403 ppm x 88.15/24.45 = 1453. NOAEL(ADJ) = 1453 x 6 hours/24 hours x

5 days/7 days = 259 mg/cu.m. The NOAEL(HEC) was calculated for a gas:extrarespiratory effect in rats assuming periodicity was attained. Because the b:a lambda values are unknown for the experimental species (a) and humans (h), a default value of 1.0 is used for this ratio. NOAEL(HEC) = NOAEL(ADJ) x [b:a lambda(a)/b:a lambda(h)] = 259 mg/cu.m.

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

Chun, J.S., H.D. Burleigh-Flayer, and W.J. Kintigh. 1992. Methyl tertiary butyl ether: vapor inhalation oncogenicity study in Fischer 344 rats (unpublished material). Prepared for the MTBE Committee by Bushy Run Research Center, Union Carbide Chemicals and Plastics Company Inc. Docket No. OPTS- 42098.

In a chronic inhalation study (Chun et al., 1992), Fischer 344 rats (50 males, 50 females/group) were exposed to analytical mean concentrations of 403, 3023, or 7977 ppm methyl tertiary-butyl ether (MTBE) vapors (1453, 10,899, or 28,760 mg/cu.m) 6 hours/day, 5 days/week for 24 months (duration- adjusted values are 259, 1946, and 5136 mg/cu.m, respectively). The control animals breathed air. Hematology (all rats) was performed halfway through the experiment (control and high-concentration groups) and prior to final sacrifice (all groups). Blood and urine samples were collected and stored, but complete serum chemistry and urinalysis were not performed. Corticosterone levels were measured on 10 rats/sex/group prior to sacrifice. Clinical signs, body weights, organ weights, and food consumption were monitored. Complete necropsy and histopathology, including examination of the nasal turbinates and lower respiratory tract, were performed on all animals.

Survival times for females were not significantly different between exposed and control rats. A slight decrease in mean survival time was observed in the males exposed to the low concentration (controls, 632 days; low-concentration group, 617 days; $p < 0.05$). Survival time clearly decreased in males exposed to both the mid and high concentrations (mid-concentration group, 587 days; high-concentration group, 516 days; $p < 0.01$), leading to earlier sacrifice times at 97 and 82 weeks, respectively. According to study pathologists, chronic, progressive nephropathy was the main cause of death in the higher concentration groups and also contributed to a slight increase in mortality in the males exposed to the low concentration (Garman, 1993a,b). In NTP oral and inhalation 2-year studies of other compounds that exacerbate rat chronic, progressive nephropathy (e.g., 1,4-dichlorobenzene, dimethyl methylphosphonate, hexachloroethane, isophorone, pentachloroethane, tetrachloroethylene, chlorothalonil, and trichloroethylene), survival rates in male rats have been low, particularly in the high-dose groups (U.S. EPA, 1991). As with MTBE, decreased survival of male rats exposed to dimethyl methylphoshponate was attributed, at least in part, to chemically related kidney toxicity (i.e., nephropathy) (NTP, 1987).

For animals exposed to the high concentration, clinical signs that were markedly increased over controls were ataxia (2-4% of controls at end of study vs. 100% of males and females at high-exposure level starting day 2) and earlier onset and increased incidence of swollen periocular tissue (<50% of controls at end of study vs. 84% of males and 100% of females starting day 12). The observation of ataxia at this exposure level is consistent with findings from the subchronic study discussed below (Dodd and Kintigh, 1989). Increased salivation was observed in males only at the high-exposure level. At the mid-concentration level, the authors did not report increased ataxia, but an increase in incidence of prostration was observed in females (6/50 controls vs. 15/50 at the mid concentration). Early onset and increased incidence of swollen periocular tissue were also reported at the mid- concentration level (68% of males and 100% of females starting days 12 and 19, respectively). Swollen periocular tissue, salivation, and prostration were not reported at any exposure level in the subchronic study (Dodd and Kintigh, 1989).

As is discussed in Section I.B.4., the corresponding subchronic study by Dodd and Kintigh (1989) assessed several neurological endpoints, including pathological examinations, brain size parameters, and functional observational batteries (FOBs). The only CNS effect found in the subchronic study at the 4000-ppm level was a slight decrease in brain length of the male rats ($p < 0.05$). Significant ($p < 0.05$) decreases in absolute brain weights of 8000-ppm males and females supported the use of this endpoint as a critical effect for derivation of the previously reported MTBE RfC, which was based on these 90- day study data. The chronic study did not measure brain length as a parameter, but did assess brain weight. The lack of brain length measurements in the chronic study is not considered a major study deficit because no significant differences in male or female brain weights were observed at any chronic exposure level.

As was observed in the subchronic study (Dodd and Kintigh, 1989), body weight gain and absolute body weight were decreased in both sexes of the high- concentration group. Just prior to sacrifice at week 81, body weight gain and absolute body weight in males were decreased 29 and 19%, respectively. Body weight gain and absolute body weight in females were decreased 22 and 13%, respectively, at the end of the study. Exposure-related, 18-25% increases in kidney and liver weights (absolute and relative to body and brain weights) were reported in females in the mid- and high-exposure groups ($p < 0.01$). No significant increases in liver or kidney weights were observed in the male rats.

No concentration-related histopathologic findings were reported in the livers of either sex. Increased incidence of hepatocellular hypertrophy (males) and degeneration (females) were observed in animals exposed to the mid concentration, but not the high concentration. No treatment-related lesions were observed in the respiratory tract in any group. Similarly, no pathologic changes were reported in the corresponding subchronic study by Dodd and Kintigh (1989).

Increases in microscopic kidney changes indicative of chronic nephropathy were seen in a concentration-related manner in all groups of exposed male rats and, to a lesser extent, in females exposed to the mid and high MTBE concentrations. Increases in the severity of mineralization and interstitial fibrosis were observed at all chronic-exposure concentrations in the male rats. Increased mineralization was not observed in females, but increases in mild to moderate glomerulosclerosis and interstitial fibrosis and tubular proteinosis were observed at the mid- and high-exposure levels in the female rats.

U.S. EPA (1991) clearly indicates that nephropathy in male rats associated with the induction of alpha-2u-globulin (a male-rat-specific protein) accumulation in hyaline droplets (located in the P2 segment of the proximal tubule cells of the kidneys) "is not an appropriate endpoint to determine noncancer (systemic) effects potentially occurring in humans." U.S. EPA (1991) further outlines the following criteria for identification of an alpha-2u-globulin toxicant: (1) increased number and size of hyaline droplets in renal proximal tubule cells of treated male rats, (2) the accumulating protein in the hyaline droplets is alpha 2u globulin, and (3) additional aspects of pathological sequence of lesions associated with alpha-2u-globulin nephropathy are present, as described in U.S. EPA (1991). For reasons discussed below, the nephropathy in the male rats (and the associated decreased survival time) is thought to be at least partially due to alpha-2u-globulin accumulation, confounding the results of the male rat chronic bioassay and precluding its use as a basis for a quantitative determination of human noncancer risk.

The first criterion listed above was addressed in the subchronic study by Dodd and Kintigh (1989). They reported that slides of kidney sections from five male rats in each treatment group and from five female rats from the high-level (7977-ppm) treatment group were independently "blind" evaluated by three pathologists for treatment-related differences in hyaline droplet formation. The average grades for extent of hyaline droplet formation based on a scale ranging from 0 (no findings) to 5 (severe) were 0 for the female rats exposed to 7977 ppm and 2.56, 1.94, 3.06, and 3.66 for the control and 800-, 4000-, and 7977-ppm males, respectively. Thus, these results indicate no hyaline droplet formation in female rats and a moderate (one-grade) increase in hyaline droplet formation for male rats at the high-exposure level. Further, hyaline droplet increases at the high dose were observed in a subchronic gavage study (Robinson et al., 1990) and in a subchronic drinking- water study (Lindamood et al., 1992) of male Fischer 344 rats exposed to tert- butyl alcohol (TBA), the principal metabolite of MTBE.

The second criterion, alpha-2u-globulin levels in the hyaline droplets, was addressed in a separate analysis of male rats from the subject subchronic study (Swenberg and Dietrich, 1991). Although they were not increased in a concentration-related manner, Swenberg and Dietrich (1991) observed an approximate doubling in the percentage of renal cortex staining for alpha 2u globulin in all male rat exposure groups of the subchronic study. Although the pattern of alpha-2u-globulin accumulation is not consistent with other known alpha-2u-globulin toxicants (e.g.,

limonene), these results suggest that the aforementioned increase in hyaline droplet formation could, at least partially, be due to the accumulation of this male-rat-specific protein.

Finally, subchronic and chronic inhalation studies reveal that MTBE does induce most of the pathologic progression (from hyaline droplet formation to acceleration of chronic progressive nephropathy to renal tubular cell tumors) identified as characteristic of alpha-2u-globulin-type toxicity (U.S. EPA 1991). Swenberg and Dietrich (1991) reported that alpha-2u-globulin-positive proteinaceous casts at the junction of the proximal tubules and the thin limb of Henle were not observed. However, Robinson et al. (1990) found that 50% of male Sprague-Dawley rats orally dosed with 1200 mg MTBE/kg displayed "small numbers of tubules which were plugged with granular casts." Further, granular casts at this part of the nephron can lead to subsequent tubular dilation (U.S. EPA, 1991), an effect that was noted in the chronically exposed male (1/50, 13/50, 14/50, and 11/50 in control and low-, mid-, and high-exposure groups, respectively), but not female (2/50, 0/50, 3/50, and 3/50 in control, low-, mid-, and high-exposure groups, respectively) rats (Chun et al., 1992). The reason this pathology was not observed following the 90-day study is not known at this time but may be related to differences in test species strain or due to differences resulting from differing administration routes.

Another indication that MTBE exacerbation of chronic progressive nephropathy (CPN) may be related to alpha 2u globulin is that MTBE accelerates CPN to a much lesser degree in animals that cannot produce alpha 2u globulin (i.e., female rats, all mice). The graded kidney lesion responses observed in male and female rats (Tables 40 and 45) were analyzed by logistic regression models to determine the extent to which MTBE impacted male and female kidneys differently. Males and females differed significantly with respect to concentration-response slopes for interstitial nephritis ($p < 0.025$), interstitial fibrosis ($p < 0.005$), and mineralization ($p < 0.005$), but not with respect to tubular proteinosis ($p > 0.1$) and glomerulosclerosis ($p > 0.1$) (Allen, 1993). In all cases where the slopes differed significantly, the slope for males was greater than the slope for females.

As with the male rats, the nephropathy present in the female MTBE-exposed rats did not differ histologically from the "spontaneous" nephropathy common in older Fischer 344 rats. The heightened degrees of nephropathy seen in relation to the MTBE exposures represent an exacerbation of this spontaneous rat nephropathy (Garman, 1993a). Of the observed kidney lesions, the study pathologist's diagnosis of tubular proteinosis was considered most representative of overall nephropathy (Garman, 1993b). An analysis of the average severity grade for these lesions in the different exposure groups (where 1 = minimal, 2 = mild, 3 = moderate, 4 = marked, and 5 = severe) revealed scores of 2.8, 2.8, 3.8, and 3.5 for females sacrificed at 24 months in the control group and 403-, 3023-, and 7977-ppm exposure groups, respectively (Eldridge, 1993). Trend analyses (using methods described by Tukey et al., 1985) of this and other kidney lesions confirm the 403-ppm NOAEL and 3023-ppm LOAEL with respect

to renal effects in the female rats (Allen, 1993). In males, 403-ppm was determined to be a NOAEL for interstitial nephritis, tubular proteinosis, and glomerulosclerosis, and a LOAEL for mineralization and interstitial fibrosis. The 403-ppm NOAEL for renal effects in the female rats was also confirmed via a blinded reevaluation of the original kidney slides by a second pathologist (Busey, 1993).

In summary, there is some evidence for alpha-2u-globulin nephropathy in male rats. This limited evidence, however, is sufficient to eliminate male rat kidney nephropathy as a possible critical endpoint for use in the derivation of an RfC. Also, the induction of nephropathy in females indicates that MTBE induces renal pathology by more than one mechanism. Because the female rat lacks alpha 2u globulin, the mechanism of pathologic induction is not considered to be unique, and renal pathology in females is thus considered to be suitable for use in the development of an RfC.

Exposure to MTBE vapor for 24 months produced various signs of toxicity in female rats exposed to 3023 ppm MTBE, including prostration, swollen periocular tissue, increased relative and absolute liver and kidney weights, and increased severity of certain renal lesions. Thus, 3023 ppm was a LOAEL [LOAEL(HEC) = 1946 mg/cu.m], and 403 ppm [NOAEL(HEC) = 259 mg/cu.m] was a NOAEL for chronic exposure to female rats.

A two-generation reproduction study (Neeper-Bradley, 1991) of Sprague- Dawley rats lends support to the NOAEL level determined in the Chun et. al. (1992) chronic study. In accordance with current U.S. EPA risk assessment policy, no adjustment is made to approximate an equivalent continuous exposure level for developmental endpoints (U.S. EPA, 1989a). As a result, the NOAEL(HEC) for this developmental endpoint is higher than the NOAEL(HEC) derived from the Chun et al. (1992) study.

Neeper-Bradley (1991) conducted a two-generation reproduction study in CD (Sprague-Dawley) rats. Male and female rats were exposed to mean MTBE concentrations of 0, 402, 3019, and 8007 ppm over two generations. F0 animals, 25/sex/concentration, were exposed for 10 weeks and then bred once to produce F1 litters. Twenty-five pups/sex/group from the F1 generation were selected randomly to be parents of the F2 generation and were exposed for at least 8 weeks prior to mating. Exposures continued through mating, through day 19 of gestation, and from lactation days 5-28 for both generations of parents. The rats were exposed for 6 hours/day, 5 days/week during the prebreeding exposure period and for 7 days/week during mating, gestation, and postnatal periods. The approximate age of the F0 animals at the start of prebreeding exposures was 6 weeks. Prebreeding exposures for the selected F1 weanlings began 29-31 days from birth. Parental animals were monitored for clinical signs of toxicity, food consumption, and body weight. All F0 and F1 parents were necropsied and examined for gross lesions; liver weights of F1 parents were measured at necropsy. Upper and lower respiratory tracts and

selected reproductive tissues from the high-concentration and control groups were examined histologically, as were tissues with gross lesions. Offspring were evaluated for viability, survival, body weight, and sex distribution.

Prebreeding exposures of 7977 ppm resulted in reduced food consumption during the first 2-3 weeks (F0 and F1 males) and body weight and body weight gain reductions throughout the exposure period (F0 and F1 males and F1 females). Other signs of parental toxicity at 7977 ppm included perioral wetness, hypoactivity, lack of startle reflex, ataxia, blepharospasm, and increased relative liver weights (F1 generation only). At 3023 ppm, adult effects included hypoactivity, lack of startle reflex, blepharospasm, increased relative liver weights (F1 males only), and transient reductions in body weight (F1 males and females). The histopathologic evaluation revealed no exposure-related lesions in the organs examined from males and females of either parental generation. The NOAEL and LOAEL for paternal effects in this study were 403 and 3023 ppm, respectively, which support the effect levels designated for the principal study (Chun et al., 1992).

Mating, fertility, and gestational indices were not adversely affected in either of the two parental generations. Body weights, weight gains, and food consumption were similar for treated and control groups throughout gestation. However, maternal exposure to 3023 and 7977 ppm resulted in statistically significant reduced body weights and reduced body weight gains in F1 pups ($p < 0.05$ at 3023 ppm; $p < 0.01$ at 7977 ppm) and F2 pups ($p < 0.01$ for both exposure groups), principally during the latter periods of lactation. A significant ($p < 0.01$) decrease in pup survival in the F1 litter on lactation days 0-4 (precull) for the 7977-ppm exposure group (91.5% survival, 259/283) compared with controls (98.6%, 289/293) was attributed to the loss of an entire litter (16 pups). The authors state that this loss was not related to MTBE toxicity, but no further explanation is provided. In the 7977-ppm F2 litters, pup survival was reduced on postnatal day 4 (93.5% survival, 275/294) compared with controls (98.1%, 305/311). A NOAEL of 403 ppm [1442 mg/cu.m; NOAEL(HEC) = 1442 mg/cu.m] and a LOAEL of 3023 ppm (10,816 mg/cu.m) for reduced body weight and body weight gain in both F1 and F2 pups during postnatal development (lactation period) were determined.

Biles et al. (1987) conducted a one-generation reproductive toxicity investigation. Sprague-Dawley rats (15 males, 30 females/group) were exposed to MTBE concentrations of 0, 290, 1180, and 2860 ppm (0, 1046, 4254, and 10,311 mg/cu.m) (males) and 0, 300, 1240, and 2980 ppm (0, 1082, 4470, and 10,743 mg/cu.m) (females), 6 hours/day, 5 days/week, during the premating interval (12 weeks for males, 3 weeks for females). There were two 5-day mating intervals (two females for every male). Males (F0 generation) continued to be exposed during and between matings, whereas F0 females were exposed 7 days/week on days 0-21 of gestation and 5 days/week on days 5-20 of lactation. After unexposed litters (F1a) were weaned, the F0 males and F0 females underwent another mating period with the same exposure regimen to

produce a second litter (F1b). F0 males were sacrificed after this mating period, and females were sacrificed after the end of F1b weaning. Thus, F0 males were exposed overall to MTBE for approximately 28 weeks, and F0 females were exposed for 16 weeks. These animals were examined for gross changes, especially in their reproductive organs. Histopathologic examination revealed an increased incidence of dilated renal pelves in females exposed to 300 (4/30, 13%) and 2980 ppm (5/30, 17%) compared with controls (1/30, 3%). However, this finding was not observed at the mid concentration of 1240 ppm (0/30, 0%), which preclude establishing an unequivocal concentration-response relationship. The pregnancy rate was not significantly affected in either mating interval (F1a and F1b), although the F1b matings were slightly reduced in the high-exposure group (18/25, 76%) compared with controls (22/25, 88%). On day 4 of lactation, each litter with greater than 10 pups was culled. Pups were sacrificed on day 21 of lactation. The pup viability indices at birth were slightly, but significantly, decreased ($p < 0.05$) in the F1b litters of the dams exposed to 1240 (95.5% viability, 278/291) and 2980 ppm (95.5% viability, 234/245) compared with litters of controls (99% viability, 292/295). The F1a litter's pup viability indices did not differ from controls. Pup survival in the F1a litter was significantly decreased ($p < 0.01$) on lactation days 0-4 (precull) for the 300- (91.4% survival, 317/347) and 1240-ppm (89.1% survival, 205/230) exposure groups compared with controls (98.2% survival, 324/330). However, the F1a high-exposure group displayed no reduction in pup survival when compared to controls, and no reduction in pup survival was seen in the F1b litters. Further, pup survival indices for lactation days 4-21 (post-cull) were not increased over controls. Consequently, the reduced pup survival in the F1a low- and mid-exposure groups is not believed to be a treatment-related effect. A NOAEL of 300 ppm [1082 mg/cu.m; NOAEL(HEC) = 1082 mg/cu.m] and a LOAEL of 1240 ppm (4470 mg/cu.m) (female rats) for decreased pup viability in F1b litters were determined.

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

UF — An uncertainty factor of 10 is applied to account for extrapolation to sensitive human subpopulations. An additional factor of 3 is used to account for interspecies extrapolation. A full 10-fold adjustment for interspecies extrapolation is not deemed necessary due to the use of dosimetric adjustments. An uncertainty factor of 3 is applied for database deficiencies because of the lack of certain information from the chronic exposure bioassay (e.g., urinalysis results, serum chemistry, and limited reporting of motor activity/clinical signs during exposure).

MF — None

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

Information on human exposure to MTBE is limited. Humans are acutely exposed to MTBE as a part of a medical treatment to dissolve cholesterol gallstones (Thistle, 1992). Injection of the gall

bladder with a high dose of MTBE can be associated with several types of health effects (e.g., nausea, vomiting, sleepiness). Minor transient mucosal damage in the gallbladder has been demonstrated with extensive exposure, but no clinically significant consequences have been reported. One patient has been reported to have developed intravascular hemolysis and renal failure following inadvertent extravasation of a large bolus of MTBE (Ponchon et al., 1988). Reliable data from epidemiology studies of human exposure to airborne MTBE are not currently available.

In a chronic inhalation study (Burleigh-Flayer et al., 1992), CD-1 mice (50 males, 50 females/group) were exposed to mean concentrations of 402, 3014, or 7973 ppm MTBE vapors (1442, 10,816, or 28,843 mg/cu.m) for 6 hours/day, 5 days/week (duration-adjusted values are 258, 1288, and 2575 mg/cu.m, respectively) for 18 months. The control animals breathed air. Hematology (all mice) and urinalysis (20 mice/sex) were performed halfway through the experiment (control and high-concentration groups) and prior to final sacrifice (all groups). In addition, corticosterone was measured on 10 mice/sex/group prior to sacrifice. Clinical signs, body weights, organ weights, and food consumption were monitored. A complete necropsy and histopathology, which included examination of the nasal turbinates and the lower respiratory tract, was performed on all animals.

Male mice from the high-exposure group exhibited an increased mortality rate, probably due to a slightly increased frequency of obstructive uropathy. However, the frequency of death due to this disease in the high-concentration group was still within the range noted for historical controls (Maita et al., 1988). Ataxia was observed in 50/50 animals (both sexes) exposed to the high MTBE concentration. In addition, prostration was noted between days 25 and 522 in 8/50 female mice exposed to the highest concentration (vs. 1/50 controls). Other effects reported in both sexes of the high-concentration group included decreased body weight gain and absolute body weight (not statistically significant for females), and a slight decrease in urinary pH. No concentration-related hematologic effects were reported.

Concentration-related increases in liver weight (absolute and relative to body and brain weights) were reported in both male and female mice. In the females, the liver weight increases were statistically significant at all but the lowest exposure level ($p < 0.01$). In males, significant increases in liver weights were observed at the lowest exposure level ($p < 0.05$), but the only measure that indicated a concentration response was liver weight relative to brain weight ($p < 0.05$).

Absolute and relative male kidney weights were significantly increased in the lowest ($p < 0.01$) and mid-exposure groups ($p < 0.05$), but, as with the male liver weights, the increases were less than 10%, and a concentration- response relationship was not apparent (i.e., there was no statistical difference at the high-exposure level and significance at the mid-exposure level was

less than at the low-exposure level). Female kidney weights were only increased significantly ($p < 0.01$) relative to body weight for animals exposed to the highest concentration.

Decreases in absolute brain weight were also reported in both sexes of the high-concentration group (6% for both sexes; $p < 0.01$). Absolute and relative spleen weights were increased for the high-exposure group females ($p < 0.01$), and absolute and relative adrenal weights were increased for the high-exposure group males ($p < 0.01$).

Histopathologic evaluation revealed no lesions in any organ except the liver. An increased incidence of hepatocellular hypertrophy was seen at the highest exposure level in both sexes, but was only significant ($p < 0.05$) in the male mice.

The increased liver, kidney, and adrenal weights, as well as the decreased brain weights, reported in this study at the highest exposure level are consistent with the subchronic rat study (Dodd and Kintigh, 1989). Although statistically significant ($p < 0.05$) increases in both absolute and relative liver and kidney weights were observed in the low- and mid-concentration groups, the male liver and kidney weights did not tend to increase with increasing exposure concentration, and the female liver and kidney weight increases (both absolute and relative) at the low- and mid-concentration levels were only 9% or less over controls. The high-exposure level is considered a LOAEL [LOAEL(HEC) = 2575 mg/cu.m] based on the significant increase in absolute (females only) and relative liver weights (around 30%; $p < 0.01$), the increased incidence of anesthetic effects, and the significant (as much as 24%) decrease in body weight. The decreased survival time in the male mice may suggest that the highest concentration exceeded the MTD, but it may also be due to increased frequency of a spontaneous obstructive uropathy common in this strain of male mice. The mid-exposure level is considered a NOAEL [NOAEL(HEC) = 1288 mg/cu.m] for this study.

In a subchronic inhalation study (Dodd and Kintigh, 1989), Fischer 344 rats (25/sex/group) were exposed to mean concentrations of 797, 3920, or 8043 ppm MTBE vapors (2873, 14,133, or 28,998 mg/cu.m) for 6 hours/day, 5 days/week (duration-adjusted values are 513, 2524, and 5178 mg/cu.m, respectively) for 13 weeks. The control animals breathed air. The high-exposure concentration was set at 50% of the LEL. Hematologic tests were performed before exposure (5/sex/group) and during weeks 5 and 14 (10/sex/group) of the study. Clinical observations were made of the groups; ophthalmic observations were made prior to the first exposure and at study end; and body weights, organ weights (15/sex/group), and food consumption were monitored. Ten rats/sex/group were perfusion-fixed for microscopic evaluation of the nervous system tissues. Brain weights and measurements were taken on all perfusion-fixed rats, and light microscopic evaluations were performed on the nervous system of 6/sex/group. The remaining 15 rats/sex/group received complete necropsy evaluations. Nasal turbinates (four sections), trachea, and lung (three sections) were examined in the control and high-exposure groups and the

lung only in the low- and mid-concentration groups. A battery of neurobehavioral tests was performed on 15 rats/sex/group prior to first exposure and at exposure weeks 1, 2, 4, 8, and 13, and motor activity was determined prior to first exposure and at exposure weeks 4, 8, and 13.

No treatment-related findings were noted for the respiratory tract. Lymphoid hyperplasia within the submandibular lymph nodes of the males in the high-exposure group was noted, but no reason was found for its occurrence.

Necropsy examination of nervous system tissue (10/sex/group) showed no evidence of treatment-related changes in exposed animals compared with the controls. However, at both the mid- and high-exposure levels, an absolute decrease in brain length was observed in male rats. Reductions in absolute brain weight in both sexes were noted at the high-exposure level, but not at the mid concentration. The authors observed no statistically significant changes in brain weight, expressed as a percentage of body weight, nor in brain width. Nevertheless, the effect on brain length was statistically significant ($p < 0.05$) and concentration related. Thus, this effect was felt to be consistent with the toxicity observed in other organ systems.

Dodd and Kintigh (1989) also evaluated the neurotoxic effects of MTBE using an FOB for 10 rats/sex/group and a motor activity test for the remaining 30 animals from each group. The mid- and high-concentration groups deviated from controls with respect to several FOB endpoints. The authors cite elevated body temperature in the high-exposure group males (day 7) and in the mid- and high-exposure group females (day 91). However, the overall downward trend in body temperature across control and exposure groups suggests an anomaly in the test procedure and calls to question the validity of these data. The authors note a decreased mean latency to rotate on the inclined screen in low- (days 14 and 28) and mid-concentration (days 7, 14, and 28) males. However, the data reported for this procedure are highly variable across groups and over time. Decreased hind limb grip strength was observed in mid-concentration males (days 28 and 91), but increased hind-limb grip strength was observed in mid-concentration females (day 91). Cumulative test- session motor activity was decreased for males exposed to the highest MTBE concentration (28% at day 55) and increased for females exposed to the lowest (20% at day 55) and mid concentrations (36% at day 55). The lack of a clearly defined concentration-response relationship calls into question the toxicological significance of these data.

Slight hematologic alterations were observed in both male and female rats exposed to mid- and high-exposure levels. All of these changes, however, were within the range of historical measurements for this species (Charles River Breeding Laboratories, 1984). The most noteworthy biochemical finding, however, was a significant ($p < 0.05$) increase in corticosterone levels for the high-exposure group, which is consistent with the observed increase of relative adrenal weight. The interaction of MTBE with the neuroendocrine system (e.g., at the hypothalamus, pituitary, or adrenal glands) is unknown.

There were no exposure-related alterations in mean body weight for rats exposed to the low concentration. Male rats in the mid-concentration group had reduced body weight gain during the first week, but their mean body weights were similar to controls after week 5. Female rats in the mid- concentration group experienced a slight body weight gain reduction during weeks 3 and 4. Body weight gains were depressed in both male and female rats in the high-exposure group for the first 3 weeks of exposure. There was a concentration-related increase in liver, kidney, and adrenal weights relative to body weight of the treatment groups compared with controls. Absolute weights of these organs were also significantly increased, and relative weights were at least 10% greater ($p < 0.01$) than controls for male and female rats in the 4000- and 8000-ppm groups. In the mid- and high-exposure groups, relative weight increases in the males were 20 and 39% in the liver, 12 and 19% in kidneys, and 18 and 55% in adrenals, whereas increases in the females were 13 and 15% in the liver, 13 and 10% in kidneys, and 13 and 29% in adrenals, respectively. The relative lung weight in the high-concentration group was 3.5-6.5% greater than the controls. An increase in the degree, but not frequency, of hemosiderosis within the spleens of males exposed to the high concentration was observed, and there was also a mild increase in number and/or size of hyaline droplets within renal proximal tubules. Consistent with the chronic studies in rats (Chun et al., 1992) and mice (Burleigh-Flayer et al., 1992), the overall weight-of-evidence indicates that the mid-exposure level is moderately adverse to several organ systems, as indicated by decreased brain length and increased relative kidney (females), adrenal, and liver weights. Thus, a NOAEL of 797 ppm (2873 mg/cu.m) and a LOAEL of 3920 ppm (14,133 mg/cu.m) were determined.

CD-1 mice and Fischer 344 rats (5/sex/species/group) were exposed to 0, 2000, 4000, and 8000 ppm (0, 7211, 14,421, and 28,843 mg/cu.m) MTBE for 6 hours/day in the 13-consecutive-day, range-finding study (Dodd and Kintigh, 1989). Duration-adjusted exposure levels are 0, 1288, 2572, and 5150 mg/cu.m, respectively. Body weights, organ weights (brain, liver, kidneys, lungs, and adrenals), and individual clinical signs were monitored. Complete necropsy was performed on each animal, and all gross lesions were submitted to microscopy. Detailed behavioral observations were performed on rats only. A statistically significant depression in body weight gain was observed in male rats at the high-exposure concentration. There were no exposure-related effects on absolute body weight or body weight gain for mice. Relative liver weights (both sexes) and relative kidney weights (males only) were increased in rats at the high- and mid-exposure concentrations. Relative adrenal weights were increased at the high concentration in both sexes. Relative brain weights in the female rats in the 8000-ppm group were also significantly reduced. For mice, relative liver weights were increased at all concentrations (females only at the low- and mid-exposure levels). There were no weight changes in the lungs, brains, adrenals, or testes of mice when compared with control mean weights. No treatment-related macroscopic lesions were observed in either species. Reversible behavioral alterations (ataxia, decreased startle and pain reflexes, and decreased muscle tone) were observed in both

sexes of rats exposed to 8000 ppm. These data suggested that 2000 ppm was a minimal effect level based on the relative liver weight changes in the female rats.

Greenough et al. (1980) exposed Sprague-Dawley rats (10/sex/group) to MTBE at 250, 500, or 1000 ppm (901, 1802, or 3605 mg/cu.m) 6 hours/day, 5 days/week for 13 weeks (duration-adjusted concentrations are 161, 322, or 644 mg/cu.m, respectively). Controls inhaled air only. Food and water consumption, body and organ weights, clinical signs, ophthalmoscopy, necropsy, and histopathology of animals were reported. Histopathology included examination of one transverse section through the nasal cavity, a series of transverse sections through the larynx and trachea, and one cut through the left lung (control and high-exposure groups) and cuts through both lungs (low- and mid- exposure groups).

No clinical signs were observed. Mean body weights were inconsistent, and differences were less than 10% compared with controls. The 1000-ppm females had significant ($p < 0.05$) reductions in absolute and relative (27% decrease) lung weights compared with controls. The 500- and 1000-ppm males showed a mean decrease of 8% in relative lung weight compared with controls. However, these findings do not appear to be concentration related, are not associated with adverse histopathologic or functional observations, and are not reproduced in the Dodd and Kintigh (1989) study. Significant ($p < 0.05$) differences in the absolute weights of the heart (male) and thymus (female) of 1000-ppm animals, kidneys of 500-ppm males, and adrenals of 250-ppm females were reported, but were not concentration-related changes. Histopathologic effects observed in the nasal cavity, larynx, trachea, and lungs of treated and control animals included focal inflammatory changes (pulmonary lymphoid vascular cuffing, localized polymorphonuclear leukocytes, and alveolar macrophages), epithelial and goblet cell hyperplasia, and congestion (lung only). Although these changes occurred in control and exposed animals, the changes did not appear to be concentration related and may be indicative of infection due to inadequate description of animal husbandry; any attempt to isolate causative organisms precludes conclusion. The possibility thus remains that respiratory effects of MTBE may have been unfounded by concomitant respiratory infection.

Hematologic and clinical chemistry tests were performed only on the control and 1000-ppm groups. Hemoglobin levels were increased ($p < 0.001$), as were BUN levels ($p < 0.05$) in 1000-ppm male rats compared with control values after 13 weeks of exposure. Female rats in the 1000-ppm group showed a significant decrease ($p < 0.05$) in LDH levels, as well as an increase in glucose and albumin levels. The mean corpuscular hemoglobin concentration (MCHC) increased significantly in 1000-ppm males ($p < 0.01$) and decreased in females ($p < 0.05$). It could not be determined if any changes were concentration related because the two low-concentration groups were not evaluated. These effects are not corroborated by the Dodd and Kintigh (1989) study at higher concentrations. A free-standing NOAEL of 1000 ppm [3600

mg/cu.m; NOAEL(HEC) = 3600 mg/cu.m] was determined for this study based on the lack of treatment-related effects in any organ or system.

Gill (1989) evaluated neurotoxicity of MTBE in a single acute inhalation study in which Fischer 344 rats (22/sex/group) were exposed to 0, 800, 4000, or 8000 ppm MTBE (0, 2884, 14,421, and 28,843 mg/cu.m) for 6 hours. Transient increases in motor activity were observed for males in the 800- and 4000-ppm exposure groups. After 1 hour of exposure, a significant ($p < 0.01$) increase in the incidence of abnormal gait was observed in the 8000-ppm group. This was evidenced by a concentration-dependent increase in the incidence and severity of ataxia and duck-walk gait in males and females at the two highest concentrations. Labored respiratory pattern, increased lacrimation, decreased muscle tone, decreased mean performance on the treadmill, increased mean latency to tail withdrawal reflex, increased mean forelimb grip strength, and increased hindlimb splay were also observed in the 8000-ppm group ($p < 0.01$) at 1 hour of exposure. None of these motor function changes remained after 6 hours of exposure. Results also show that a 6-hour exposure to 8000 ppm MTBE significantly affected the motor activity of rats, especially during the first 50 minutes of the test session. The NOAEL based on these neurologic effects is 4000 ppm (14,421 mg/cu.m), and the LOAEL is 8000 ppm (28,843 mg/cu.m).

A 9-day inhalation study was performed (Bio/Dynamics, 1984) on Sprague- Dawley rats (20/sex/group) in which fasted and nonfasted animals were exposed to concentrations of 101, 300, 1020, and 2970 ppm MTBE vapors (364, 1082, 3677, and 10,708 mg/cu.m) 6 hours/day, 5 days/week. Lacrimation, conjunctival swelling, and corneal changes were observed in both treated and control animals; however, statistical significance was not reported. Although data were not shown, the authors report that there was a greater incidence of these clinical signs in males. A significant increase in the relative liver weight was evident in the fasted animals at 2970 ppm. Relative adrenal weights were significantly elevated in nonfasted, 300-ppm females and relative kidney weights were increased ($p < 0.05$) in nonfasted females exposed to 300 and 2970 ppm. Because a similar trend was not seen in fasted females at these exposure levels, and because these findings apparently were not concentration related, these observations in the nonfasted females are not considered treatment related. Both the nasal mucosa and the trachea were examined microscopically in controls and rats exposed to 1020 and 2970 ppm. Microscopic examinations revealed a significant increase in incidence of chronic inflammation in the nasal mucosa and the trachea at 1020 and 2970 ppm compared with pretest controls, but lung weight was not different from controls.

Savolainen et al. (1985) exposed 3-month-old male Wistar rats (20/group) to 50, 100, or 300 ppm MTBE vapor (181, 361, or 1082 mg/cu.m) 6 hours/day, 5 days/week for 2-15 weeks (duration-adjusted concentrations are 32, 64, or 193 mg/cu.m., respectively). Five animals from each chamber were weighed and sacrificed after weeks 2, 6, 10, and 15. The rats were bled, and

their cerebral hemispheres, livers, kidneys, samples of right gluteal muscle (1 g), and samples of perirenal fat (1 g) were taken at autopsy. Although body weights did not differ significantly between groups early in the study, exposed rats did have higher weights than controls by week 15; mean weights were 365 g, 408 g (12% increase), 420 g (15% increase), and 407 g (12% increase) in animals exposed to 0, 50, 100, and 300 ppm, respectively. A significant ($p < 0.05$) concentration-dependent increase in microsomal uridine diphosphate-glucuronosyltransferase activity in liver and kidney, as well as NADPH cytochrome c-reductase activity in kidney, occurred after 2 weeks of exposure. These effects were not observed after 15 weeks of exposure. The study was limited because histopathology was not conducted and organs were not weighed.

Conaway et al. (1985) exposed pregnant Sprague-Dawley rats (23-25/group) and pregnant CD-1 mice (24-29/group) to 0, 260, 1100, or 3300 ppm MTBE (0, 937, 3965, or 11,897 mg/cu.m) 6 hours/day during gestational days 6-15. Maternal body weights were recorded for both species on days 0, 6, 12, 15, and 18 and on day 20 for rats. Physical examinations for signs of toxicity were performed at the same time as weights were recorded. Food and water consumption was recorded for days 6-9, 9-12, 12-15, and 15-18 and for days 18- 20 for rats. Dams were sacrificed on day 20 (rats) or day 18 (mice) by carbon dioxide inhalation. Laparotomies were performed, and dams and pups were examined for gross abnormalities. Each fetus was weighed, and crown-rump distance was recorded. Late and early resorptions were scored. When no uterine implantation sites were observed, the uterus was stained to examine the foci of implantation. One-third of the fetuses in each litter were examined for soft-tissue abnormalities, and two-thirds of the fetuses were examined for skeletal abnormalities.

The pregnancy rate in rats was similar for all groups. Organ weights were not significantly different in exposed animals compared with control values. The mean number of corpora lutea, implantations, resorptions, and live fetuses was not significantly different among groups. Fetuses were weighed and examined for deformities, but no significant incidence of soft-tissue or skeletal anomalies was observed. A free-standing NOAEL of 3300 ppm [11,897 mg/cu.m; NOAEL(HEC) = 11,897 mg/cu.m] for reproductive and developmental toxicity effects was determined for rats with no reported maternal toxicity.

In mice, a slight increase in the incidence of lacrimation was observed among females (groups not specified) during exposure. The number of implantations in treatment groups was not statistically different compared with controls. The numbers of resorptions were 17, 11, and 17.3% in the 260-, 1100-, and 3300-ppm groups, respectively, compared with 9% in controls. These differences are of questionable significance because they do not appear to be concentration dependent, and the high number of resorptions in the low- and high-exposure groups were due to nearly complete resorptions in two females of the low-exposure group and complete resorption in two females of the high- exposure groups. Excluding the data for these four females, resorption data for these groups did not differ from controls. Mean fetal weights in

treated animals were not significantly different from the controls. Soft-tissue anomalies per litter or per fetus were not found to be different among groups. Although not statistically significant, concentration-related skeletal variations per litter were found to be 2/27 (7.4%) in the control group and 3/26 (11.5%), 4/25 (16%), and 6/27 (22.2%) in the 260-, 1100-, and 3300-ppm groups, respectively. Cleft palates were noted in control (0.7%, 2/281), 260- ppm (0%, 0/265), 1100-ppm (0.4%, 1/251), and 3300-ppm (0.7%, 2/290) groups. A free-standing NOAEL of 3300 ppm [11,977 mg/cu.m; NOAEL(HEC) = 11,977 mg/cu.m] for developmental effects was determined for mice with minimal indications of maternal toxicity.

Pregnant CD-1 mice (30/group) were exposed to MTBE at concentrations of 0, 1035, 4076, and 8153 ppm (0, 3731, 14,695, and 29,394 mg/cu.m) 6 hours/day from gestational days 6 to 15 (Bushy Run Research Center, 1989a). No animals died and none aborted during the exposure period. Three dams at 0 ppm and two dams at 400 ppm delivered early and were removed from the study. The remaining dams were sacrificed on day 18 of gestation. No signs of maternal toxicity were observed in the dams exposed to 1035 ppm. At 4076 ppm, there were slight, but not statistically significant, indications of reduced maternal body weight and body weight gain. Though the only observation for this exposure group reported was lacrimation in one dam, the authors indicate in the abstract and text of the report that hypoactivity and ataxia were observed in dams at 4076 and 8153 ppm. Clinical signs of maternal toxicity, including hypoactivity, ataxia, prostration, labored respiration, lacrimation, and periocular encrustation, were significantly increased at 8153 ppm. Significant reductions in food consumption, body weight, and body weight gain were also observed in dams exposed to 8153 ppm. A NOAEL of 1035 ppm [3731 mg/cu.m; NOAEL(HEC) = 3731 mg/cu.m] and a LOAEL of 4076 ppm [14,695 mg/cu.m; LOAEL(HEC) = 14,695 mg/cu.m] were determined for maternal toxicity.

MTBE did not affect the number of corpora lutea, total implants, or preimplantation loss per litter in any exposure group. There were significant ($p < 0.01$) increases in the number of nonviable implantations per litter, late resorptions, and dead fetuses; and significant reductions in the number of viable implantations ($p < 0.01$), percent of live fetuses ($p < 0.01$), and percent of male fetuses ($p < 0.05$) in the 8153-ppm group. Fetal body weight per litter (male and female) were significantly ($p < 0.01$) decreased at 4076 and 8153 ppm. A significant reduction in the incidence of partial fetal atelectasis and an increase in fetal atelectasis occurred at 8153 ppm. There were 24 skeletal variations (i.e., defects in cervical, thoracic, and caudal centra, forepaws, hindpaws, sternebrae, and skull plates/bones), all indicative of reduced ossification, that were significantly elevated in fetuses at 8153 ppm. There was a decreased incidence of unossified intermediate phalanges of the hindlimb at the high concentration. At 4076 ppm, there were seven skeletal variations related to reduced ossification (cervical centra, forepaw, hindpaw, and sternebrae) that showed a significantly increased incidence. At 1035 ppm, a significantly increased incidence of poorly ossified intermediate phalanges of the hindlimb was found. This finding was probably not treatment related because the alteration was not seen at the higher

concentrations. In general, the effects were significant at the $p < 0.01$ level. A NOAEL of 1035 ppm [3725 mg/cu.m; NOAEL(HEC) = 3725 mg/cu.m] and a LOAEL of 4076 ppm (14,670 mg/cu.m) were determined for mice based on fetal body weight reductions with minimal maternal toxicity.

Developmental toxicity in rabbits was also investigated by Bushy Run Research Center (1989b). Pregnant New Zealand white rabbits (15/group) were exposed to 0, 1021, 4058, and 8021 ppm MTBE (0, 3681, 14,630, and 28,918 mg/cu.m) 6 hours/day, during gestational days 6-18. None of the does died, aborted, delivered early, or had to be removed from the study. There were no differences in maternal body weights among the groups. Reduced maternal body weight gain and food consumption were observed during the major period of organogenesis at 4058 and 8021 ppm. However, there were large standard deviations across the groups for body weight gain measurements. Relative liver weight was significantly increased by 14% ($p < 0.05$), and absolute liver weight was slightly, but not significantly, increased in does exposed to 8021 ppm. No histopathologic examination of the liver was conducted. The number of corpora lutea, resorptions, and viable and nonviable implantations were not significantly different among groups. Fetal body weights per litter were not statistically different among groups. There was no significant difference in the incidence of fetal malformations. This study identifies a free-standing NOAEL for developmental toxicity in rabbits of 8021 ppm [28,918 mg/cu.m; NOAEL(HEC) = 28,918 mg/cu.m].

Groups of male and female rats received a single 6-hour exposure to MTBE vapor in nose-only inhalation chambers at targeted MTBE concentrations of 400 and 8000 ppm and daily repeat 6-hour exposures for 15 days at a targeted MTBE concentration of 400 ppm (Ferdinandi et al., 1990). Four rats/sex/group were then euthanized and examined. Steady-state plasma concentrations were reached at approximately 4 to 6 hours for MTBE and roughly 6.5 hours for TBA, the principal metabolite of MTBE. MTBE-metabolizing enzymes were saturated during high-concentration exposure. The elimination half-life (t1/2) of MTBE was approximately the same after single low- and high-concentration exposures (0.52 and 0.63 hours, respectively). After the repeat exposures, the MTBE t1/2 was slightly shorter (0.48 and 0.51, respectively). The TBA t1/2 ranged from 2.8 to 3.4 hours after the low- and high-concentration single exposures. After the repeat exposure regimen, the TBA t1/2 was significantly lower (1.8 and 1.5 hours in the male and female rats, respectively). There was a slight, but statistically significant, sex difference in the pharmacokinetics of MTBE (e.g., plasma clearance was faster in females), but no sex differences in the elimination kinetics of TBA were observed.

I.B.5. Confidence in the Inhalation RfC

Study — Medium
Database — Medium
RfC — Medium

Confidence in the study is medium. It was well-designed (e.g., with respect to exposure protocol, number of animals, and exposure duration), identified a consistent LOAEL and NOAEL for a constellation of organ systems, and involved extensive histopathology on both sexes. However, the results of the rat study are confounded by the high mortality in the males, which is presumed to be the result of rat chronic nephropathy. Further, the lack of certain information from the chronic bioassay reduces confidence in the study (e.g., urinalysis results, serum chemistry, and limited reporting of motor activity/clinical signs during exposure). Confidence in the database is medium to high because of the existence of chronic and subchronic bioassays in more than one species, developmental studies in several different species, and the existence of single- and two-generation reproductive studies in the rat. Medium to high confidence in the RfC follows.

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

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

Other EPA Documentation — U.S. EPA, 1989, 1993

Agency Work Group Review — 06/13/1991, 04/01/1993, 07/21/1993

Verification Date — 07/21/1993

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 (internet address).

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Methyl tert-butyl ether (MTBE)
CASRN — 1634-04-4

Not available at this time.

VI. Bibliography

Substance Name — Methyl tert-butyl ether (MTBE)
CASRN — 1634-04-4

VI.A. Oral RfD References

None

VI.B. Inhalation RfC References

Allen, B. 1993. ICF Kaiser. Telefaxed communication to Jeffrey S. Gift of U.S. EPA. Description of logistic model: Summary of test for trend (unpublished material), June 23.

Biles, R.W., R.E. Schroeder, and C.E. Holdsworth. 1987. Methyl tertiary butyl ether inhalation in rats: A single generation reproduction study. Toxicol. Indust. Health. 3: 519-534.

Bio/Dynamics Inc. 1984. A nine-day inhalation toxicity study of MTBE in the rat (final report vol. I) (unpublished material). TSCATS/301698. EPA/OTS No. 86870000264.

Burleigh-Flayer, H.D., J.S. Chun, and W.J. Kintigh. 1992. Methyl tertiary butyl ether: Vapor inhalation oncogenicity study in CD-1 mice (unpublished material). Prepared for the MTBE Committee by Bushy Run Research Center, Union Carbide Chemicals and Plastics Company Inc. Docket No. OPTS-42098.

Busey, W.M. 1993. Histopathologic evaluation of kidneys from male and female rats utilized in a vapor inhalation oncogenicity study of methyl tertiary butyl ether. MTBE Task Force Study No. 91N00138 dated July 19, 1993 (unpublished material).

Bushy Run Research Center, Union Carbide Chemicals and Plastics Company Inc. 1989a. Developmental toxicity study of inhaled methyl tertiary butyl ether in CD-1 mice (final report). TSCATS/403186. EPA/OTS No. FYI-OTS-0889-0689.

Bushy Run Research Center, Union Carbide Chemicals and Plastics Company Inc. 1989b. Developmental toxicity study of inhaled methyl tertiary butyl ether in New Zealand white rabbits (final report). TSCATS/403186. EPA/OTS No. FYI- OTS-0889-0689.

Chun, J.S., H.D. Burleigh-Flayer, and W.J. Kintigh. 1992. Methyl tertiary butyl ether: Vapor inhalation oncogenicity study in Fischer 344 rats (unpublished material). Prepared for the MTBE Committee by Bushy Run Research Center, Union Carbide Chemicals and Plastics Company Inc. Docket No. OPTS- 42098.

Conaway, C.C., R.E. Schroeder, and N.K. Synder. 1985. Teratology evaluation of methyl tertiary butyl ether in rats and mice. J. Toxicol. Environ. Health. 16(6): 797-809.

Charles River Breeding Laboratories. 1984. Baseline hematology and clinical chemistry values for Charles River Fischer-344 rats-CDF (F-344)CrlBR as a function of sex and age. January 1984 Technical Bulletin published by the Charles River Breeding Laboratories, Vol. 8, No. 1.

Dodd, D.E. and W.J. Kintigh. 1989. Methyl tertiary butyl ether (MTBE): Repeated (13-week) vapor inhalation study in rats with neurotoxicity evaluation (unpublished material). Prepared for the MTBE Committee by Bushy Run Research Center, Union Carbide Chemicals and Plastics Company Inc. TSCATS 403187. EPA/OTS No. FYI-OTS-0889-0689.

Eldridge, S.R. 1993. Nephropathy in female F344 rats: A summary of the MTBE oncogenicity study and review of historical findings (unpublished material). Attachment to letter to Mr. John Kneiss (Chair of the Synthetic Organic Chemical Manufacturers Association, MTBE Task Force), May 20.

Ferdinandi, E.S., L. Buchanan, and R.G. Alexander. 1990. Pharmacokinetics of methyl tert-butyl ether (MTBE) and tert-butyl alcohol (TBA) in male and female Fischer-344 rats after single and repeat inhalation nose-only exposures to MTBE (unpublished material). Prepared for the MTBE Committee by Bushy Run Research Center, Union Carbide Chemicals and Plastics Company Inc. Docket No. OPTS-42098.

Garman, R.H. 1993a. Bushy Run Research Center. Correspondence to Larry S. Andrews of ARCO Chemical Company. May 3.

Garman, R.H. 1993b. Bushy Run Research Center. Correspondence to Larry S. Andrews of ARCO Chemical Company. May 15.

Gill, M.W. 1989. Methyl tertiary butyl ether single exposure vapor inhalation neurotoxicity study in rats (unpublished material). Bushy Run Research Center, Union Carbide Chemicals and Plastics Company Inc.

Greenough, R.J., P. McDonald, P. Robinson et al. 1980. Methyl tertiary-butyl ether (Driveron) three-month inhalation toxicity in rats (unpublished material). Prepared for Chemische Werke

Huls AG, West Germany, by Inveresk Research International. TSCATS/303353. EPA/OTS No. 86-870000172.

Lindamood, C., III, D.R. Farnell, H.D. Giles et al. 1992. Subchronic toxicity studies of t-butyl alcohol in rats and mice. Fund. Appl. Toxicol. 19: 91-100.

Maita, K., M. Hirano, T. Harada et al. 1988. Mortality, major cause of moribundity, and spontaneous tumors in CD-1 mice. Toxicol. Pathol. 16: 340-349.

Neeper-Bradley, T.L. 1991. Two-generation reproduction study of inhaled methyl tert-butyl ether in CD Sprague-Dawley rats (unpublished material). Bushy Run Research Center, Union Carbide Chemicals and Plastics Company Inc.

NTP (National Toxicology Program). 1987. Toxicology and carcinogenisis studies of dimethyl methylphosphonate (CAS No. 756-79-6) in F344/N rats and B6C3F1 mice (gavage studies). NIH Publication No. 88-2579.

Ponchon, T., J. Baroud, B. Pugol et al. 1988. Renal failure during dissolution of gallstones by methyl tert-butyl ether. Lancet. 2: 276-277.

Robinson, M., R.H. Bruner, and G.R. Olson. 1990. Fourteen- and ninety-day oral toxicity studies of methyl tertiary-butyl ether in Sprague-Dawley rats. J. Am. Coll. Toxicol. 9: 525-539.

Savolainen, H., P. Pfaffli, and E. Elovaara. 1985. Biochemical effects of methyl tertiary-butyl ether in extended vapour exposure of rats. Arch. Toxicol. 57: 285-288.

Swenberg, J.A. and D.R. Dietrich. 1991. Immunohistochemical localization of alpha-2u-globulin in kidneys of treated and control rats of a 13-week vapor inhalation study undertaken with methy tertiary butyl ether (MTBE). Report to John Kneiss (Manager, MTBE Task Force), July 26, 1991.

Thistle, J.L. 1992. Direct contact dissolution therapy. Clin. Gastroenterol. 6: 715-725.

Tukey, J.W., J.L. Ciminera, and J.F. Heyse. 1985. Testing the statistical certainty of a response to increasing doses of a drug. Biometrics. 41: 295-301.

U.S. EPA. 1989a. Proposed amendments to the guidelines for the health assessment of suspect developmental toxicants. Federal Register. 54: 9386-9403.

U.S. EPA. 1989b. Reportable Quantity Document for Methyl Tertiary Butyl Ether. Prepared by Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1991. Alpha-2u-globulin: Association with chemically induced renal toxicity and neoplasia in the male rat. Risk Assessment Forum. EPA/625/3- 91/019F.

U.S. EPA. 1993. MTBE-oxygenated gasolines and public health issues. Office of Research and Development, Washington, DC.

VI.C. Carcinogenicity Assessment References

None

VII. Revision History

Substance Name — Methyl tert-butyl ether (MTBE)
CASRN — 1634-04-4

Date	Section	Description
12/01/1991	I.B.	Inhalation RfC on-line
08/01/1993	I.B.	Withdrawn; new RfC verified (in preparation)
09/01/1993	I.B.	Inhalation RfC replaced; RfC changed

VIII. Synonyms

Substance Name — Methyl tert-butyl ether (MTBE)
CASRN — 1634-04-4
Last Revised — 12/01/1991

- 1634-04-4
- Propane, 2-methoxy-2-methyl-
- methyl tert-butyl ether
- T-BUTYL METHYL ETHER
- Ether methyl tert-butylique [French]
- Ether, tert-butyl methyl
- HSDB 5847
- METHYL 1,1-DIMETHYLETHYL ETHER
- METHYL-tert-BUTYL ETHER
- Methyl-tert-butylether
- Metil-terc-butileter [Spanish]
- tert-Butyl methyl ether
- 2-METHOXY-2-METHYLPROPANE
- 2-METHYL-2-METHOXYPROPANE