Toxicological Profile for Methyl *tert*-Butyl Ether (MTBE)

Draft for Public Comment

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Agency for Toxic Substances and Disease Registry

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FOREWORD

This toxicological profile is prepared in accordance with guidelines developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for these toxic substances described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a relevance to public health discussion which would allow a public health professional to make a real-time determination of whether the presence of a particular substance in the environment poses a potential threat to human health. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to the protection of public health are identified by ATSDR and EPA.

Each profile includes the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a toxic substance to ascertain the levels of significant human exposure for the substance and the associated acute, intermediate, and chronic health effects;

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine the levels of exposure that present a significant risk to human health due to acute, intermediate, and chronic duration exposures; and

(C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public. ATSDR plans to revise these documents in response to public comments and as additional data become available. Therefore, we encourage comments that will make the toxicological profile series of the greatest use.

Electronic comments may be submitted via: www.regulations.gov. Follow the on-line instructions for submitting comments.

Written comments may also be sent to: Agency for Toxic Substances and Disease Registry
Office of Innovation and Analytics
Toxicology Section
1600 Clifton Road, N.E.
Mail Stop S102-1
Atlanta, Georgia 30329-4027

The toxicological profiles are developed under the Comprehensive Environmental Response, Compensation, and Liability Act of 1980, as amended (CERCLA or Superfund). CERCLA section 104(i)(1) directs the Administrator of ATSDR to "…effectuate and implement the health related authorities" of the statute. This includes the preparation of toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL) and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. In addition, ATSDR has the authority to prepare toxicological profiles for substances not found at sites on the NPL, in an effort to "…establish and maintain inventory of literature, research, and studies on the health effects of toxic substances" under CERCLA Section 104(i)(1)(B), to respond to requests for consultation under section 104(i)(4), and as otherwise necessary to support the site-specific response actions conducted by ATSDR.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staffs of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and is being made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

Patrick N. Breysse, Ph.D., CIH
Director, National Center for Environmental Health and
Agency for Toxic Substances and Disease Registry
Centers for Disease Control and Prevention

Christopher M. Reh, Ph.D.
Associate Director
Agency for Toxic Substances and Disease Registry
Centers for Disease Control and Prevention

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CONTRIBUTORS & REVIEWERS

CHEMICAL MANAGER TEAM

Jennifer Przybyla, Ph.D. (Lead)
Mike Fay, Ph.D.

ATSDR, Office of Innovation and Analytics, Toxicology Section, Atlanta, GA

Kimberly Zaccaria, Ph.D., D.A.B.T.
Mario Citra, Ph.D.
Lisa Ingerman, Ph.D., D.A.B.T.
Sabah Tariq, M.S.
David W. Wohlers, Ph.D.
SRC, Inc., North Syracuse, NY

REVIEWERS

Interagency Minimal Risk Level Workgroup:

Includes ATSDR; National Center for Environmental Health (NCEH); National Institute for Occupational Safety and Health (NIOSH); U.S. Environmental Protection Agency (EPA); National Toxicology Program (NTP).

Additional reviews for science and/or policy:

ATSDR, Office of Community Health and Hazard Assessment; ATSDR, Office of Capacity Development and Applied Prevention Science; ATSDR, Office of Science; NCEH, Division of Laboratory Science; NCEH, Division of Environmental Health Science and Practice; EPA.

PEER REVIEWERS

1. Clifford P. Weisel, Ph.D.; Professor; Environmental and Occupational Health Sciences Institute; SPH - Rutgers University; 170 Frelinghuysen Road; Piscataway, New Jersey

2. Deborah A. Cory-Slechta, Ph.D.; Professor of Environmental Medicine, Pediatrics and Public Health Sciences; Department of Environmental Medicine, Box EHSC; University of Rochester Medical Center; Rochester, New York

3. James V. Bruckner, Ph.D.; Emeritus; Interdisciplinary Toxicology Program, Professor Pharmaceutical and Biomedical Sciences, College of Pharmacy; University of Georgia, Athens, Georgia

These experts collectively have knowledge of toxicology, chemistry, and/or health effects. All reviewers were selected in conformity with Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

ATSDR scientists review peer reviewers' comments and determine whether changes will be made to the profile based on comments. The peer reviewers' comments and responses to these comments are part of the administrative record for this compound.

The listing of peer reviewers should not be understood to imply their approval of the profile's final content. The responsibility for the content of this profile lies with ATSDR.

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CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

Methyl *tert*-butyl ether (MTBE) is a volatile organic compound (VOC) that was added to gasoline beginning in the 1980s. An amendment to the Clean Air Act established that reformulated gasoline must contain at least 2% oxygen by weight; this requirement led to a rapid expansion in the production and use of MTBE as part of the oxyfuel program. When MTBE started being detected in groundwater, several states enacted a ban on its use in gasoline, and the Energy Policy Act of 2005 removed the oxygenate requirement and replaced it with a renewable fuel standard, which mandated that gasoline sold in the United States was to contain a minimum volume of renewable fuels such as ethanol. While MTBE is still used as an oxygenate in many countries, it is no longer used as an additive in gasoline in the United States. However, MTBE is still manufactured in large quantities in the United States and exported to other nations.

MTBE has also been used as a non-surgical pharmaceutical treatment (intracystic MTBE therapy) to dissolve gallstones in cases in which surgical or endoscopic treatments are considered too risky. However, medical use of MTBE has not been approved in the United States since 2015.

MTBE released to soil or water will tend to volatilize; however, it is also very mobile in soils and degrades slowly. When it was added to gasoline, it was commonly stored in underground storage tanks (USTs); when these tanks leaked, they would release MTBE to the adjacent soil where it would leach into neighboring groundwater. Contamination of groundwater was a major concern and consideration in eliminating MTBE as a gasoline additive.

Levels of MTBE in the environment and in biological matrices have declined markedly since its discontinued use as a gasoline additive after 2005. Data from the U.S. Environmental Protection Agency (EPA) Air Quality System database showed that the highest daily arithmetic mean concentration of MTBE in air was >130 ppbv in 2005, but the largest daily arithmetic mean concentration of MTBE in 2010 was <1 ppbv (EPA 2019a). Moreover, the geometric mean concentration and 95th percentile concentration of MTBE in blood samples collected under the National Health and Nutrition Examination Survey (NHANES) 2001–2002 were 16.4 and 188 pg/mL, respectively, for the entire U.S. population (CDC 2019). By the 2007–2008 survey years, the 95th percentile concentration was 7.27 pg/mL and a geometric mean could not be calculated because the proportion of results below the limit of detection was

too high to provide a valid result. By the 2015–2016 survey, both the geometric mean and the 95th percentile concentration were below the limit of detection.

The most likely route of exposure to the general population is through inhalation of air and ingestion of MTBE containing water. Vapor intrusion of MTBE into structures from contaminated groundwater may result in indoor air levels of MTBE in buildings and residences. Dermal exposure and inhalation may also occur during bathing or washing activities if the water contains MTBE. Since MTBE has been detected at hazardous waste sites, populations living near contaminated sites may be exposed. Since MTBE is still produced and exported to other nations, occupational exposure through inhalation and dermal contact may occur.

1.2 SUMMARY OF HEALTH EFFECTS

Information on the noncancer toxicity of MTBE comes primarily from studies in laboratory animals; however, a few controlled exposure studies, epidemiological studies of humans exposed to gasoline containing MTBE, and side effects reported in patients given MTBE via a tube inserted into their gallbladder for gallstone dissolution contribute to the identification of primary toxicity targets. Eighty-four laboratory animal toxicity studies with health effects data have been identified: 40 inhalation, 38 oral, and 6 dermal.

As illustrated in Figure 1-1, the most sensitive noncancer effects in laboratory animals following inhalation exposure appear to be respiratory, neurological, and hepatic effects. Other noncancer toxicity effects are generally only observed at or above concentrations associated with overt signs of clinical toxicity (central nervous system [CNS] depression), including decreased body weight, and endocrine (adrenal), renal, immunological, female reproductive, and developmental effects. Ocular irritation was also reported in several inhalation studies; however, this effect is attributed to direct contact with vapors as opposed to systemic effects attributable to inhalation exposure. As illustrated in Figure 1-2, the most sensitive noncancer effects in laboratory animals following oral exposure include hepatic, neurological, lymphoreticular, and male reproductive effects. As with inhalation exposure, other noncancer toxicity effects are generally only observed at or above oral doses associated with overt signs of clinical toxicity (CNS depression), including decreased body weight, and endocrine (adrenal), respiratory, hematological, and renal effects. Gastrointestinal effects consistent with irritation of the gastric mucosa were also observed in gavage studies; however, these findings may not be relevant endpoints for environmental exposures, in which oral exposure is expected to be predominantly via drinking water.

Available data following inhalation or oral exposure to MTBE in humans and animals did not indicate adverse effects in the cardiovascular, dermal, or musculoskeletal systems. Data regarding adverse effects associated with inhalation or oral exposure are discussed briefly below.

Figure 1-1. Health Effects Found in Animals Following Inhalation Exposure to Methyl *tert*-Butyl Ether (MTBE)

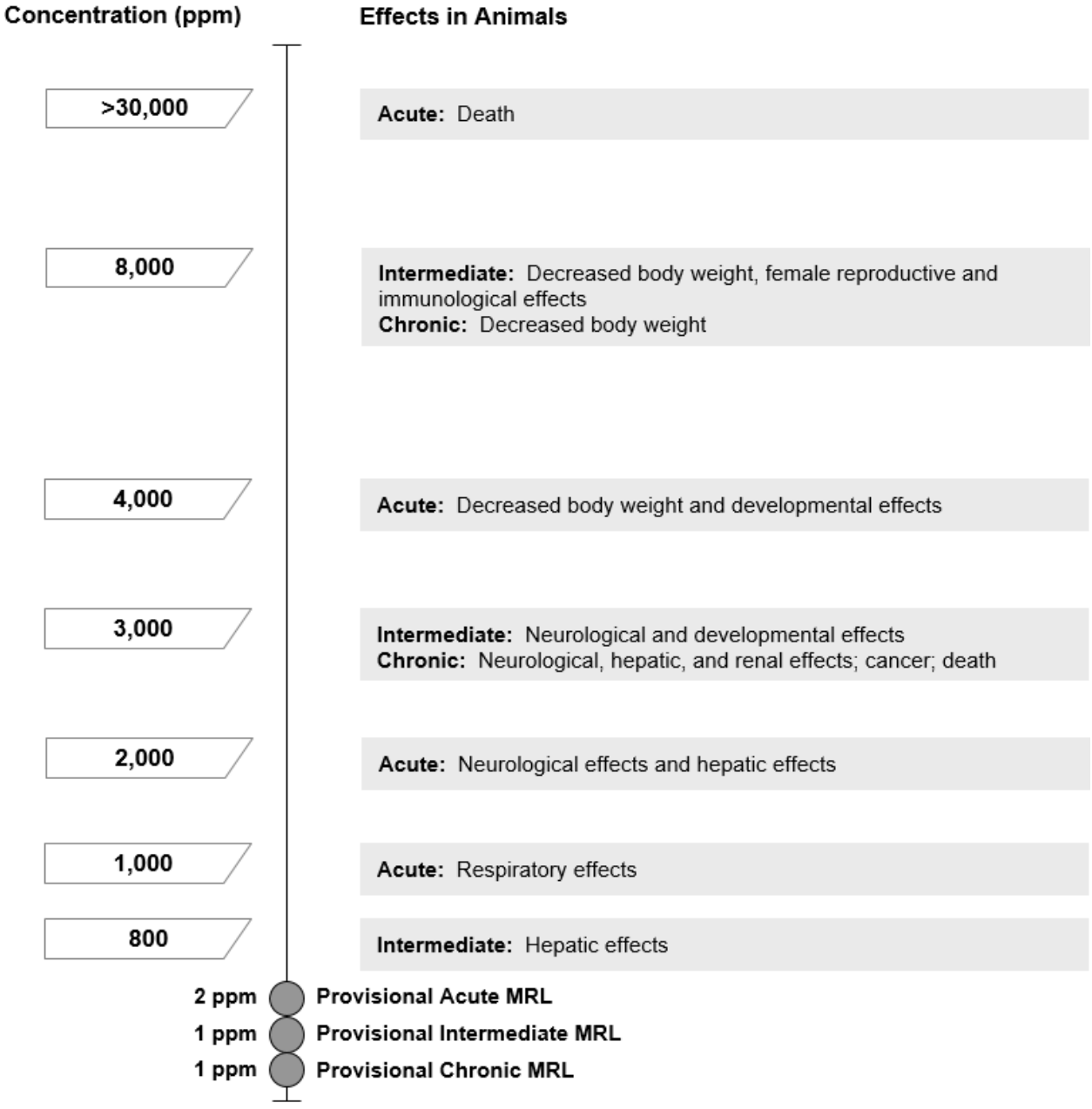
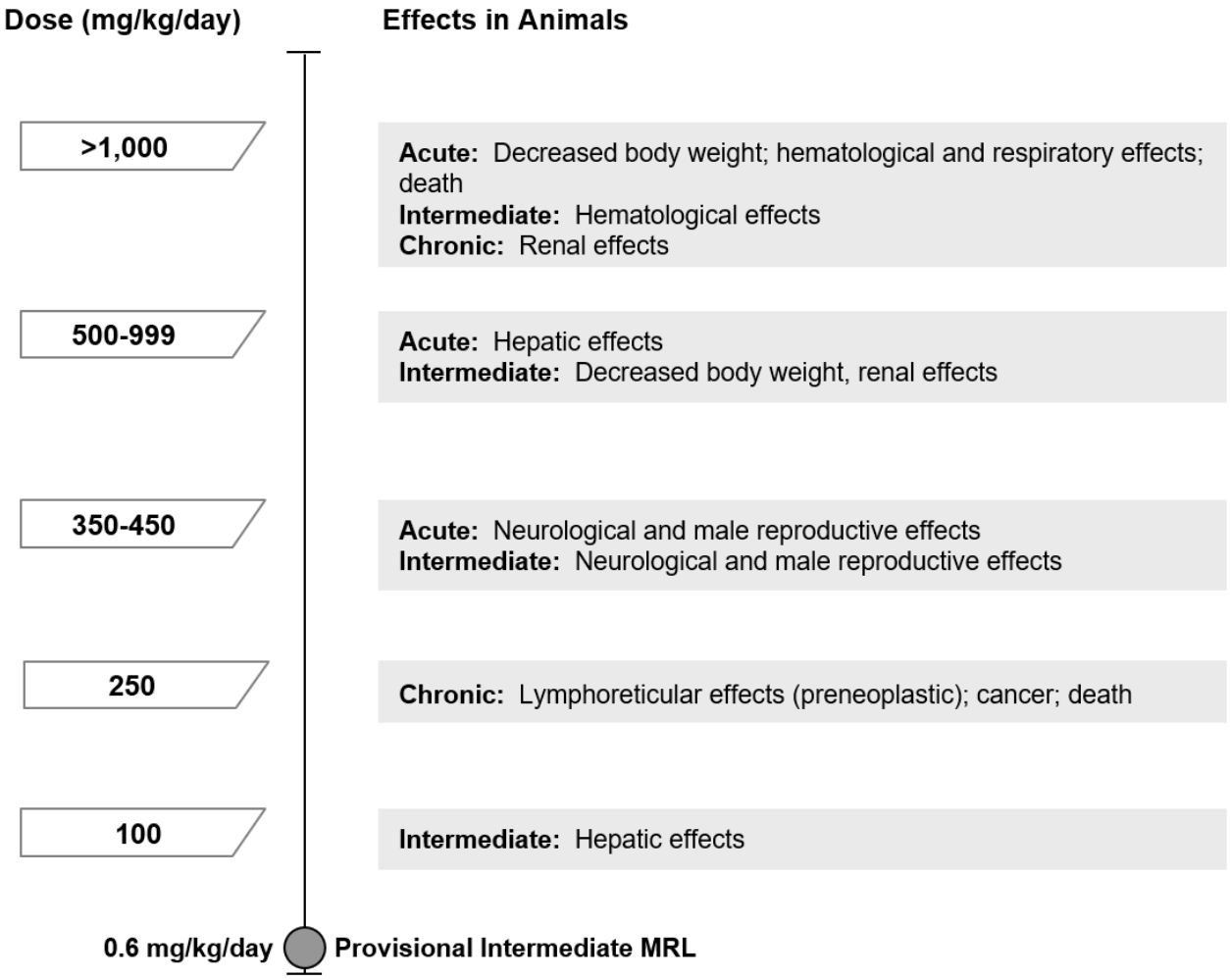


Figure 1-2. Health Effects Found in Animals Following Oral Exposure to Methyl *tert*-Butyl Ether (MTBE)



Respiratory Effects. Some occupational and population-based studies observed respiratory symptoms with introduction of MTBE into fuel during the oxyfuel program in the early 1990s (Alaska DHSS 1992a, 1992b; Moolenaar et al. 1994; Wisconsin DHSS 1995), while other studies did not observe such symptoms (CDC 1993a, 1993b; Gordian et al. 1995; Mohr et al. 1994). However, no clear conclusions can be drawn from these studies due to several limitations. In controlled exposure human studies, there is no evidence of respiratory symptoms in volunteers following acute exposure to low levels of MTBE (Cain et al. 1996; Johanson et al. 1995; Prah et al. 1994). In animal studies, evidence of respiratory irritation and/or inflammation was observed at high inhalation (Tepper et al. 1994; Texaco Inc. 1981) and oral exposure levels (ARCO 1980). Very high inhalation levels associated with lethality resulted in hyperpnea, labored breathing, and respiratory failure (ARCO 1980; Bevan et al. 1997a). However, no evidence of lung damage was observed in animal studies.

Gastrointestinal Effects. Numerous human studies in patients receiving intracystic MTBE therapy for gallstone dissolution report gastrointestinal side effects, including vomiting, nausea, anorexia, emesis, duodenitis, retching, upper abdominal burning sensation during infusion, gas, and duodenal ulcer (see Section 2.6 for citations). Several epidemiology studies also report nausea and/or vomiting with inhalation exposure to gasoline containing MTBE; however, these symptoms are likely related to neurological effects associated with MTBE exposure (see ***Neurological Effects*** below). In animals, the gastrointestinal tract appears to be a target of toxicity following exposure to high gavage doses, including diarrhea and inflammation of the gastrointestinal tract (Amoco 1992; Robinson et al. 1990); gastrointestinal effects were not observed in animals in drinking water or inhalation exposure studies. Observed effects in humans and animals are consistent with irritative effects on the gastrointestinal mucosa. Effects associated with intracystic MTBE therapy or bolus gavage exposure in animals may not be relevant endpoints for environmental exposures, in which oral exposure is expected to be predominantly via drinking water.

Hepatic Effects. Numerous human studies in patients receiving intracystic MTBE therapy for gallstone dissolution report hepatic side effects in cases of accidental overflow of MTBE or bile leakage during the procedure, including slight elevations of serum aminotransaminases, increased bilirubin, and alterations in bile duct structure or function (see Section 2.9 for citations). In animal studies, elevated liver weight, hepatocellular hypertrophy, and induction of hepatic enzymes were consistently observed at high exposure levels associated with overt clinical signs of toxicity (e.g., CNS depression) following inhalation (Bevan et al. 1997a; Bevan et al. 1997b; Bird et al. 1997; Dodd and Kintigh 1989; Lington et al. 1997; Moser et al. 1996; Texaco Inc. 1981) or oral (Amoco 1992; Dong-mei et al. 2009; de Peyster et al. 2003,

2014; Robinson et al. 1990; Williams et al. 2000) exposure. These effects may represent adaptive changes following MTBE exposure and are of uncertain toxicological significance. Elevated serum cholesterol was also observed in some oral studies (Robinson et al. 1990; Saeedi et al. 2017); however, the biological significance of this is also unclear due to lack of associated hepatic lesions (e.g., fatty liver).

Renal Effects. One case report indicates renal side effects in a patient receiving intracystic MTBE therapy for gallstone dissolution following accidental overflow of MTBE during the procedure (Ponchon et al. 1988); no renal side effects were noted in other case reports (Allen et al. 1985a; Uchida et al. 1994). No additional human data are available. Renal toxicity has been consistently observed in male rats at exposure levels at or below those associated with overt clinical signs (e.g., CNS depression) following inhalation (Bird et al. 1997; Lington et al. 1997; Prescott-Matthews et al. 1997) and oral exposure (Amoco 1992; Bermudez et al. 2012; Dodd et al. 2013; Robinson et al. 1990; Williams et al. 2000). Findings in male rats are likely due, in part, to α2u-globulin accumulation, which is not relevant to human health (Ahmed 2001; Bogen and Heilman 2015; McGregor 2006; Phillips et al. 2008). Renal toxicity (elevated kidney weights, increased incidence and severity of chronic progressive nephropathy) has also been reported in female rats via an unknown mechanism(s); however, findings were less severe and/or at higher exposure levels compared to male rats (exposure levels at or above those associated with overt clinical signs of toxicity) (Bird et al. 1997; Dodd et al. 2013). Renal effects included in Figures 1-1 and 1-2 are limited to those with potential relevance to humans (i.e., effects in female rats).

Lymphoreticular Effects. No human data are available. Data from inhalation and oral studies in laboratory animals provide limited evidence of proliferation of lymphoreticular tissues in rats (Belpoggi et al. 1995, 1997; Lington et al. 1997). These lesions may be preneoplastic in nature (see ***Cancer Effects*** below).

Neurological Effects. Some occupational and population-based studies observed effects consistent with transient CNS depression with introduction of MTBE into fuel during the oxyfuel program in the early 1990s, including headache, nausea or vomiting, dizziness, and a feeling of spaciness or disorientation (Alaska DHSS 1992a, 1992b; CDC 1993a; Moolenaar et al. 1994; Wisconsin DHSS 1995), while other studies did not observe such effects (CDC 1993b; Gordian et al. 1995; Mohr et al. 1994). Effects consistent with CNS depression have also been reported in patients following intracystic MTBE therapy for gallstone dissolution (see Section 2.15 for citations). No subjective symptoms or alterations in neurobehavioral tests were observed in volunteers following acute exposure to low air levels of MTBE

(≤50 ppm) (Cain et al. 1996; Johanson et al. 1995; Prah et al. 1994). In laboratory animals, MTBE is a CNS depressant following inhalation exposure to ≥2,000 ppm (ARCO 1980; Bevan et al. 1997a, 1997b; Bird et al. 1997; Daughtrey et al. 1997; Dodd and Kintigh 1989; Greenough et al. 1980; Lington et al. 1997; Moser et al. 1996; MTBE Committee 1990a; Vergnes and Chun 1994; Vergnes and Morabit 1989) and gavage doses ≥400 mg/kg/day (Amoco 1992; ARCO 1980; de Peyster et al. 2003, 2008, 2014; Dong-mei et al. 2009; MTBE Committee 1990b; Robinson et al. 1990). Effects are exposure-related but transient, generally subsiding within hours of exposure, and do not increase in severity with duration of the study. Exposure to MTBE via drinking water, as opposed to bolus gavage doses, does not appear to cause CNS-depressive effects (Bermudez et al. 2012; Dodd et al. 2013). There is no evidence of structural damage to the central or peripheral nervous systems via inhalation or oral exposure.

Reproductive Effects. No human data are available. No changes in fertility or pregnancy outcomes were reported in a 2-generation inhalation study in rats (Bevan et al. 1997b). Based on other inhalation toxicity studies, the male and female reproductive tract in rats and the male reproductive tract in mice do not appear to be primary targets of MTBE toxicity (Biles et al. 1987; Bird et al. 1997; Dodd and Kintigh 1989; Greenough et al. 1980; Lington et al. 1997; Texaco Inc. 1981). In female mice, alterations in reproductive organ weight and histology were reported only at very high concentrations associated with frank systemic toxicity (Moser et al. 1998). Based on animal oral studies, there is some evidence of male reproductive toxicity in rats (decreased fertility, decreased serum testosterone, abnormal sperm, decreased testicular weight, histopathological changes in the testes) at doses associated with overt clinical signs of toxicity (e.g., CNS depression); however, findings are inconsistent across studies and exposure durations (de Peyster et al. 2003, 2014; Gholami et al. 2015; Khalili et al. 2015; Li et al. 2008). There is no evidence of impaired female fertility or damage to the female reproductive system following oral exposure (Berger and Horner 2003; Ward et al. 1994).

Developmental Effects. Human data are limited to a single cohort study reporting a potential association between MTBE exposure during birth year and diagnosis of autism spectrum disorder (Kalkbrenner et al. 2018). In animals, developmental toxicity (litter resorption, post-implantation loss, reduced live fetuses, decreased offspring weight, delayed ossification, cleft palate) was only observed following inhalation exposure to high concentrations associated with frank parental toxicity (e.g., neurotoxicity) (Bevan et al. 1997a, 1997b; Biles et al. 1987; Conaway et al. 1985). No adequate oral developmental toxicity studies in animals were available.

Cancer. No studies were located regarding cancer in humans following exposure to MTBE. Cancer bioassays in animals are available for rats and mice via inhalation exposure and for rats via oral exposure. Increased renal tubular cell tumors were reported in male rats and hepatocellular adenomas were reported in female mice following chronic inhalation exposure to MTBE (Bird et al. 1997). Increased testicular Leydig cell tumors were reported in male rats and lymphomas and leukemia were reported in female rats following chronic gavage exposure to MTBE (Belpoggi et al. 1995, 1997). No exposure-related tumors were observed following chronic drinking water exposure in rats (Dodd et al. 2013).

The International Agency for Research on Cancer (IARC) has determined that MTBE was not classifiable as to its carcinogenicity in humans (IARC 1999). The EPA (IRIS 1993) and the Department of Health and Human Services (HHS) (NTP 2016) have not classified the potential for MTBE to cause cancer in humans.

1.3 MINIMAL RISK LEVELS (MRLs)

The inhalation database was considered adequate for deriving provisional acute-, intermediate-, and chronic-duration MRLs. As presented in Figure 1-3, the available inhalation data for MTBE suggest that the respiratory, neurological, and hepatic systems are the most sensitive targets of toxicity in laboratory animals following inhalation exposure.

The oral database was considered adequate for deriving an intermediate-duration provisional MRL. An MRL was not derived for acute-duration oral exposures because available studies were inadequate to support derivation. An MRL was not derived for chronic-duration oral exposure because no adverse, nonneoplastic effects relevant to human health were reported at doses below the dose associated with serious effects (death and cancer). As presented in Figure 1-4, the available oral data for MTBE suggest that the hepatic, male reproductive, neurological, and lymphoreticular systems are the most sensitive targets of toxicity in laboratory animals following oral exposure.

The MRL values are summarized in Table 1-1 and discussed in greater detail in Appendix A.

Figure 1-3. Summary of Sensitive Targets of Methyl *tert*-Butyl Ether (MTBE) – Inhalation

The hepatic, respiratory, and neurological systems are the most sensitive targets of MTBE inhalation exposure.

Numbers in circles are the lowest LOAELs for all health effects in animals; no adequate human data were identified.

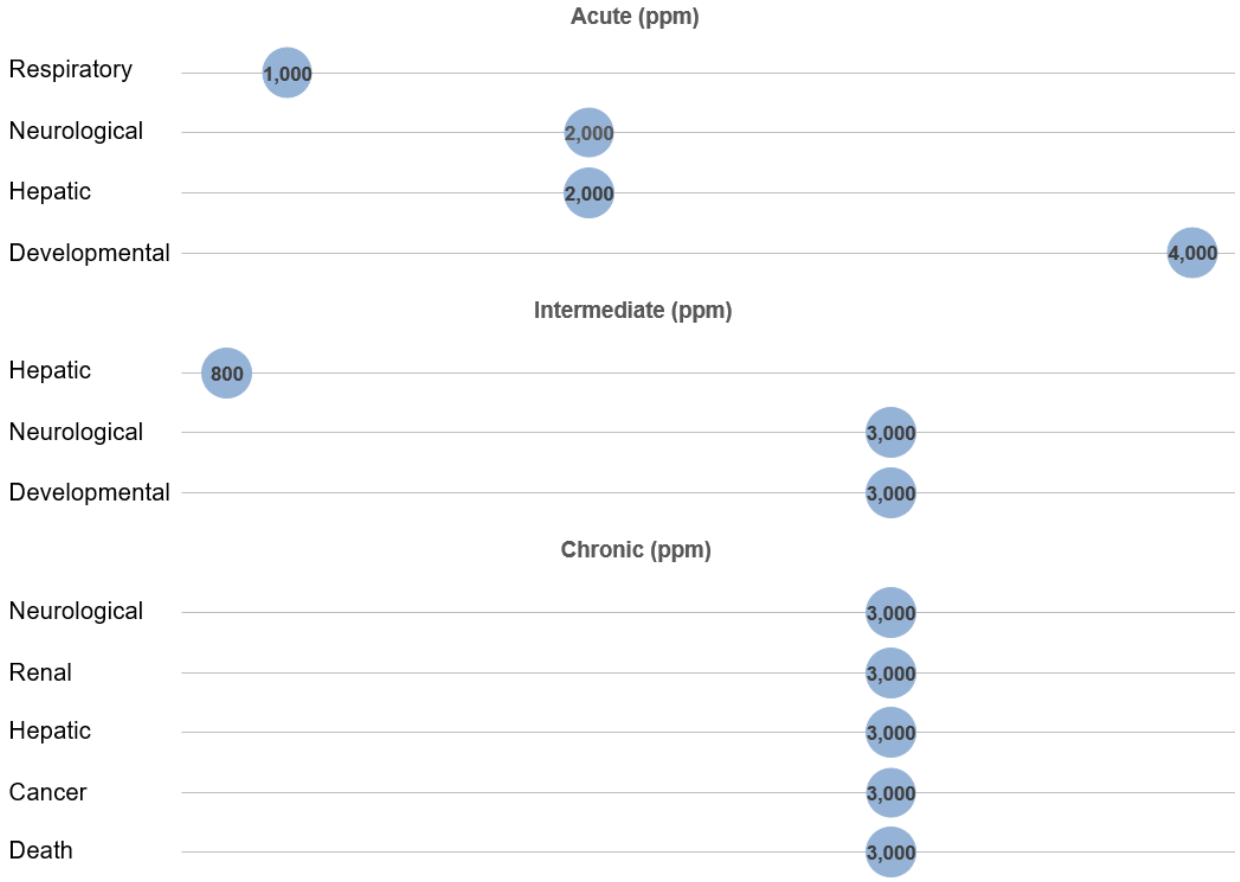


Figure 1-4. Summary of Sensitive Targets of Methyl *tert*-Butyl Ether (MTBE) – Oral

The hepatic, male reproductive, neurological, and lymphoreticular systems are the most sensitive targets of MTBE oral exposure.

Numbers in circles are the lowest LOAELs for all health effects in animals; no data were available for humans.

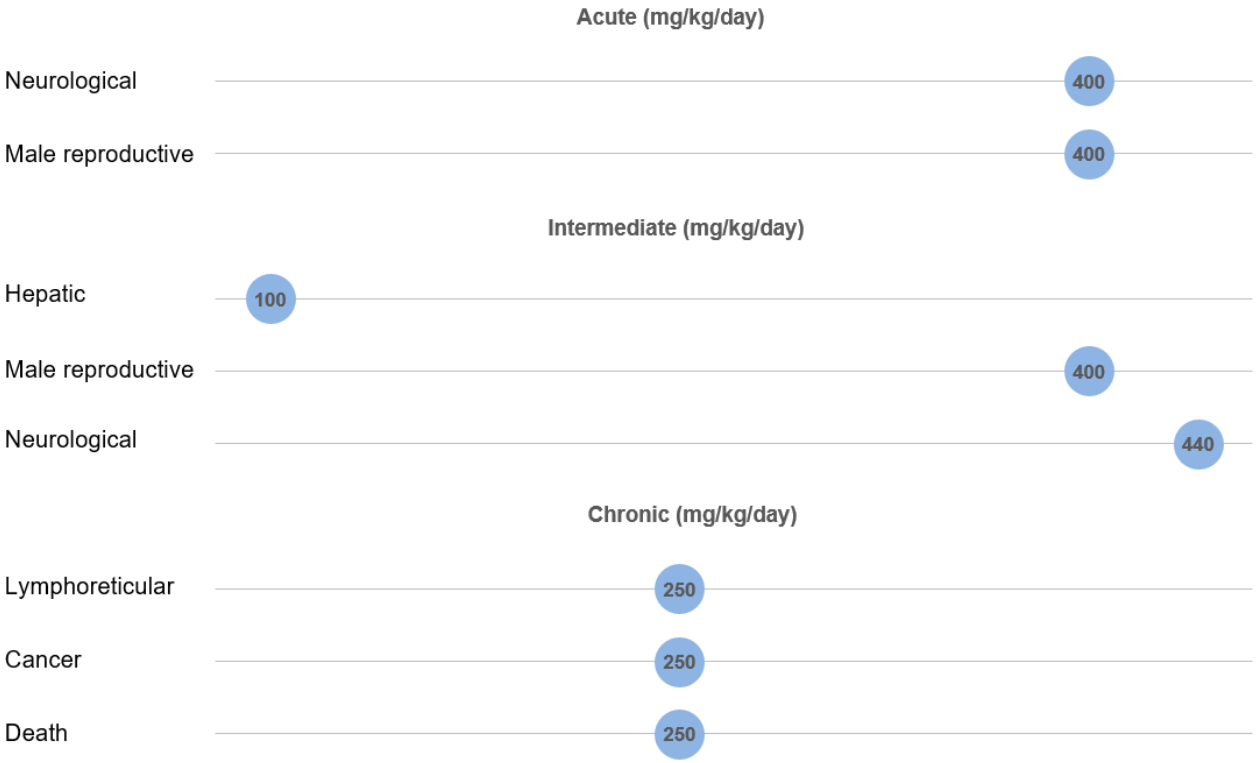


Table 1-1. Minimal Risk Levels (MRLs) for Methyl *tert*-Butyl Ether (MTBE)[a]

Exposure duration	MRL	Critical effect	Point of departure/ human equivalent concentration	Uncertainty factor	Reference
Inhalation exposure (ppm)					
Acute (provisional)	**2**	Neurobehavior (altered gait)	$BMCL_{10}$ = 454 ($BMCL_{HEC}$ = 70.1)	30	Daughtrey et al. 1997; Gill 1989[b]
Intermediate (provisional)	**1**	CNS depression and hepatic effects	NOAEL = 400 ($NOAEL_{HEC}$ = 43.9)	30	Bevan et al. 1997b; Bird et al. 1997
Chronic (provisional)	**1**	Renal effects in females	NOAEL = 400 ($NOAEL_{HEC}$ = 43.9)	30	Bird et al. 1997; Chun et al. 1992[c]
Oral exposure (mg/kg/day)					
Acute	Insufficient data for MRL derivation				
Intermediate (provisional)	**0.6**	CNS depression (hypoactivity)	NOAEL = 90 ($NOAEL_{ADJ}$ = 64)	100	Amoco 1992
Chronic	Insufficient data for MRL derivation				

[a]See Appendix A for additional information.

[b]Gill (1989) is the unpublished report associated with Daughtrey et al. (1997). Raw data for benchmark dose modeling was acquired from Gill (1989) (not available in published report).

[c]Chun et al. (1992) is the unpublished report associated with Bird et al. (1997).

ADJ = adjusted; BMCL = 95% lower confidence limit on the benchmark dose (BMC); CNS = central nervous system; HEC = human equivalent concentration; NOAEL = no-observed-adverse-effect level

CHAPTER 2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of MTBE. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health. When available, mechanisms of action are discussed along with the health effects data; toxicokinetic mechanistic data are discussed in Section 3.1.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized by health effect. These data are discussed in terms of route of exposure (inhalation, oral, and dermal) and three exposure periods: acute (≤14 days), intermediate (15–364 days), and chronic (≥365 days).

As discussed in Appendix B, a literature search was conducted to identify relevant studies examining health effect endpoints. Figure 2-1 provides an overview of the database of studies in humans or experimental animals included in this chapter of the profile. These studies evaluate the potential health effects associated with inhalation, oral, or dermal exposure to MTBE, but may not be inclusive of the entire body of literature.

Summaries of the human observational studies are presented in Table 2-1. Animal inhalation studies are presented in Table 2-2 and Figure 2-2, animal oral studies are presented in Table 2-3 and Figure 2-3, and dermal data are presented in Table 2-4.

Levels of significant exposure (LSEs) for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects (SLOAELs) are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR

acknowledges that a considerable amount of judgment may be required in establishing whether an endpoint should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these endpoints. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health. Levels of exposure associated with cancer (Cancer Effect Levels, CELs) of MTBE are indicated in Tables 2-2 and 2-3 and Figures 2-2 and 2-3.

A User's Guide has been provided at the end of this profile (see Appendix C). This guide should aid in the interpretation of the tables and figures for LSEs and MRLs.

The health effects of MTBE have been evaluated in 15 human studies and 84 animal studies. As illustrated in Figure 2-1, most of the health effects data come from inhalation exposure studies in animals. For the purposes of Figure 2-1, all human and animal inhalation studies were classified as such; however, it is acknowledged that dermal and ocular effects associated with inhalation studies are likely attributable to direct contact with MTBE vapors. Therefore, ocular and dermal effects from animal inhalation studies are counted as dermal exposure in Figure 2-1 and listed in the dermal LSE table. For animal data, inhalation and oral studies are available for all health effect and exposure duration categories. The dermal animal database is limited to five acute studies and one intermediate-duration study, evaluating limited endpoints. The most examined endpoints were death, body weight, neurological, reproductive, and hepatic effects. The available human studies, most of which were in humans exposed to gasoline containing MTBE (not MTBE alone), were predominantly focused on evaluation of respiratory, neurological, and ocular effects.

The results of the animal studies, along with limited human data, suggest potential associations between MTBE exposure and the following health outcomes:

- **Respiratory effects:** Some occupational and population-based studies suggest an increase in respiratory symptoms with introduction of MTBE into fuel during the oxyfuel program in the early 1990s. There is no evidence of respiratory symptoms in volunteers following acute exposure to low levels of MTBE. In animal studies, evidence of respiratory irritation and/or

inflammation was observed at high inhalation and oral exposure levels. Hyperpnea, labored breathing, and respiratory failure were observed at lethal air concentrations. However, no evidence of lung damage was observed in animal studies.

- **Gastrointestinal effects:** Several epidemiology studies report nausea and/or vomiting with inhalation exposure to gasoline containing MTBE; however, these symptoms are likely related to neurological effects associated with MTBE exposure (see **Neurological effects** below). Other human studies are limited to patients receiving intracystic MTBE therapy for gallstone dissolution that report gastrointestinal side effects during and/or after treatment (e.g., vomiting, nausea, burning sensation, duodenal ulcer). In animals, the gastrointestinal tract only appears to be a target of toxicity following exposure to high gavage doses, including diarrhea and inflammation of the gastrointestinal tract. Observed effects in humans and animals are consistent with irritative effects on the gastrointestinal mucosa. Effects associated with intracystic MTBE therapy or bolus gavage exposure in animals may not be relevant endpoints for environmental exposures, in which oral exposure is expected to be predominantly via drinking water.

- **Hepatic effects:** Data from medical intervention studies report hepatic side effects in patients receiving intracystic infusions of MTBE for gallstone dissolution in cases of accidental overflow of MTBE or bile leakage during the procedure. Additional human data for this endpoint are limited to a single cross-sectional study reporting no association between non-alcoholic fatty liver disease (NAFLD) and low-level occupational MTBE exposure. In inhalation and oral animal studies, elevated liver weight, hepatocellular hypertrophy, and induction of hepatic enzymes was consistently observed at high exposure levels associated with overt clinical signs of toxicity (CNS depression). These effects may represent adaptive changes following MTBE exposure. Elevated serum cholesterol was also observed in some studies; however, the biological significance of this is unclear due to lack of associated hepatic lesions (e.g., fatty liver).

- **Renal effects:** Data from patients treated intracystically with MTBE for the dissolution of gallstones do not consistently report renal side effects. No additional human data are available. Renal toxicity has been consistently observed in male rats at inhalation and oral exposure levels at or below those associated with overt clinical signs (e.g., CNS depression). Renal toxicity has also been reported in female rats, but findings were less severe and at higher exposure levels compared to male rats. Findings in male rats are likely due, in part, to α2u-globulin accumulation, which is not relevant to human health.

- **Lymphoreticular effects:** No human data are available. Data from inhalation and oral studies in laboratory animals provide limited evidence of proliferation of lymphoreticular tissues in rats. These lesions may be preneoplastic in nature (see **Cancer effects** below).

- **Neurological effects:** Effects consistent with transient CNS depression have been reported in humans exposed to MTBE in fuel or via MTBE therapy for gallstone dissolution, but no changes in subjective symptoms or neurobehavioral function were observed in volunteers exposed to low air levels of pure MTBE. The predominant and immediate effect of exposure to high levels of MTBE is CNS depression, including hypoactivity, ataxia, and anesthesia. Effects are transient, generally subsiding within hours of exposure and do not increase in severity with duration of study. There is no evidence of structural damage to the central or peripheral nervous systems in exposed animals.

- **Reproductive system:** No human data are available. Based on animal oral studies, there is some evidence of male reproductive toxicity in rats (decreased fertility, decreased serum testosterone, abnormal sperm, decreased testicular weight, histopathological changes in the testes) at doses

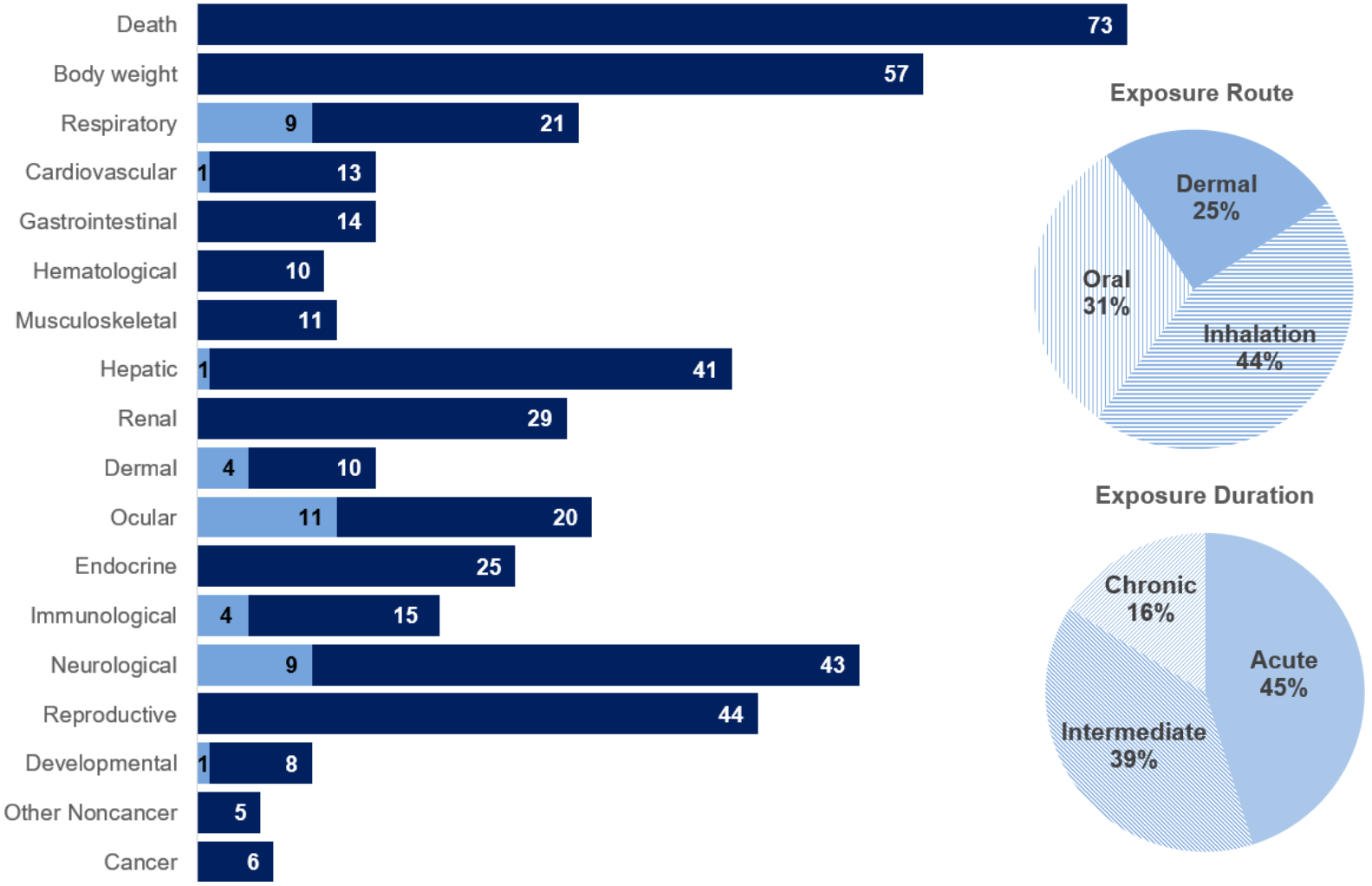
associated with overt clinical signs of toxicity (CNS depression); however, findings are inconsistent across studies and exposure durations. There is no evidence of impaired female fertility or damage to the female reproductive system following oral exposure. In animal inhalation studies, the male and female reproductive tract do not appear to be primary targets of MTBE toxicity, with alterations in female reproductive organs occurring in mice only at exposure levels associated with frank systemic toxicity.

- **Developmental effects:** Human data are limited to a single cohort study reporting a potential association between MTBE exposure during birth year and diagnosis of autism spectrum disorder (ASD). In animals, developmental toxicity (litter resorption, post-implantation loss, reduced live fetuses, decreased offspring weight, delayed ossification, cleft palate) was only observed following inhalation exposure to high concentrations associated with overt parental toxicity (e.g., clinical signs of CNS depression). No adequate oral developmental toxicity studies in animals were available.

- **Cancer effects:** No human data are available. In animals, chronic inhalation exposure was associated with increased renal tubular cell tumors in male rats and hepatocellular adenomas in female mice and chronic gavage exposure was associated with increased testicular Leydig cell tumors in male rats and lymphomas and leukemia in female rats. No exposure-related tumors were observed following chronic drinking water exposure in rats.

Figure 2-1. Overview of the Number of Studies Examining MTBE Health Effects

Most studies examined the potential body weight, neurological, reproductive, and hepatic effects of MTBE
Fewer studies evaluated health effects in **humans** than **animals** (counts represent studies examining endpoint)



*Includes studies discussed in Chapter 2. A total of 99 studies (including those finding no effect) have examined toxicity; most studies examined multiple endpoints.

Table 2-1. Health Effects in Humans Exposed to Methyl *tert*-Butyl Ether (MTBE)—Epidemiological Studies

Reference and study population	Exposure	Outcomes
Occupational studies		
Alaska DHSS 1992a Cross-sectional study United States (Fairbanks, Alaska) Exposure groups: taxi drivers (n=12) and health-care workers (n=90) who traveled routinely in motor vehicles Referent group: university students (n=101)	Subjects exposed to MTBE in oxyfuel gasoline during travel for an average of 69 hours/week (taxi drivers), 7.7 hours/week (health-care workers), or 0.8 hours/week (students). Exposure levels not reported; exposure expected to be primarily via inhalation, with potential for dermal exposure. Surveyed 1 or 2 months after oxyfuel program began.	Subjects meeting case definition (increase in headaches or an increase in two or more of the following: nausea or vomiting; burning sensation in the nose, mouth, or throat; cough; dizziness; spaciness or disorientation; eye irritation): Taxi drivers: 4/12 (33%) Symptoms reported during travel: 3/4 (75%) Symptoms reported during fueling: 1/4 (25%) Health-care workers: 26/90 (29%) Symptoms reported during travel: 11/26 (42%) Symptoms reported during fueling: 9/26 (35%) Students (referent): 15/101 (15%) Symptoms reported during travel: 3/15 (20%) Symptoms reported during fueling: 3/15 (20%) Specific complaints in subjects meeting case definition: Burning sensation in nose or throat: Taxi drivers: 0/4 (0%) Health-care workers: 2/26 (8%) Students: 3/15 (20%) Cough: Taxi drivers: 1/4 (25%) Health-care workers: 8/26 (31%) Students: 3/15 (20%) Eye irritation: Taxi drivers: 1/4 (25%) Health-care workers: 9/26 (35%) Students: 3/15 (20%) Headache: Taxi drivers: 3/4 (75%) Health-care workers: 21/26 (81%) Students: 10/15 (67%) Nausea or vomiting: Taxi drivers: 3/4 (75%) Health-care workers: 9/26 (35%) Students: 6/15 (40%)

Table 2-1. Health Effects in Humans Exposed to Methyl *tert*-Butyl Ether (MTBE)—Epidemiological Studies

Reference and study population	Exposure	Outcomes
		Spaciness: Taxi drivers: 1/4 (25%) Health-care workers: 1/26 (4%) Students: 2/15 (13%)
CDC 1993a Cross-sectional study United States (Albany, New York) Exposure groups: Group 1: 34 automobile repair shop workers and service station attendants exposed to gasoline fumes Group 2: 48 policemen, toll booth workers, and parking garage attendants exposed to automobile exhaust Referent group: Group 3: 182 office workers and college students who may have been exposed to minute amounts of automobile emissions, but who were not occupationally exposed to gasoline	Subjects exposed to MTBE in oxyfuel gasoline. Median (range) blood MTBE concentration (µg/L): Group 1: Nonsmokers (n=7): 0.38 (<LOD–0.58) Smokers (n=4): 0.46 (0.09–1.50) Group 2: Nonsmokers: (n=6): 0.05 (<LOD–0.15) Smokers (n=3): 0.08 (<LOD–0.11) Group 3: Nonsmokers (n=16): <LOD Smokers (n=4): <LOD Median (range) MTBE in ambient workplace air (µg/m^3): Group 1 (n=3): <LOD Group 2 (n=8): <LOD Median (range) MTBE in personal breathing zone workplace air (µg/m^3): Group 1 (n=13): <LOD (<LOD–505) Group 2 (n=11): <LOD	"Key" symptoms reported by subjects: Burning sensation in nose or throat: Group 1: 2/34 (6%) Group 2: 2/48 (4%) Group 3: 24/182 (13%) Cough: Group 1: 5/34 (15%) Group 2: 12/48 (25%) Group 3: 37/182 (20%) Nausea: Group 1: 2/34 (6%) Group 2: 3/48 (6%) Group 3: 14/182 (8%) Dizziness: Group 1: 3/34 (9%) Group 2: 6/48[a] (12%) Group 3: 5/182 (3%) Spaciness or disorientation: Group 1: 0/34 (0%) Group 2: 2/48 (4%) Group 3: 13/182 (7%) Headache: Group 1: 7/34 (21%) Group 2: 23/48[a] (47%) Group 3: 44/182 (24%) Any key symptom: Group 1: 14/34 (41%) Group 2: 28/48 (59%) Group 3: 95/182 (52%) Two or more key symptoms: Group 1: 3/34 (9%) Group 2: 13/48[a] (27%)

Table 2-1. Health Effects in Humans Exposed to Methyl *tert*-Butyl Ether (MTBE)—Epidemiological Studies

Reference and study population	Exposure	Outcomes
		Group 3: 36/182 (20%)"Other" symptoms reported by subjects: Difficulty breathing: Group 1: 0/34 (0%) Group 2: 7/48 (14%) Group 3: 25/182 (14%) Diarrhea: Group 1: 2/34 (6%) Group 2: 4/48 (8%) Group 3: 21/182 (12%) Skin irritation: Group 1: 3/34 (9%) Group 2: 5/48 (10%) Group 3: 17/182 (9%) Fatigue: Group 1: 6/34 (18%) Group 2: 8/48 (16%) Group 3: 44/182 (24%) Fainting: Group 1: 0/34 (0%) Group 2: 0/48 (0%) Group 3: 3/182 (2%)
Alaska DHSS 1992b Cross-sectional study United States (Anchorage, Alaska) Exposure group: taxi drivers (n=25) and health-care workers (n=137) who traveled routinely in motor vehicles Referent group: none	Subjects exposed to MTBE in oxyfuel gasoline during travel; average travel time per week not reported. Exposure levels not reported; exposure expected to be primarily via inhalation, with potential for dermal exposure. Surveyed 1 or 2 months after oxyfuel program began.	Subjects meeting case definition (increase in headaches or an increase in two or more of the following: nausea or vomiting; burning sensation in the nose, mouth, or throat; cough; dizziness; spaciness or disorientation; eye irritation): Taxi drivers: 12/25 (48%): Symptoms reported during travel: 12/12 (100%) Symptoms reported during fueling: 9/12 (75%) Health-care workers: 36/137 (26%): Symptoms reported during travel: 27/36 (75%) Symptoms reported during fueling: 19/36 (53%) Specific complaints in subjects meeting case definition: Burning sensation in nose or throat: Taxi drivers: 5/12 (42%) Health-care workers: 13/36 (36%)

Table 2-1. Health Effects in Humans Exposed to Methyl *tert*-Butyl Ether (MTBE)—Epidemiological Studies

Reference and study population	Exposure	Outcomes
		Cough: Taxi drivers: 4/12 (33%) Health-care workers: 13/36 (36%) Eye irritation: Taxi drivers: 8/12 (67%) Health-care workers: 13/36 (36%) Headache: Taxi drivers: 11/12 (92%) Health-care workers: 31/36 (86%) Nausea or vomiting: Taxi drivers: 5/12 (42%) Health-care workers: 9/36 (25%) Dizziness: Taxi drivers: 4/12 (33%) Health-care workers: 7/36 (19%) Spaciness: Taxi drivers: 4/12 (33%) Health-care workers: 3/36 (8%)
Duffy 1994 Cross-sectional study United States (Fairbanks, Alaska) Exposure group: 22 volunteers occupationally exposed to automobile emissions between late November and early December 1992 Referent group: none	Subjects exposed to gasoline containing MTBE during the oxyfuel program. Exposure levels not reported; exposure expected to be primarily via inhalation, with potential for dermal exposure.	Mean±SD interleukin-6 levels Pre-shift: 2.50±2.4 pg/mL Post-shift: 2.53±2.6 pg/mL Mean±SD interleukin-1 levels Pre-shift: <LOD Post-shift: <LOD

Table 2-1. Health Effects in Humans Exposed to Methyl *tert*-Butyl Ether (MTBE)—Epidemiological Studies

Reference and study population	Exposure	Outcomes
Mohr et al. 1994 Cross-sectional study United States (New Jersey) Exposure group: 115 automobile mechanics in northern New Jersey exposed to MTBE during wintertime oxyfuel program Referent group: 122 garage workers in southern New Jersey 10 weeks after the phase-out date for oxyfuel program	Exposure group was exposed to gasoline containing MTBE from November 15, 1992 to April 30, 1993. Survey data for this group were collected in April 1993. Referent group was exposed to gasoline containing MTBE only from November 15, 1992 to February 28, 1993. Survey data for this group were collected in May 1993. 8-Hour TWA MTBE in air (1-hour active sampling) Exposure: 1.66–6.1 ppm Referent: <0.28 (LOD)–0.83 ppm	Symptoms reported by subjects to have occurred at least once over the past 30 days: Cough: Exposed: 12% Referent: 17% p-value: 0.23 Eye irritation: Exposed: 22% Referent: 27% p-value: 0.39 Headache: Exposed: 36% Referent: 39% p-value: 0.82 Lightheadedness: Exposed: 10% Referent: 13% p-value: 0.41 Sleepiness while driving: Exposed: 20% Referent: 24% p-value: 0.37 Daytime sleepiness: Exposed: 13% Referent: 24% p-value: 0.001 Nausea: Exposed: 27% Referent: 35% p-value: 0.03 Mean summary score for all symptoms: Exposed: 4.3 Referent: 5.1 p-value: 0.09

Table 2-1. Health Effects in Humans Exposed to Methyl *tert*-Butyl Ether (MTBE)—Epidemiological Studies

Reference and study population	Exposure	Outcomes
		Mean postshift summary score for all symptoms in exposed subjects who pumped gas for >5 hours/day and matched referents: Exposed (n=11): 3.37 Control (n=11): 2.00 Time effect p-value 0.81 Group effect p-value: 0.66 Time x group effect p-value: 0.33
Moolenaar et al. 1994; CDC 1993c Cohort study United States (Fairbanks, Alaska) Exposure group (Phase I): 18 workers heavily exposed to gasoline fumes in December 1992, during oxyfuel program (10 mechanics/workers at service stations and automobile dealerships and 8 workers who spent most of their workdays in motor vehicles, including animal control officers, meter and telephone technicians, and a garbage collector) Referent group (Phase II): 28 workers heavily exposed to gasoline fumes in February 1993, after the oxyfuel program ended (12 subjects from Phase I plus16 additional workers from service stations and garages)	Subjects exposed to gasoline containing 15% MTBE during Phase I; gasoline did not contain MTBE during Phase II. Median 8-hour TWA (range) of MTBE in workplace air of service stations and dealership garages: Phase I: 0.2* (0.001–0.81) ppm Phase II: 0.04 (<LOD–0.14) ppm Median preshift concentrations (range) of MTBE in blood of exposed workers: Phase I: 1.15* (0.1–27.8) µg/L Phase II: 0.20 (0.05–4.35) µg/L Median postshift concentrations (range) of MTBE in blood of exposed workers: Phase I: 1.80* (0.2–37.0) µg/L Phase II: 0.24 (0.05–1.44) µg/L	Symptoms reported by subjects: Burning sensation in nose or throat: Phase I: 9/18[a] (50%) Phase II: 0/28 (0%) Cough Phase I: 5/18[a] (28%) Phase II: 0/28 (0%) Eye irritation: Phase I: 12/18[a] (67%) Phase II: 2/28 (7%) Nausea/vomiting: Phase I: 6/18[a] (33%) Phase II: 1/28 (4%) Dizziness: Phase I: 8/18[a] (44%) Phase II: 0/28 (0%) Spaciness or disorientation: Phase I: 6/18[a] (33%) Phase II: 0/28 (0%) Headache: Phase I: 13/18[a] (72%) Phase II: 1/28 (4%) Symptoms reported during Phase I by quartile (Q): Any symptom: Phase I Q4 (>9.6 µg/L postshift): 4/4 Phase I Q1-Q3: 9/14

Table 2-1. Health Effects in Humans Exposed to Methyl *tert*-Butyl Ether (MTBE)—Epidemiological Studies

Reference and study population	Exposure	Outcomes
CDC 1993b; White et al. 1995 Cross-sectional study United States (Stamford, Connecticut) Exposure groups: Group 1 (mechanics): 48 male mechanics or gasoline station attendants Group 2 (professional drivers): 57 male taxi or limousine drivers Group 3 (other): 12 male workers who spent most of their time around traffic or motor vehicles (e.g., meter readers) Referent group: Group 4 (commuters): 59 men not occupationally exposed, but commuted to work in their cars	Subjects exposed to gasoline containing 15% MTBE during work and/or travel from April 5 to 16, 1993 (~5 months after oxyfuel program began). MTBE levels in personal breathing zones (range) Mechanics: <0.03 to 12.04 ppm Drivers: NR Other: <0.03 (LOD) Commuters: NR Median post-shift concentration (range) of MTBE in blood Mechanics (n=21): 1.73 (0.17–36.7) µg/L Gas station (n=3): 15 (7.6–28.9) µg/L Drivers: NR Other (n=6): 0.1 µg/L (range not reported) Commuters: (n=14): 0.11 (<0.05–2.60) µg/L	Symptoms reported by subjects: Burning sensation in nose or throat: Group 1: 7/48 (15%) Group 2: 0/57 (0%) Group 3: 4/12[a] (33%) Group 4: 4/59 (7%) Cough: Group 1: 7/48 (15%) Group 2: 3/57 (5%) Group 3: 5/12 (42%) Group 4: 9/59 (15%) Eye irritation: Group 1: 10/48 (21%) Group 2: 4/57 (7%) Group 3: 2/12[a] (17%) Group 4: 11/59 (19%) Nausea: Group 1: 1/48 (2%) Group 2: 0/57 (0%) Group 3: 1/12 (8%) Group 4: 0/59 (0%) Dizziness: Group 1: 3/48 (6%) Group 2: 3/57 (5%) Group 3: 2/12 (17%) Group 4: 1/59 (2%) Spaciness or disorientation: Group 1: 5/48 (10%) Group 2: 1/57 (2%) Group 3: 1/12 (8%) Group 4: 2/59 (3%) Headache (1 or more times): Group 1: 13/48 (27%) Group 2: 15/57 (26%) Group 3: 5/12 (42%) Group 4: 15/59 (25%) Headache (2 or more times): Group 1: 12/48 (25%) Group 2: 12/57 (21%)

Table 2-1. Health Effects in Humans Exposed to Methyl *tert*-Butyl Ether (MTBE)—Epidemiological Studies

Reference and study population	Exposure	Outcomes
		Group 3: 5/12 (42%) Group 4: 14/59 (24%) Headache (5 or more times): Group 1: 4/48 (8%) Group 2: 5/57 (9%) Group 3: 1/12 (8%) Group 4: 3/59 (5%) Odds ratio (CI) to report of one or more key symptoms (listed above): Median blood level ≥2.4 µg/L (n=11) = 8.9 (1.2–75.6)* Median blood level >3.8 µg/L (n=8) = 21.0 (1.8–539)*
Yang et al. 2016 Cross-sectional study China Exposure group: 71 gas station attendants (41 males, 30 females) employed in Southern China from April to September 2014 for >3 years; any workers with alcohol intake >20 g/day, hepatitis B, hepatitis C, autoimmune hepatitis, primary biliary cirrhosis, or other chronic liver disease with a clear cause were excluded	Mean (SD) personal MTBE air exposure concentrations (3 consecutive 8-hour workdays) NAFLD group (n=11): 292.98±154.90 µg/m^3 (0.081 ppm) Non-NAFLD group (n=60): 286.64±122.28 µg/m^3 (0.079 ppm)	Adjusted[c] odds ratio (CI) for diagnosis of NAFLD: Males+females (11 NAFLD, 60 non-NAFLD): MTBE ≤100 µg/m^3 (n=11): 1.00 (referent) MTBE 100–200 µg/m^3 (n=12): 1.31 (0.85–1.54) MTBE 200–300 µg/m^3 (n=34): 1.14 (0.81–1.32) MTBE ≥300 µg/m^3 (n=14): 1.52 (0.93–1.61) Males (10 NAFLD, 31 non-NAFLD): MTBE ≤100 µg/m^3 (n=4): 1.00 (referent) MTBE 100–200 µg/m^3 (n=4): 1.64 (0.84–1.83) MTBE 200–300 µg/m^3 (n=25): 1.32 (0.80–1.63) MTBE ≥300 µg/m^3 (n=7): 1.21 (0.77–1.73) Females (1 NAFLD, 29 non-NAFLD) MTBE ≤100 µg/m^3 (n=7): 1.00 (referent) MTBE 100–200 µg/m^3 (n=8): 1.17 (0.79–1.32) MTBE 200–300 µg/m^3 (n=9): 1.02 (0.79–1.26) MTBE ≥300 µg/m^3 (n=7): 1.11 (0.75–1.41)

Table 2-1. Health Effects in Humans Exposed to Methyl *tert*-Butyl Ether (MTBE)—Epidemiological Studies

Reference and study population	Exposure	Outcomes
General population studies		
Wisconsin DHSS 1995 Cross-sectional study United States (Milwaukee, Wisconsin; Chicago, Illinois) Exposure groups: residents of metropolitan Milwaukee (n=527; 43% male) and metropolitan Chicago (n=485; 45% male); interviewed between February 24, 1995 and March 19, 1995 Referent group: residents of Wisconsin, excluding metropolitan areas participating in oxyfuel program (n=501; 45% male); interviewed between February 24, 1995 and March 19, 1995	Subjects living in metropolitan areas were exposed to gasoline containing MTBE during the oxyfuel program; gasoline in non-metropolitan areas did not contain MTBE. Mean (range) of ambient MTBE exposure at University of Wisconsin, North Campus (metropolitan Milwaukee): 0.20 (<0.025 ppb (LOD)–0.85) ppb Range of ambient MTBE exposure at gas stations: Milwaukee: 0.25–4.58 ppb Chicago: NR Referent: <0.025 ppb (LOD) Range of personal breathing zone MTBE exposure at gas stations while fueling: Milwaukee: 70–5,930 ppb Chicago: NR	Adjusted[d] risk ratios for symptoms in individuals who reported buying oxyfuel since induction of program on November 1, 1994, compared to referent group: Throat irritation: Milwaukee: 3.8* Chicago: not calculated (incidence too small) Difficulty breathing: Milwaukee: 1.8 Chicago: not calculated (incidence too small) Sinus congestion: Milwaukee: 2.6* Chicago: 0.8 Rashes: Milwaukee: 2.2 Chicago: not calculated (incidence too small) Eye irritation: Milwaukee: 3.8* Chicago: not calculated (incidence too small) Headache: Milwaukee: 4.2* Chicago: 1.8 Nausea: Milwaukee: 2.9 Chicago: 3.0 Dizziness: Milwaukee: 1.8 Chicago: 1.2 Spaciness: Milwaukee: 2.1 Chicago: 1.5 Any unusual symptom: Milwaukee: 2.8* Chicago: 2.3 Incidence of any “unusual” symptoms: Milwaukie: 23% Chicago: 6% Referent: 6%

Table 2-1. Health Effects in Humans Exposed to Methyl *tert*-Butyl Ether (MTBE)—Epidemiological Studies

Reference and study population	Exposure	Outcomes
Gordian et al. 1995 Ecological study United States (Fairbanks and Anchorage, Alaska) Study population: Alaska state employees, retirees, and dependents in Anchorage (n=~15,000) and Fairbanks (n=~4,900) Exposure period: November 1992–February 1993 (Anchorage); November 1992–December 1992 (Fairbanks) Referent period: November 1990–February 1991 and November–February 1992 (both cities)	Subjects were exposed to gasoline containing 16% MTBE during winter of 1992–1993; gasoline in prior years did not contain MTBE. Exposure levels were not reported; exposure expected to be primarily via inhalation.	Odds ratios (95% CI) for winter outpatient visits during the oxyfuel program (1992–1993) versus prior to the oxyfuel program: Upper respiratory illness: Anchorage: 1992–1993 versus 1990–1991: 0.94 (0.84–1.05) 1992–1993 versus 1991–1992: 0.94 (0.84–1.05) Fairbanks: 1992 versus 1990–1991: 0.95 (0.81–1.13) 1992 versus 1991–1992: 1.07 (0.90–1.27) Bronchitis: Anchorage: 1992–1993 versus. 1990–1991: 0.90 (0.73–1.11) 1992–1993 versus 1991–1992: 0.85 (0.069–1.05) Fairbanks: 1992 versus 1990–1991: 1.33 (0.90–1.99) 1992 versus 1991–1992: 0.96 (0.67–1.38) Asthma: Anchorage: 1992–1993 versus 1990–1991: 1.05 (0.76–1.47) 1992–1993 versus 1991–1992: 0.99 (0.72–1.37) Fairbanks: 1992 versus 1990–1991: 1.16 (0.75–1.81) 1992 versus 1991–1992: 1.00 (0.66–1.52) Headaches: Anchorage: 1992–1993 versus 1990–1991: 1.54 (0.94–2.52) 1992–1993 versus 1991–1992: 0.52 (0.35–0.75) Fairbanks: 1992 versus 1990–1991: 1.43 (0.71–2.94) 1992 versus 1991–1992: 1.30 (0.67–2.58)

Table 2-1. Health Effects in Humans Exposed to Methyl *tert*-Butyl Ether (MTBE)—Epidemiological Studies

Reference and study population	Exposure	Outcomes
Joseph and Weiner 2002 Ecological study United States (Philadelphia, Pennsylvania) Study population: Patients visiting the General Medicine Division of the Clinical Practices at the University of Pennsylvania in 1992 (n=14,900) and 1997 (n=26,644) Number and fraction of visits in 1997 (6th year of oxyfuel program) compared to number and fraction of visits in 1992 (1st year of oxyfuel program).	Subjects were exposed to gasoline containing 11–15% MTBE from 1992 to 1997 (4-month winter period of November–February only for 1992, 1993, and 1994; year-round 1995–1997). Exposure levels were not reported; exposure expected to be primarily via inhalation.	Number (fraction) of diagnostic codes pertaining to MTBE-related symptoms[b]: Burning throat: 1992: 198 (0.013) 1997: 1,104 (0.041)* Burning nose: 1992: 179 (0.012) 1997: 774 (0.029)* Cough: 1992: 59 (0.0039) 1997: 333 (0.0125)* Eye irritation: 1992: 20 (0.0013) 1997: 62 (0.0023)* Headache: 1992: 139 (0.0093) 1997: 659 (0.024)* Nausea: 1992: 14 (0.00094) 1997: 107 (0.0040)* Dizziness: 1992: 143 (0.0096) 1997: 430 (0.0161)* Spaciness 1992: 0 (0.0) 1997: 30 (0.0006) Number (fraction) of diagnostic codes for symptoms related to respiration (not directly linked to MTBE): Wheezing: 1992: 45 (0.003) 1997: 484 (0.018)* Upper Respiratory Infection: 1992: 397 (0.026) 1997: 1,531 (0.057)* Asthma: 1992: 393 (0.026) 1997: 737 (0.028)

Table 2-1. Health Effects in Humans Exposed to Methyl *tert*-Butyl Ether (MTBE)—Epidemiological Studies

Reference and study population	Exposure	Outcomes
		Otitis media: 1992: 34 (0.0023) 1997: 116 (0.0043)* Allergic rhinitis: 1992: 179 (0.012) 1997: 774 (0.029)* Number (fraction) of diagnostic codes for symptoms attributed anecdotally to MTBE in gasoline: Skin rash: 1992: 74 (0.005) 1997: 1,062 (0.040)* General allergy: 1992: 13 (0.0009) 1997: 115 (0.0043)* Anxiety: 1992: 27 (0.0018) 1997: 390 (0.0146) Insomnia: 1992: 61 (0.0041) 1997: 259 (0.0097)* Cardiac (tachycardia, palpitations, murmurs): 1992: 84 (0.0056) 1997: 239 (0.0089)* Malaise and fatigue: 1992: 162 (0.011) 1997: 871 (0.032)* Number (fraction) of diagnostic codes for symptoms unrelated to air pollution (considered “referent” conditions”): Diabetes: 1992: 1,100 (0.0738) 1997: 1,853 (0.0695) Hypertension (summed across years): 1992–1993: 9,554 (0.314) 1996–1997: 16,862 (0.327)*

Table 2-1. Health Effects in Humans Exposed to Methyl *tert*-Butyl Ether (MTBE)—Epidemiological Studies

Reference and study population	Exposure	Outcomes
		Liver disease: 1992: 146 (0.0097) 1997: 296 (0.0111) Back pain: 1992: 225 (0.0151) 1997: 338 (0.0127) Abdominal pain: 1992: 492 (0.0330) 1997: 973 (0.0365) Diverticulosis: 1992: 65 (0.0043) 1997: 129 (0.0048)
Kalkbrenner et al. 2018 Case-control study United States Subjects: 1,540 cases of ASD and 477 controls from the AGRE family-based study cohort 1,272 cases and controls (combined) were evaluated for autism severity using the CSS and 1,380 cases and controls (combined) were evaluated for autism-related traits using the SRS	Exposure estimated based on birth year from average annual concentration reported in the EPA emissions-based National-scale Air Toxics Assessment.	Adjusted[e] odds ratio (CI) between measure of ASD and log-transformed MTBE concentration: ASD diagnosis: 2.33 (1.31–4.15)[†] Change in CSS: 0.07 (-0.54–0.68) Change in SRS: 5.88 (-0.30–12.36) Adjusted[e] odds ratio (CI) between ASD diagnosis and log-transformed MTBE concentration, adjusted for additional air toxics: Adjusted for log-transformed diesel particular matter: 2.03 (1.02–4.05)[†] Adjusted for log-transformed xylene: 2.10 (1.03–4.27)[†]

[a]Statistically significant (P<0.05) compared to the reference group, as calculated for this review (2-tailed Fischer's Exact Probability Test).
[b]Symptoms linked to MTBE (headache, eye irritation, burning nose or throat, cough, nausea, dizziness, spaciness), as determined by the CDC.
[c]Adjusted for age, physical exercise, body mass index, systolic and diastolic blood pressure, ALT, white blood cells, total cholesterol, triglycerides, LDL, and HDL.
[d]Adjusted for age, race, sex, smoking status, asthma diagnosis, having a cold since 11/1/94, perception of living in a reformulated gas area, and heard of MTBE.
[e]Adjusted for participant's birth year, median mean exposure level in the family, and census block group variables (population density, education, median rent).

* = statistically significant (p<0.05), as reported by the study authors; [†] = statistically significant from the null after correcting for multiple comparisons using the false discovery rate (set at 0.1), as reported by the study authors; AGRE = Autism Genetic Resource Exchange; ALT = alanine aminotransferase; ASD = autism spectrum disorder; CDC = Centers for Disease Control and Prevention; CI = confidence interval; CSS = calibrated severity score; EPA = U.S. Environmental Protection Agency; HDL = high-density lipoprotein; LDL = low-density lipoprotein; LOD = level of detection; NAFLD = non-alcoholic fatty liver disease; NR = not reported; SD = standard deviation; SRS = Social Responsiveness Score; TWA = time-weighted average

Table 2-2. Levels of Significant Exposure to Methyl *tert*-Butyl Ether (MTBE) – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
ACUTE EXPOSURE									
1	Human 22 M, 21 F	1 hour (WB)	0, 1.7	CS, NX, OP	Resp	1.7			
					Neuro	1.7			
Cain et al. 1996 (data also available in unpublished report by Cain et al. 1994)									
2	Human 10 M	2 hours	5, 25, 50	CS, NX	Resp	50 M			
					Neuro	50 M			
Johanson et al. 1995; Nihlén et al. 1998a									
3	Human 19 M, 18 F	1 hour	0, 1.39	CS, NX, BI	Resp	1.39			
					Neuro	1.39			
Prah et al. 1994									
4	Rat (NS) NS	4 hours (WB)	18,892, 34,127, 38,657, 41,860, 63,953	CS, LE	Death			33,370	
					Resp			18,892	Nasal discharge, tachypnea, respiration slowing until death
					Neuro			18,892	Incoordination, loss of righting reflex
ARCO 1980 (commercial MTBE [99.1% purity])									
5	Rat (NS) (NS)	4 hours (WB)	19,621, 29,681, 39,406, 55,784	CS, LE	Death			39,395	4-hour LC_{50}
					Resp			19,621	Irregular respiration, hyperpnea
					Neuro			19,621	Ataxia, loss of righting reflex, incoordination, prostration
ARCO 1980 (ARCO MTBE [96.2% purity])									
6	Rat (Fischer-344) 5 M, 5 F	5 days 6 hours/day (WB)	0, 400, 3,000, 8,000	BI	Renal	8,000 F 400 M	3,000 M		Increased proliferation of epithelial cells in the proximal convoluted tubules in males
Bird et al. 1997 (data also available in unpublished report by Chun and Kintigh 1993)									
7	Rat (Sprague-Dawley 25 F	10 days GDs 6–15 6 hours/day (WB)	0, 250, 1,000, 2,500	BW, OW, LE, FI, WI, GN, DX, CS	Bd wt	2,500 F			
					Hepatic	2,500 F			
					Develop	2,500			
Conaway et al. 1985									

Table 2-2. Levels of Significant Exposure to Methyl *tert*-Butyl Ether (MTBE) – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
8	Rat (Fischer-344) 22 M, 22 F	6 hours (WB)	0, 800, 4,000, 8,000	CS, NX, LE, BW	Bd wt	8,000			
					Neuro	800[b] F 4,000 M	4,000 F 8,000 M	8,000 F	Females: Altered gait and decreased hind-leg grip strength at ≥4,000 ppm; ataxia, incoordination, and altered motor activity at 8,000 ppm Males: Ataxia, altered gait, hindleg splay, decreased muscle tone, incoordination, and altered motor activity ($BMCL_{10}$ for altered gait in female rats = 454 ppm)
Daughtrey et al. 1997 (data also available in unpublished report by Gill 1989)									
9	Rat (Fischer 344) 5 M, 5 F	13 days 6 hours/day (WB)	0, 2,000, 4,000, 8,000	BW, OW, GN, CS, NX, LE	Bd wt	4,000 F 2,000 M		8,000 F 4,000 M	36% decrease in body weight gain on days 1–7 in females; 65% decrease in body weight gain on days 1–3 in males
					Resp	8,000			
					Hepatic	2,000	4,000		10–13% increase in relative liver weight
					Renal	8,000			
					Endocr	4,000	8,000		Increased relative adrenal weight in males (39%) and females (13%)
					Immuno	8,000			
					Neuro		2,000	4,000	Hypoactivity at ≥2,000 ppm; ataxia at ≥4,000 ppm; decreased reflexes, decreased muscle tone at 8,000 ppm
Dodd and Kintigh 1989									
10	Rat (Fischer 344) 1–6 M, 1–6 F	6 hours (N)	0, 400, 8,000	CS, LE	Neuro	400		8,000	Ataxia, drowsiness
MTBE Committee 1990a									

Table 2-2. Levels of Significant Exposure to Methyl *tert*-Butyl Ether (MTBE) – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
11	Rat (Fischer-344) 5 M, 5 F	10 days 6 hours/day (WB)	0, 400, 1,500, 3,000	OW, HP, BI	Bd wt	3,000			
					Renal	3,000 F 400 M	1,500 M		Proximal tubule necrosis, α2u-globulin droplet accumulation, and cell proliferation in males; epithelial cell exfoliation in the tubule lumen at 3,000 ppm in males
Prescott-Mathews et al. 1997									
12	Rat (Wistar) 5 M	2 weeks 5 days/week 6 hours/day (WB)	0, 50, 100, 300	BW	Bd wt	300 M			
Savolainen et al. 1985									
13	Rat (Sprague-Dawley) 20 M, 20 F	9 days 5 days/week 6 hours/day (WB)	0, 100, 300, 1,000, 3,000	BW, OW, GN, HP, BC, CS, UR, HE, LE	Bd wt	3,000			
					Resp		1,000		Inflammation of nasal mucosa and trachea
					Cardio	3,000			
					Gastro	3,000			
					Hemato	3,000			
					Musc/skel	3,000			
					Hepatic	3,000			
					Renal	3,000			
					Endocr	3,000			
					Immuno	3,000			
					Neuro	3,000			
					Repro	3,000			
Texaco Inc. 1981									
14	Rat (Fischer-344) 5 M, 5 F	5 days 6 hours/day (WB)	0, 800, 4,000, 8,000	BW, CS	Bd wt	4,000 F		8,000	90% decrease in body weight gain in females, body weight loss in males
					Neuro	4,000		8,000	Ataxia
Vergnes and Morabit 1989									

Table 2-2. Levels of Significant Exposure to Methyl *tert*-Butyl Ether (MTBE) – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
15	Mouse (CD-1) 30 F	10 days (GDs 6–15) 6 hours/day (WB)	0, 1,000, 4,000, 8,000	BW, FI, CS, GN, OW, DX	Bd wt	4,000 F	8,000 F		>10% reduction in maternal body weight and >25% reduction in body weight gain during and post-exposure; reduced food consumption ~30% during exposure only
					Resp	4,000 F		8,000 F	Labored breathing
					Hepatic	8,000 F			
					Neuro	1,000 F		4,000 F	Hypoactivity, ataxia
					Develop	1,000	4,000	8,000	7% decrease in fetal weights and decreased skeletal ossification at 4,000 ppm; increased litter resorption and post-implantation loss, 29% reduction in live fetuses, 21% decrease in fetal weights, and cleft palate at 8,000 ppm
Bevan et al. 1997a (data also available in unpublished report by Tyl and Neeper-Bradley 1989)									
16	Mouse (CD-1) 5 M, 5 F	5 days 6 hours/day (WB)	0, 400, 3,000, 8,000	BI	Hepatic	3,000 F 8,000 M	8,000 F		Increased hepatic cell proliferation
Bird et al. 1997 (data also available in unpublished report by Chun and Kintigh 1993)									
17	Mouse (CD-1) 30 F	10 days GDs 6–15 6 hours/day (WB)	0, 250, 1,000, 2,500	BW, OW, LE, FI, WI, GN, DX, CS	Bd wt	2,500 F			
					Hepatic	2,500 F			
					Develop	2,500			
Conaway et al. 1985									
18	Mouse (CD-1) 5 M, 5 F	13 days 6 hours/day (WB)	0, 2,000, 4,000, 8,000	BW, OW, GN, CS, LE	Bd wt	8,000			
					Hepatic	4,000 M	2,000 F 8,000 M		13% increase in relative liver weight
					Endocr	8,000			
					Neuro		2,000	4,000	Hypoactivity at ≥2,000 ppm; ataxia at ≥4,000 ppm
					Repro	8,000 M			
Dodd and Kintigh 1989									

Table 2-2. Levels of Significant Exposure to Methyl *tert*-Butyl Ether (MTBE) – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
19	Mouse (B6C3F1) 6 F	3 days 6 hours/day (WB)	0, 8,000	OW, CS, BW, HP, BC, BI	Bd wt	8,000 F			
					Hepatic		8,000 F		20% increase in relative liver weight, slight centrilobular hypertrophy, increased hepatic DNA synthesis, liver enzyme induction
					Neuro		8,000 F		Transient abnormal gait, hypoactivity, and decreased muscle tone
Moser et al. 1996									
20	Mouse (CD-1) 6 F	3 days 6 hours/day (WB)	0, 8,000	OW, CS, BW, HP,BC, BI	Bd wt	8,000 F			
					Hepatic		8,000 F		19% increase in relative liver weight, slight centrilobular hypertrophy, increased hepatic DNA synthesis, liver enzyme induction
					Neuro		8,000 F		Transient abnormal gait, hypoactivity, and decreased muscle tone
Moser et al. 1996									
21	Mouse (Swiss albino) 20M	10 minutes (WB)	82,700, 122,000, 167,100, 200,500, 219,100	LE	Death			180,000 M	10-minute LC_{50}
Snamprogetti 1980									
22	Mouse (Swiss albino) 40 M	3–12 minutes (WB)	209,300	LE	Death			209,300 M	LT_{50} = 5.6 minutes
Snamprogetti 1980									
23	Mouse (Swiss-Webster) 4 M	1 hour (WB)	83, 277, 832, 2,774, 8,321	CS, BI, OF	Resp		4,604 M		RD_{50} (indicative of sensory irritation)
Tepper et al. 1994									

Table 2-2. Levels of Significant Exposure to Methyl *tert*-Butyl Ether (MTBE) – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
24	Mouse (CD-1) 10 M, 10 F	2 days 6 hours/day (WB)	0, 400, 3,000, 8,000	CS	Neuro	400	3,000	8,000	Hypoactivity, lack of startle response at ≥3,000 ppm; ataxia, prostration at 8,000 ppm
Vergnes and Chun 1994									
25	Mouse (CD-1) 5–10 M, 5–10 F	1–2 days 6 hours/day (WB)	0, 400, 3,000, 8,000	BW, CS	Bd wt	8,000			
					Neuro	8,000			
Vergnes and Kintigh 1993									
26	Rabbit (New Zealand) 15 F	13 days (GDs 6–18) 6 hours/day (WB)	0, 1,000, 4,000, 8,000	BW, FI, CS, GN, OW, HP, DX	Bd wt	8,000 F			
					Hepatic	4,000 F	8,000 F		15% increase in maternal relative liver weight
					Neuro	4,000 F		8,000 F	Hypoactivity and ataxia
					Develop	8,000			
Bevan et al. 1997a (data also available in unpublished report by Tyl 1989)									
INTERMEDIATE EXPOSURE									
27	Rat (Sprague-Dawley) 25 M, 25 F	2 generations ~14–19 weeks/ generation 5 days/week 6 hours/day (WB)	0, 400, 3,000, 8,000	CS, BW, FI, DX, GN, OW, HP, NX, RX	Bd wt	8,000 F 3,000 M	8,000 M		11–12% decrease in F0 and F1 adult male body weight
					Resp	8,000			
					Gastro	8,000			
					Hepatic	3,000 F 400 M	8,000 F 3,000 M		>10% increase in relative liver weight in F1 adult animals
					Endocr	8,000			
					Immuno	8,000			
					Neuro	400[c]	3,000	8,000	Hypoactivity, blepharospasms, lack of startle reflex in F0 and F1 adults at ≥3,000 ppm; ataxia at 8,000 ppm
					Repro	8,000			

Table 2-2. Levels of Significant Exposure to Methyl *tert*-Butyl Ether (MTBE) – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
					Develop	400	3,000		~10% decrease in body weight during lactation in F1 females and F2 males and females
Bevan et al. 1997b (data also available in unpublished report by Neeper-Bradley 1991)									
28	Rat (Sprague-Dawley) 15 M, 30 F	16–28 weeks 5–7 day/week 6 hours/day (WB)	0, 250, 1,000, 2,500	BW, OW, GN, HP, CS, DX, LE	Bd wt	2,500			
					Resp	2,500			
					Repro	2,500			
					Develop	2,500			
Biles et al. 1987									
29	Rat (Fischer-344) 10–15 M, 10–15 F	28 days 5 days/week 6 hours/day (WB)	0, 400, 3,000, 8,000	BW, OW, GN, HP, BC, CS, BI, UR, LE	Bd wt	8,000 F 3,000 M		8,000 M	24–35% decreased body weight gain
					Hepatic	400[c]	3,000		8–13% increase in relative liver weight
					Renal	8,000 F 400 M	3,000 M		Increased protein accumulation and proliferation of epithelial cells in proximal convoluted tubules
					Endocr	400 F 3,000 M	3,000 F 8,000 M		8–23% increase in relative adrenal weight in females at ≥3,000 ppm; 53% increase in relative adrenal weight in males at 8,000 ppm
					Neuro	400[c]		3,000	Ataxia, hypoactivity, lack of startle response, blepharospasm
Bird et al. 1997 (data also available in unpublished report by Chun and Kintigh 1993)									
30	Rat (Fischer-344) 15 M, 15 F	13 weeks 5 days/week 6 hours/day (WB)	0, 800, 4,000, 8,000	BW, CS, NX, OW, HP	Bd wt	8,000			
					Neuro	4,000		8,000	Ataxia (weeks 1–4 only)
Daughtrey et al. 1997 (data also available in unpublished report by Dodd and Kintigh 1989)									

Table 2-2. Levels of Significant Exposure to Methyl *tert*-Butyl Ether (MTBE) – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
31	Rat Sprague-Dawley 10 M, 10 F	13 weeks 5 days/week 6 hours/day (WB)	0, 250, 500, 1,000	BW, FI, WI, GN, HP, BC, CS, LE, UR, HE, OP	Bd wt	1,000			
					Resp	1,000			
					Cardio	1,000			
					Gastro	1,000			
					Hemato	1,000			
					Musc/skel	1,000			
					Hepatic	1,000			
					Renal	1,000			
					Endocr	1,000			
					Immuno	1,000			
					Repro	1,000			
					Other noncancer	1,000			
Greenough et al. 1980									
32	Rat (Fischer-344) 25 M, 25 F	13 weeks 5 days/week 6 hours/day (WB)	0, 800, 4,000, 8,000	CS, BW, HE, BC, GN, HP, OW	Bd wt	8,000			
					Resp	8,000			
					Cardio	8,000			
					Gastro	8,000			
					Hemato	8,000			
					Musc/skel	8,000			
					Hepatic	800 F	800 M 4,000 F		>8–39% increase in relative liver weights in males at ≥800 ppm; 13–15% increase in relative liver weights in females at ≥4,000 ppm
					Renal	8,000 F	800 M		>5–19% increase in relative kidney weight at ≥800 ppm; increased size of hyaline droplets at ≥4,000 ppm
					Endocr	800	4,000		13–55% increase in relative weights of adrenal glands at ≥4,000 ppm; 3-fold increase in corticosterone levels at 8,000 ppm

Table 2-2. Levels of Significant Exposure to Methyl *tert*-Butyl Ether (MTBE) – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
					Immuno	8,000 F	8,000 M		Increased incidence of lymphoid hyperplasia (not examined at 800 or 4,000 ppm)
					Neuro	800	4,000	8,000	Transient hypoactivity at ≥4,000 ppm; ataxia at 8,000 ppm
					Repro	8,000			
					Other noncancer	8,000			
Lington et al. 1997 (data also available in unpublished report by Dodd and Kintigh 1989)									
33	Rat (Wistar) 15 M	6–15 weeks 5 days/week 6 hours/day (WB)	0, 50, 100, 300	BW, BI	Bd wt	300 M			
Savolainen et al. 1985									
34	Mouse (CD-1) 10–15 M, 10–15 F	28 days 5 days/week 6 hours/day (WB)	0, 400, 3,000, 8,000	BW, OW, GN, HP, LE, BC, CS, BI, UR	Bd wt	8,000			
					Hepatic	400 F 3,000 M	3,000 F 8,000 M		9–13% increase in relative liver weight in females at ≥3,000 ppm; 12% increase in relative liver weight in males at 8,000 ppm
					Renal	8,000			
					Endocr	8,000			
					Neuro	400		3,000	Ataxia, hypoactivity, lack of startled response
Bird et al. 1997 (data also available in unpublished report by Chun and Kintigh 1993)									

Table 2-2. Levels of Significant Exposure to Methyl *tert*-Butyl Ether (MTBE) – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
35	Mouse (B6C3F1) 6 F	3 weeks 5 days/week 6 hours/day (WB)	0, 8,000	OW, CS, BW, BC, BI, HP	Bd wt	8,000 F			
					Hepatic		8,000 F		26% increase in relative liver weight, increased enzyme activity, decreased hepatic DNA synthesis
					Neuro		8,000 F		Transient abnormal gait, hypoactivity, and decreased muscle tone
Moser et al. 1996									
36	Mouse (CD-1) 6 F	3 weeks 5 days/week 6 hours/day (WB)	0, 8,000	OW, CS, BW, BC, BI, HP	Bd wt	8,000 F			
					Hepatic		8,000 F		13% increase in relative liver weight, increased enzyme activity, increased hepatic DNA synthesis
					Neuro		8,000 F		Transient abnormal gait, hypoactivity, and decreased muscle tone
Moser et al. 1996									
37	Mouse (B6C3F1) 12 F	32 weeks 5 days/week 6 hours/day (WB)	0, 8,000	OW, CS, BW, BC, GN, HP	Bd wt		8,000 F		19–24% decrease in body weight
					Hepatic		8,000 F		50–90% increase in relative liver weight, mild hepatic hypertrophy
					Neuro		8,000 F		Transient abnormal gait, hypoactivity, and decreased muscle tone
					Cancer				No evidence of hepatic tumor promotion
Moser et al. 1996 (initiation-promotion study: half of control and exposed animals were initiated with DEN ~6 weeks prior to MTBE exposure)									
38	Mouse (B6C3F1) 12 F	16 weeks 5 days/week 6 hours/day (WB)	0, 8,000	OW,CS, BW, BC, BI, GN, HP	Bd wt		8,000 F		17% decrease in body weight
					Hepatic		8,000 F		34–41% increase in relative liver weight, mild hepatic hypertrophy, elevated liver enzymes
					Neuro		8,000 F		Transient abnormal gait, hypoactivity, and decreased muscle tone
					Cancer				No evidence of hepatic tumor promotion
Moser et al. 1996 (initiation-promotion study: half of control and exposed animals were initiated with DEN ~6 weeks prior to MTBE exposure)									

Table 2-2. Levels of Significant Exposure to Methyl *tert*-Butyl Ether (MTBE) – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
39	Mouse (B6C3F1) 12 F	4 months 5 days/week 6 hours/day (WB)	0, 8,000	BW, OW, HP, BC	Bd wt		8,000 F		17% decrease in body weight
					Endocr		8,000 F		32% decrease in relative pituitary weight; histopathological changes in adrenal and pituitary glands
					Repro		8,000 F		79% decrease in relative uterus weight; 48% decrease in relative ovary weight; histopathological changes in uterus, cervix, and vagina; decreased cell proliferation in uterus
Moser et al. 1998									
40	Mouse (B6C3F1) 12 F	8 months 5 days/week 6 hours/day (WB)	0, 8,000	BW, OW, HP	Bd wt		8,000 F		19% decrease in body weight
					Endocr		8,000 F		20% decrease in relative pituitary weight; histopathological changes in adrenal and pituitary glands
					Repro		8,000 F		77% decrease in relative uterus weight; 46% decrease in relative ovary weight; histopathological changes in uterus, cervix, and vagina; decreased cell proliferation in uterus
Moser et al. 1998									
41	Mouse (Swiss albino) 30 M	30 days 5 day/week 5–10 minutes/ day (WB)	0, 50,000, 80,000	CS, LE, NX	Neuro	80,000 M			
Snamprogetti 1980									

Table 2-2. Levels of Significant Exposure to Methyl *tert*-Butyl Ether (MTBE) – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
CHRONIC EXPOSURE									
42	Rat (Fischer-344) 50 M, 50 F	24 months 5 days/week 6 hours/day (WB)	0, 400, 3,000, 8,000	BW, CS, BC, OW, GN, HP, HE, LE, UR	Death			3,000 M	Decreased survival due to chronic progressive nephropathy
					Bd wt	3,000		8,000	13–19% decrease in terminal body weight; 22–29% decrease in body weight gain
					Resp	8,000			
					Cardio	8,000			
					Gastro	8,000			
					Hemato	8,000			
					Musc/skel	8,000 F	400 M		Osteodystrophy (secondary to nephropathy)
					Hepatic	400 F 8,000 M	3,000 F		24% increase in relative liver weight
					Renal	400[d] F	3,000 F 400 M		22% increase in relative kidney weight in females; increased incidence and severity of chronic progressive nephropathy
					Endocr	8,000 F	400 M		Hyperplasia of parathyroid (secondary to nephropathy); and altered corticosterone levels at ≥3,000 ppm
					Immuno	8,000			
					Neuro	3,000		8,000	Ataxia in both sexes; salivation in males
					Repro	8,000			
					Cancer			3,000 M	CEL: Renal tubular adenomas and carcinomas in males; no exposure-related tumors in females

Bird et al. 1997 (data also available in unpublished report by Chun et al. 1992)

Table 2-2. Levels of Significant Exposure to Methyl *tert*-Butyl Ether (MTBE) – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
43	Mouse (CD-1) 50 M, 50 F	18 months 5 days/week 6 hours/day (WB)	0, 400, 3,000, 8,000	CS, BW, BI, OW, WI, HE, UR, GN, HP, LE	Death			8,000 M	Decreased survival due to obstructive uropathy
					Bd wt	3,000	8,000 M	8,000 F	24% decrease in body weight gain in females; 16% decrease in body weight gain in males
					Resp	8,000			
					Cardio	8,000			
					Gastro	8,000			
					Hemato	8,000			
					Musc/skel	8,000			
					Hepatic	3,000	8,000		39% increase in relative liver weight in females; hepatocellular hypertrophy in males
					Renal	3,000	8,000 F	8,000 M	13% increase in relative kidney weight in females at 8,000 ppm; obstructive uropathy and decreased urinary pH and increased urinary gamma globulin fraction in males at 8,000 ppm
					Endocr	8,000 F 3,000 M	8,000 M		3-fold increase in corticosterone levels; 60% increase in relative adrenal weight
					Immuno	8,000			
					Neuro	3,000		8,000	Ataxia

Table 2-2. Levels of Significant Exposure to Methyl *tert*-Butyl Ether (MTBE) – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
					Repro	8,000			
					Cancer			8,000 F	CEL: Increased hepatocellular adenomas (10/50) compared to controls (2/50); no exposure-related tumors in males

Bird et al. 1997 (data also available in unpublished report by Burleigh-Flayer et al. 1992)

[a]The number corresponds to entries in Figure 2-2; differences in levels of health effects and cancer effects between male and females are not indicated in Figure 2-2. Where such differences exist, only the levels of effect for the most sensitive sex are presented.
[b]Used to derive a provisional acute-duration inhalation minimal risk level (MRL) of 2 ppm for MTBE; based on a rat $BMCL_{10}$ of 454 ppm, adjusted to continuous exposure and converted to a human equivalent concentration ($BMCL_{HEC}$) of 70.1 ppm, and divided by an uncertainty factor of 30 (3 for animal to human with dosimetric adjustments and 10 for human variability); see Appendix A for more detailed information regarding the provisional MRL.
[c]Used to derive a provisional intermediate-duration inhalation MRL of 1 ppm for MTBE. The NOAEL of 400 ppm was adjusted to continuous exposure and converted into a $NOAEL_{HEC}$ of 43.9 ppm and divided by and uncertainty factor of 30 (3 for animal to human with dosimetric adjustments and 10 for human variability); see Appendix A for more detailed information regarding the provisional MRL.
[d]Used to derive a provisional chronic-duration inhalation MRL of 1 ppm for MTBE. The NOAEL of 400 ppm was adjusted to continuous exposure and converted into a $NOAEL_{HEC}$ of 43.9 ppm and divided by and uncertainty factor of 30 (3 for animal to human with dosimetric adjustments and 10 for human variability; see Appendix A for more detailed information regarding the provisional MRL.

BC = blood chemistry; Bd wt or BW = body weight; BI = biochemical changes; BMC = benchmark concentration; BMCL = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); Cardio = cardiovascular; CEL = cancer effect level; CS = clinical signs; DEN = *N*-nitrosodiethylamine; Develop = developmental; DNA = deoxyribonucleic acid; DX = developmental effects; Endocr = endocrine; F = female(s); FI = food intake; Gastro = gastrointestinal; GD = gestation day; GN = gross necropsy; HE = hematology; HEC = human equivalent concentration; Hemato = hematological; HP = histopathology; Immuno = immunological; LC_{50} = concentration producing 50% death; LE = lethality; LOAEL = lowest-observed-adverse-effect level; LT_{50} = exposure time producing 50% death; M = male(s); Musc/skel = muscular/skeletal; (N) = nose-only; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; NX = neurological function; OF = organ function; OP = ophthalmology; OW = organ weight; RD_{50} = concentration that results in 50% decrease in respiratory rate; Repro = reproductive; Resp = respiratory; RX = reproductive function; UR = urinalysis; (WB) = whole body; WI = water intake

Figure 2-2. Levels of Significant Exposure to Methyl *tert*-Butyl Ether (MTBE) – Inhalation
Acute (≤14 days)

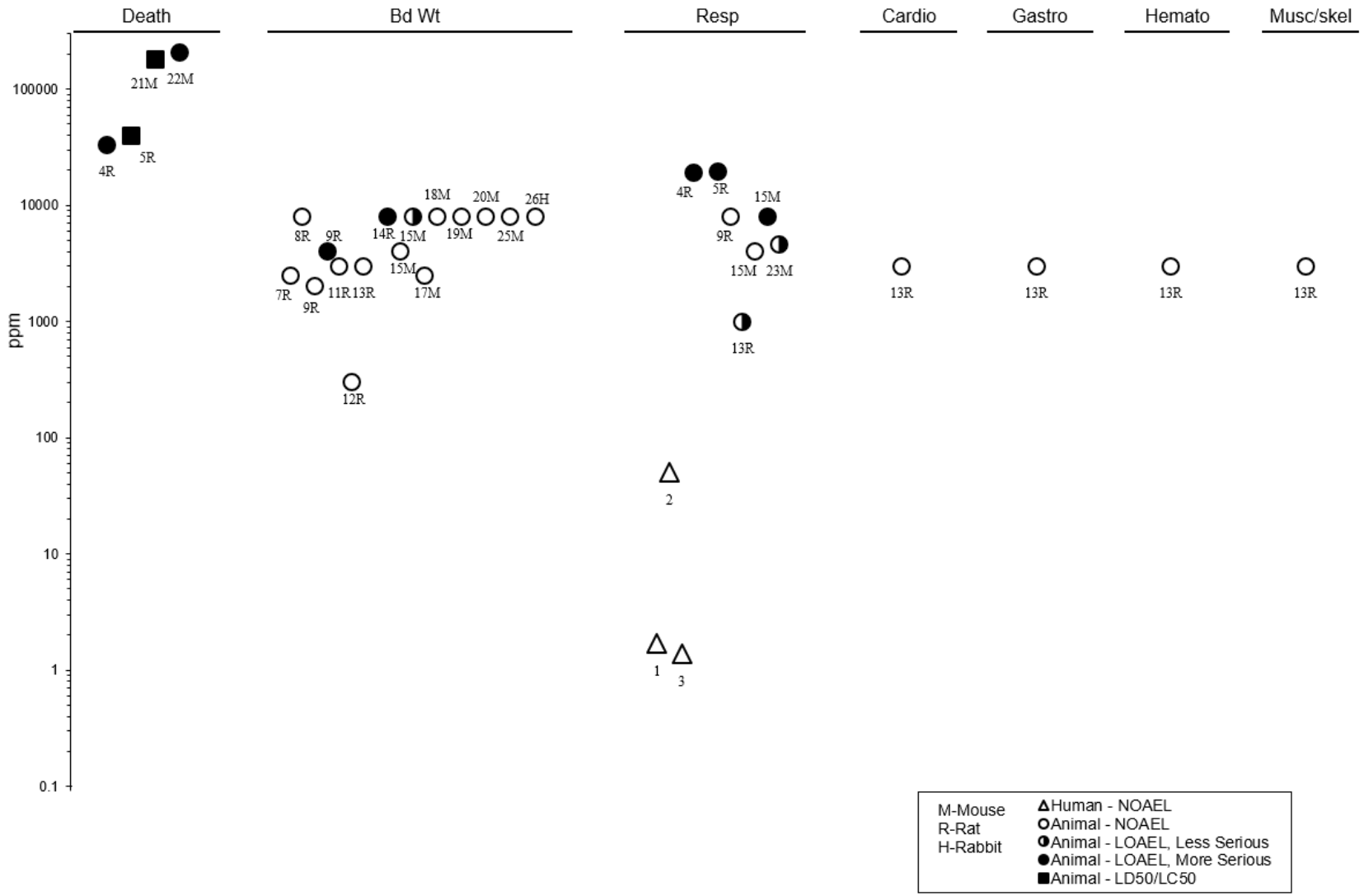


Figure 2-2. Levels of Significant Exposure to Methyl *tert*-Butyl Ether (MTBE) – Inhalation

Acute (≤14 days)

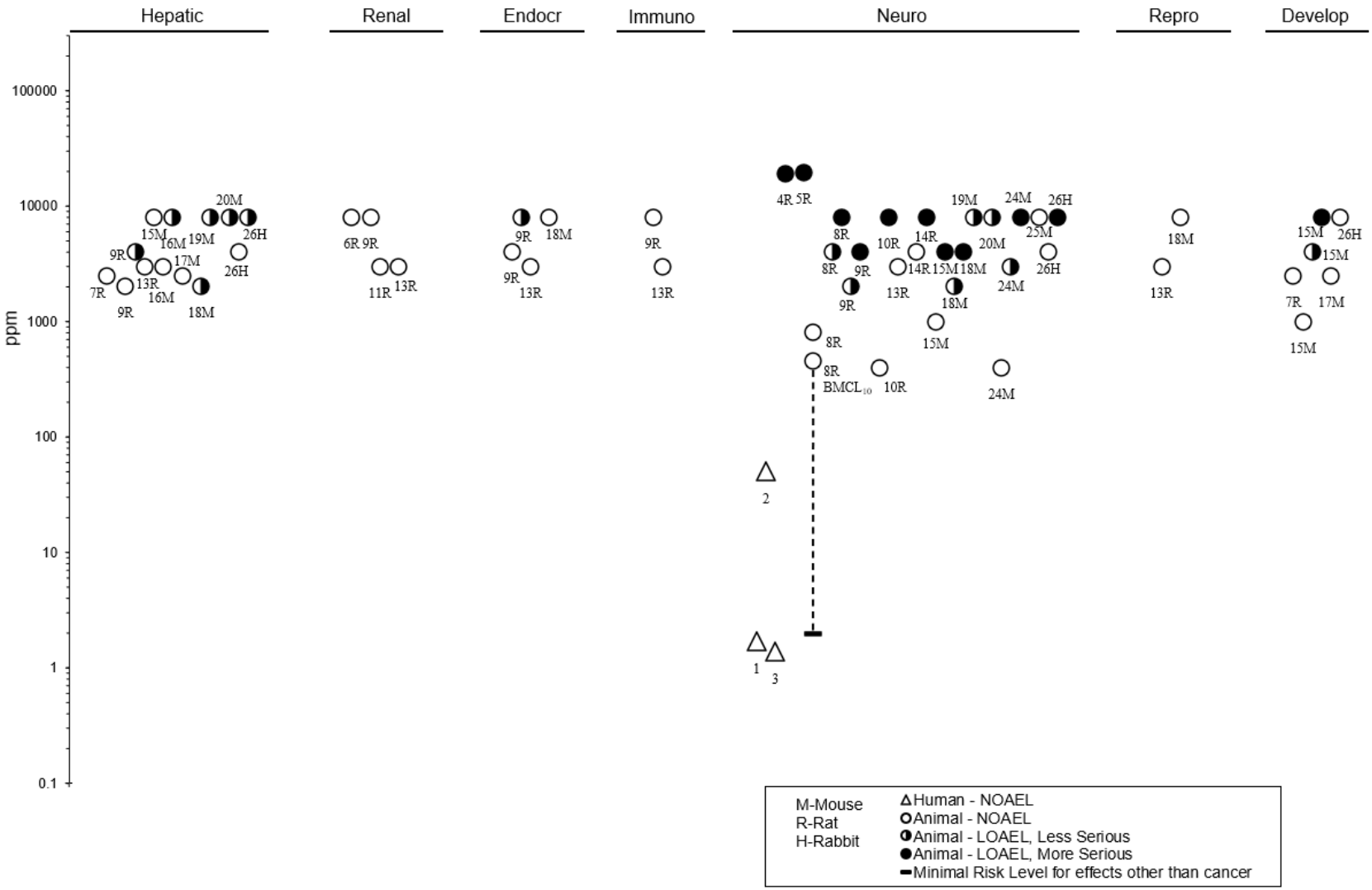


Figure 2-2. Levels of Significant Exposure to Methyl *tert*-Butyl Ether (MTBE) – Inhalation

Intermediate (15-364 days)

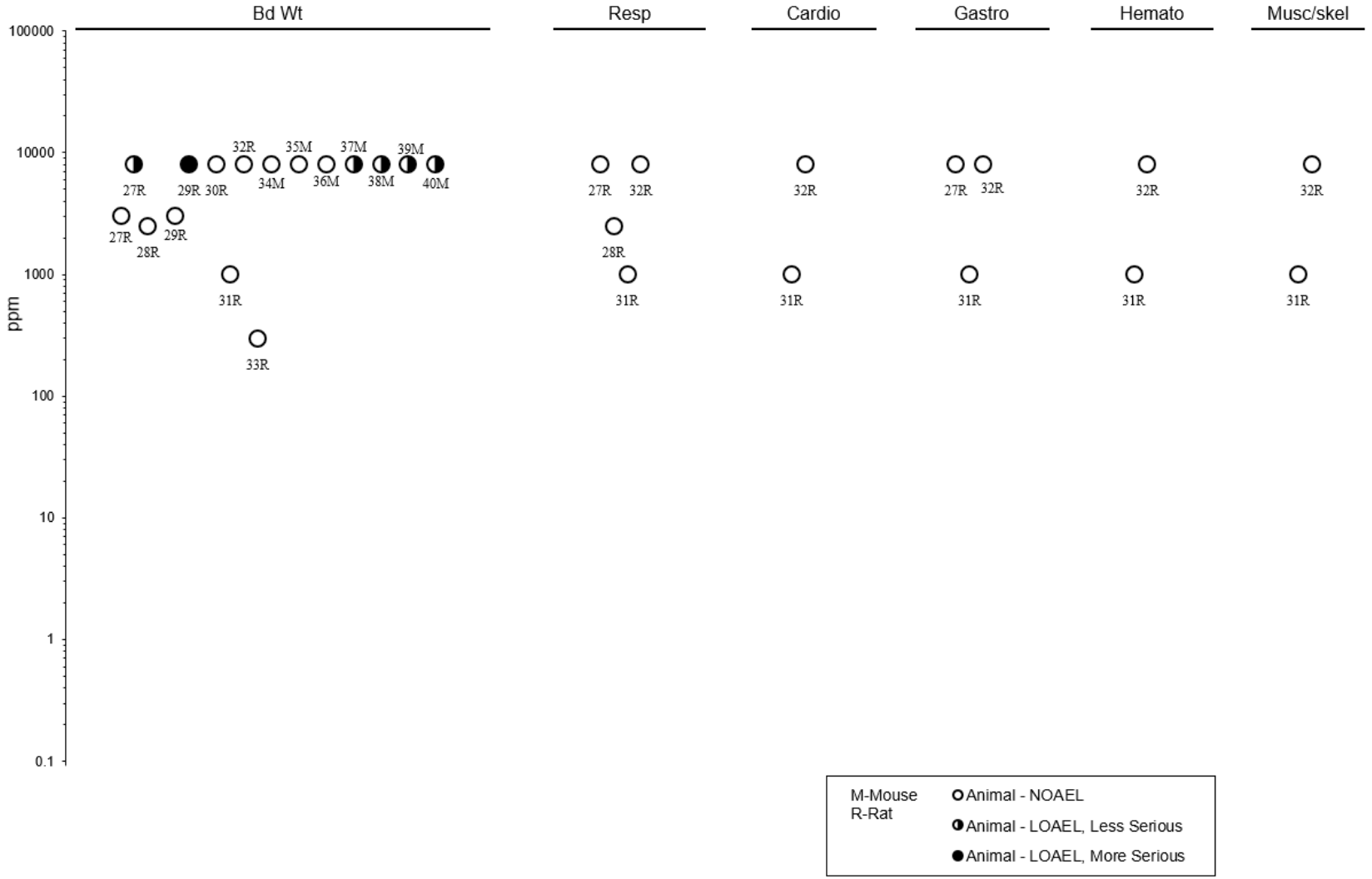


Figure 2-2. Levels of Significant Exposure to Methyl *tert*-Butyl Ether (MTBE) – Inhalation

Intermediate (15-364 days)

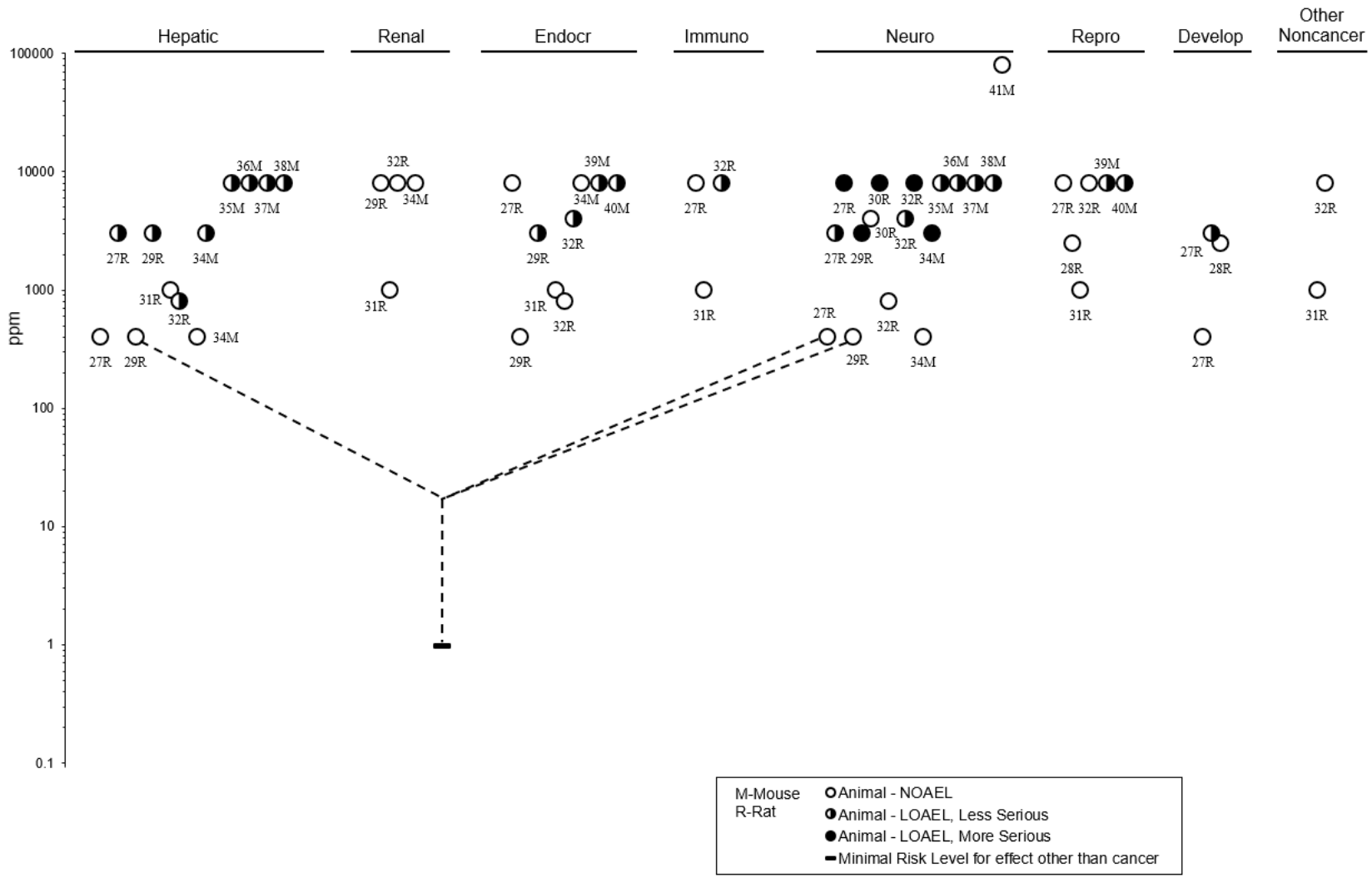


Figure 2-2. Levels of Significant Exposure to Methyl *tert*-Butyl Ether (MTBE) – Inhalation

Chronic (≥365 days)

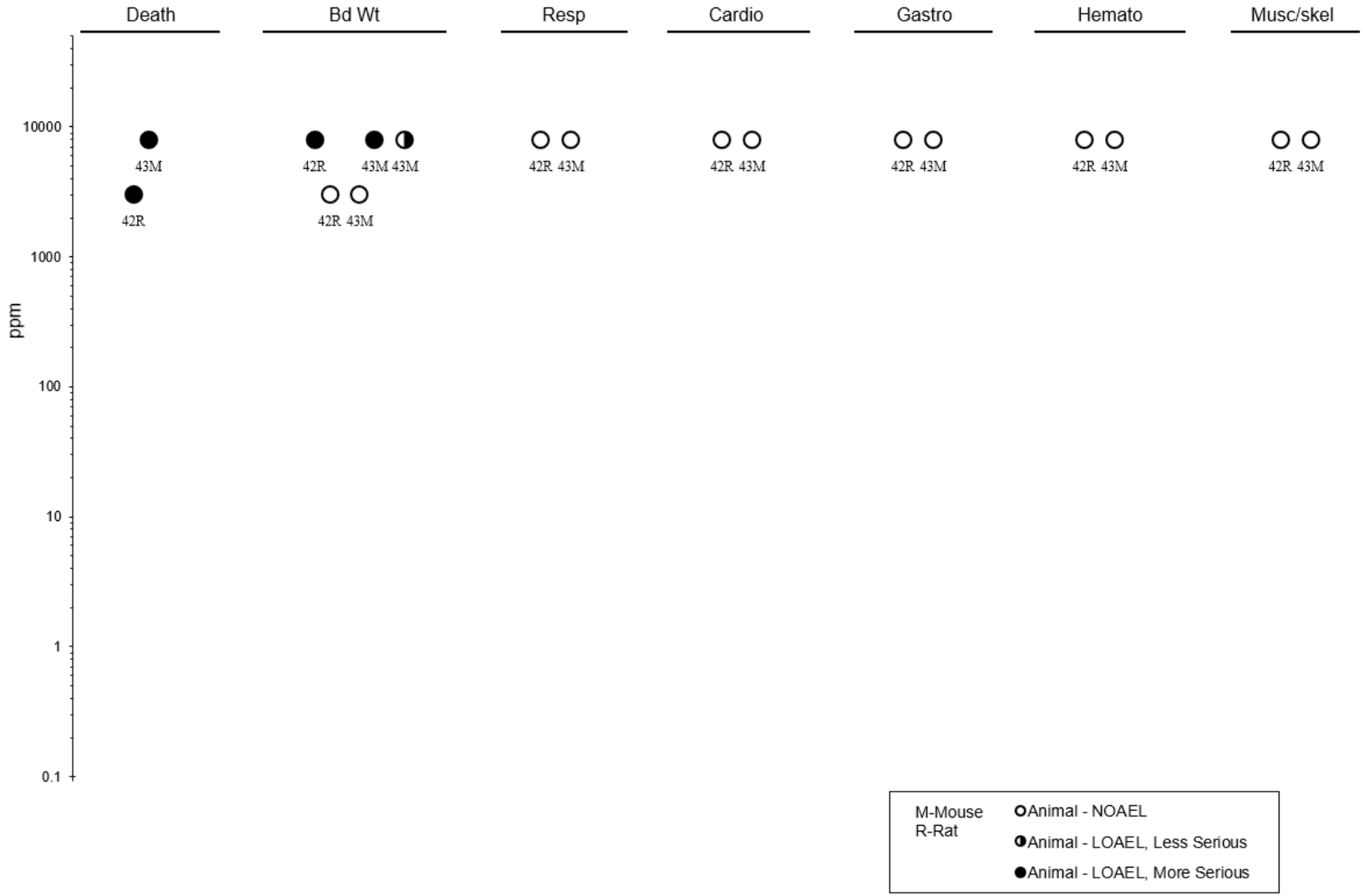


Figure 2-2. Levels of Significant Exposure to Methyl *tert*-Butyl Ether (MTBE) – Inhalation

Chronic (≥365 days)

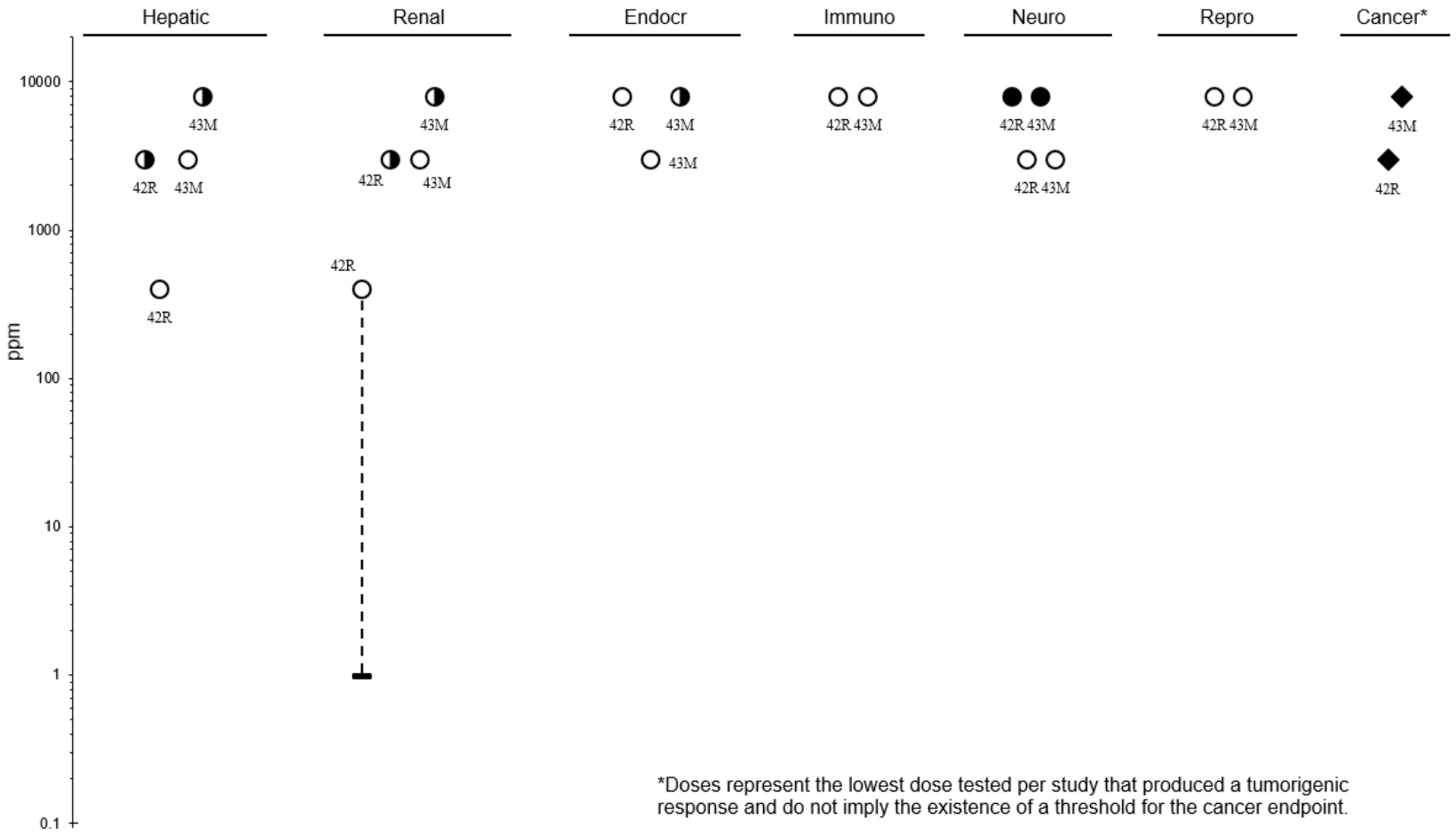


Table 2-3. Levels of Significant Exposure to Methyl *tert*-Butyl Ether (MTBE) – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
ACUTE EXPOSURE									
1	Rat (NS) 5 M, 5 F	Once (G)	1,900, 2,450, 3,160, 4,080, 5,270, 6,810	GN, CS, LE	Death			3,866	LD_{50}
					Resp	1,900	2,450	4,080	Gross evidence of respiratory tract irritation at 2,450 mg/kg/day; labored respiration at 4,080 mg/kg/day;
					Neuro		1,900	2,450	Slight to marked CNS depression; ataxia at ≥2,450 mg/kg/day
ARCO 1980									
2	Rat (Sprague-Dawley) 6 F	2 weeks (W)	0, 520	RX, BW	Bd wt	520 F			
					Repro	520 F			
Berger and Horner 2003									
3	Rat (Wistar) 5 M, 5 F	1 week (W)	M: 0, 37, 209, 972 F: 0, 50, 272, 1,153	BI, HP	Renal	1,153 F 209 M	972 M		Hyaline droplets, elevated α2u-globulin
					Repro	972 M			
Bermudez et al. 2012									
4	Rat (Sprague-Dawley) 10 M	14 days (GO)	0, 1,200	BC, BI, BW, OW	Bd wt	1,200 M			
					Hepatic		1,200 M		18% increase in relative liver weight
					Repro		1,200 M		51% decrease in serum testosterone, 10% decrease in serum LH, 36% increase in serum estradiol
de Peyster et al. 2003									
5	Rat (Sprague-Dawley) 12 M	12 days; every other day (GO)	0 (naïve), 0 (vehicle), 1,000, 1,500	BW, BC, CS	Bd wt	1,000 M		1,500 M	Body weight loss
					Neuro			1,000 M	Sedation, ataxia
					Repro	1,000 M	1,500 M		74% decrease in serum testosterone (4–5 hours after initial dose)
de Peyster et al. 2003									

Table 2-3. Levels of Significant Exposure to Methyl *tert*-Butyl Ether (MTBE) – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
6	Rat (Sprague-Dawley) 10 M	2 weeks 6–7 days/ week (GO)	0, 600, 1,200	CS, BC, BI, BW, LE, OW	Death			1,200 M	3/10 died
					Bd wt	600 M	1,200 M		10% decrease in body weight
					Hepatic	1,200 M			
					Renal	1,200 M			
					Endocr		600 M		2-fold increase in serum corticosterone; 10–12% increase in absolute and relative adrenal weight
					Neuro		600 M		Lethargy; transient ataxia in some animals
					Repro	1,200 M			
de Peyster et al. 2014									
7	Rat (Sprague-Dawley) 10 M	2 weeks (GO)	0, 400/500, 800/1,000, 1,200/1,500	CS, BC, BI, BW, OW	Bd wt	1,350 M			
					Hepatic	900 M	1,350 M		13% increase in relative liver weight
					Renal	900 M	1,350 M		12% increase in relative kidney weight
					Neuro		450 M		Lethargy; transient ataxia in some animals
					Repro	450 M	900 M		≥75% decrease in serum testosterone
de Peyster et al. 2014 (doses listed for week 1/week 2; TWA doses of 0, 450, 900, and 1,350 mg/kg/day)									
8	Rat (Sprague-Dawley) 5 M	2 weeks (GO)	0, 1,200	CS, BC, BI, BW, OW	Bd wt	1,200 M			
					Hepatic	1,200 M			
					Renal	1,200 M			
					Endocr		1,200 M		21% increase in relative adrenal weight
					Neuro		1,200 M		Lethargy; transient ataxia in some animals
de Peyster et al. 2014									

Table 2-3. Levels of Significant Exposure to Methyl *tert*-Butyl Ether (MTBE) – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
9	Rat (Sprague-Dawley) 10 M	2 weeks (GO)	0, 400, 800, 1,600	CS, BW, FI, LE, HE, OW, BC	Bd wt	1,600 M			
					Hemato	800 M	1,600 M		Transient changes in hematology (2-fold increase in total WBC count; 2–5-fold increase in percentage of lymphocytes, granulocytes, and eosinophils)
					Hepatic	800 M	1,600 M		Transient increases in serum cholesterol and relative liver weight
					Renal	1,600 M			
					Neuro		1,600 M		Transient signs of CNS depression
					Repro		400 M		Transient decreases in relative testes weight
Dong-mei et al. 2009									
10	Rat (Sprague-Dawley) 10 M	2 weeks (GO)	0, 400, 800, 1,600	BC, HP	Repro		400 M		40–50% increase in LH at ≥400 mg/kg/day; 60–70% decrease in testosterone and 40–70% increase in FSH at ≥800 mg/kg/day; altered testicular histology at 1,600 mg/kg/day
Li et al. 2008									
11	Rat (Fischer 344) 6 M, 6 F	Once (GW)	0, 40, 400	CS, LE	Neuro	40	400		Drowsiness
MTBE Committee 1990b									
12	Rat Sprague-Dawley 10 M, 10 F	14 days (GO)	0, 357, 714, 1,071, 1,428	BW, OW, FI, WI, GN, HP, CS, LE, HE, BC	Bd wt	1,428			
					Resp	1,428			
					Cardio	1,428			
					Gastro		357		Diarrhea
					Hemato	1,428 F 714	1,071 M		33% decrease in percent monocytes in males

Table 2-3. Levels of Significant Exposure to Methyl *tert*-Butyl Ether (MTBE) – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Hepatic	357 F 714 M	714 F 1,071 M		29% increase in serum cholesterol in females; 74% increase in AST and 4-fold increase in LDH at 1,071 mg/kg/day and 59% increase in serum cholesterol at 1,428 mg/kg/day in males
					Renal	1,428 F			
						1,071 M	1,428 M		Renal tubule nephropathy characterized by increased hyaline droplets
					Endocr	1,428			
					Immuno	1,428			
					Neuro	1,071		1,428	Transient anesthesia
					Repro	1,428			
					Other noncancer	1,071 F 1,428 M	1,428 F		17% increase in serum glucose
Robinson et al. 1990									
13	Mouse (CD-1) 5 M	1 week, 3 days/week (GO)	0, 400, 1,000, 2,000	BW, BC, HP, OW	Bd wt	2,000 M			
					Repro	2,000 M			
Billitti et al. 2005									
14	Mouse (CD-1) 6 M	1 week 3 days/week (GO)	0, 400, 1,000, 2,000	BC, BW, OW, HP	Bd wt	2,000 M			
					Neuro	1,000 M		2,000 M	Ataxia, lethargy
					Repro	2,000 M			
de Peyster et al. 2008									
15	Mouse (NS) NS	once (G)		LE	Death			4,000	LD_{50}
Little et al. 1979									

Table 2-3. Levels of Significant Exposure to Methyl *tert*-Butyl Ether (MTBE) – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
INTERMEDIATE EXPOSURE									
16	Rat Sprague-Dawley 10 M, 10 F	4 weeks 5 days/week (G)	0, 90, 440, 1,750	BW, OW, GN, HP, BC, CS, LE, HE	Bd wt	1,750			
					Resp	1,750			
					Cardio	1,750			
					Gastro	440	1,750		Submucosal edema
					Hemato	1,750			
					Musc/skel	1,750			
					Hepatic	440	1,750		9–13% increase in relative liver weight and increased serum cholesterol
					Renal	440 F 90 M	1,750 F 440 M		8–9% increase in relative kidney weight; hyaline droplets in proximal convoluted tubules in males
					Dermal	1,750			
					Ocular	1,750			
					Endocr	1,750 F 440 M	1,750 M		23% increase in relative adrenal gland weight in males
					Immuno	1,750			
					Neuro	90[b] M 440 F	440 M	1,750	Hypoactivity in males at ≥440 mg/kg/day; ataxia in both sexes at 1,750 mg/kg/day
					Repro	1,750			
Amoco 1992									
17	Rat (Wistar) 10 M, 10 F	13 weeks (W)	M: 0, 37, 209, 514, 972 F: 0, 50, 272, 650, 1,153	BW, FI, WI, CS, UR, OW, HP	Bd wt	1,153 F 972 M			
					Resp	1,153 F 972 M			
					Cardio	1,153 F 972 M			
					Gastro	1,153 F 972 M			
					Musc/skel	1,153 F 972 M			

Table 2-3. Levels of Significant Exposure to Methyl *tert*-Butyl Ether (MTBE) – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Hepatic	1,153 F 972 M			
					Renal	272 F 209 M	650 F 514 M		19–21% increase in relative kidney weights in both sexes and increased incidence of hyaline droplets in males; increased tubular epithelial regeneration in males at 972 mg/kg/day
					Ocular	1,153 F 972 M			
					Endocr	1,153 F 972 M			
					Immuno	1,153 F 972 M			
					Neuro	1,153 F 972 M			
					Repro	1,153 F 972 M			
Bermudez et al. 2012									
18	Rat (Wistar) 5 M, 5 F	4 weeks (W)	M: 0, 37, 209, 972 F: 0, 50, 272, 1,153	BI, HP	Renal	1,153 F 209 M	972 M		Elevated cell replication of cortical proximal tubule cells, elevated α2u-globulin in males
					Repro	972 M			
Bermudez et al. 2012									
19	Rat (Wistar) 5 M, 5 F	13 weeks (W)	M: 0, 37, 209, 972 F: 0, 50, 272, 1,153	BI, HP	Renal	1,153 F 37 M	209 M		Hyaline droplets in males
					Repro	972 M			
Bermudez et al. 2012									
20	Rat (Wistar) 5 M	6 months (W)	0, 29, 166, 384	BW, FI, WI, CS, UR, OW, HP	Bd wt	384 M			
					Resp	384 M			
					Cardio	384 M			
					Gastro	384 M			
					Musc/skel	384 M			

Table 2-3. Levels of Significant Exposure to Methyl *tert*-Butyl Ether (MTBE) – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Hepatic	384 M			
					Renal	384 M			
					Ocular	384 M			
					Endocr	384 M			
					Immuno	384 M			
					Neuro	384 M			
					Repro	384 M			
Bermudez et al. 2012									
21	Rat (Sprague-Dawley) 12 M	28 days; every other day (GO)	0 (naïve), 0 (vehicle), 1,000/500, 1,500/750	BW, BC, BI, CS, OW	Hepatic	357 M	536 M		Induction of hepatic enzymes
					Repro	536 M			
de Peyster et al. 2003 (doses reduced on day 13, after six treatments; TWA doses over 28-day exposure period were 357 and 536 mg/kg/day)									
22	Rat (Sprague-Dawley) 12–13 M	28 days (GO)	0, 40, 400, 800	BW, BC, OW	Bd wt	400 M	800 M		11% decrease in body weight
					Endocr	400 M	800 M		2-fold increase in serum corticosterone; 26% increase in relative adrenal gland weight
					Repro	400 M	800 M		42% decrease in serum testosterone
de Peyster et al. 2003									
23	Rat (Sprague-Dawley) 12 M	28 days (GO)	0, 1,000	BC, BI, BW, OW, HP	Hepatic		1,000 M		11% increase in relative liver weight, increased AST and ALT
de Peyster et al. 2003									
24	Rat (Sprague-Dawley) 10 M	4 weeks (GO)	0, 400, 800, 1,600	CS, BW, FI, LE, HE, OW, BC	Bd wt	1,600 M			
					Hemato	1,600 M			
					Hepatic	1,600 M			
					Renal	1,600 M			
					Neuro		1,600 M		Transient CNS depression
Dong-mei et al. 2009									

Table 2-3. Levels of Significant Exposure to Methyl *tert*-Butyl Ether (MTBE) – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
25	Rat (Sprague-Dawley) 5 M	30 days (GO)	0, 400, 800, 1,600	BW, FI, OW, HP	Bd wt	1,600 M			
					Repro		400 M		Pyknosis, decreased cell layers, increased cell distance, and vacuoles in seminiferous tubules; increased seminiferous tubule diameter and decreased spermatocytes and spermatids at ≥800 mg/kg/day; decreased interstitial cells at 1,600 mg/kg/day
Gholami et al. 2015									
26	Rat (Sprague-Dawley) 5 M	30 days (GO)	0, 400, 800, 1,600	CS, BW, FI, BC, DX, OF	Bd wt	1,600 M			
					Repro	800 M	1,600 M		40% decrease in fertility; 58% decrease in serum testosterone
					Develop	1,600			
Khalili et al. 2015 (offspring evaluated for number, sex ratio, and gross anomalies only)									
27	Rat (Sprague-Dawley) 10 M	4 weeks (GO)	0, 400, 800, 1,600	CS, BW, FI, BC, OW, HP	Bd wt	1,600 M			
					Repro		400 M	1,600 M	~1.6-fold increase in percent abnormal sperm at 400 mg/kg/day; 2.4-fold increase in percent abnormal sperm at 1,600 mg/kg/day; altered serum testosterone and testicular histology at ≥800 mg/kg/day
Li et al. 2008									
28	Rat Sprague-Dawley 10 M, 10 F	90 days (GO)	0, 100, 300, 900, 1,200	BW, OW, FI, WI, GN, HP, CS, NX, HE, BC	Bd wt	1,200			
					Resp	1,200			
					Cardio	1,200			
					Gastro		100		Diarrhea
					Hemato	900	1,200		55% increase in percent monocytes in males; 40% decrease in WBC count in females

Table 2-3. Levels of Significant Exposure to Methyl *tert*-Butyl Ether (MTBE) – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Hepatic	100 M	100 F 300 M		Females: 15% increase in serum cholesterol Males: 52% increase in AST; increase in relative liver weight at ≥900 mg/kg/day
					Renal	1,200 F 300 M	900 M		16% increase in relative kidney weight; hyaline droplets and granular casts at 1,200 mg/kg/day
					Endocr	1,200			
					Immuno	1,200			
					Neuro	900		1,200	Transient anesthesia
					Repro	1,200			
					Other noncancer	100 F 1,200 M	300 F		17% decrease in serum glucose
Robinson et al. 1990									
29	Rat (Sprague-Dawley) 11–15 M	28 days (GO)	0, 250, 500, 1,000, 1,500	BW, OW, HP, BC, CS	Bd wt	1,000 M	1,500 M		7–12% decrease in body weight from day 15 to 28
					Hepatic	250 M	500 M		Centrilobular hypertrophy; 11–16% increase in relative liver weight at ≥1,000 mg/kg/day
					Renal		250 M		10–22% increase in relative kidney weight, increased incidence and severity of protein droplet nephropathy
					Endocr	1,500 M			
					Repro	1,000 M	1,500 M		17% increase in relative testes weight, 20% decrease in serum LH, 45% decrease in serum dihydrotestosterone
Williams et al. 2000									

Table 2-3. Levels of Significant Exposure to Methyl *tert*-Butyl Ether (MTBE) – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
30	Rat (Sprague-Dawley) 15 M	15 days (GO)	0, 1,500	BW, OW, HP, BC, CS	Bd wt	1,500 M			
					Hepatic		1,500 M		Centrilobular hypertrophy
					Renal		1,500 M		12% increase in relative kidney weights; increased incidence and severity of protein droplet nephropathy
					Endocr	1,500 M			
					Repro		1,500 M		>50% decrease in serum testosterone, serum prolactin, and testicular testosterone
Williams et al. 2000									
31	Rat (Sprague-Dawley) 12–15 M	15 days (GO)	0, 250, 500, 1,000	BW, OW, BC, CS	Bd wt	1,000 M			
					Hepatic	1,000 M			
					Renal	1,000 M			
					Endocr	1,000 M			
					Repro	1,000 M			
Williams et al. 2000									
32	Mouse (BALB/c) 6 M	28 days (W)	0, 0.01, 0.1, 1	BW, BC, BI, HP, OW, WI	Bd wt	1 M			
					Repro	1 M			
de Peyster et al. 2008									
33	Mouse (BALB/c) 10 M	51 days PNDs 25/26–76/77 (W)	0, 0.02, 0.2, 2	DX	Develop	2 M			
de Peyster et al. 2008 [endpoints evaluated at PNDs 76–77 were primarily reproductive toxicity]									
34	Mouse (CD-1) 10 M, 10 F	3 weeks 5 days/week (GO)	0, 1, 10, 100, 1,000	LE, BW, CS, HP	Bd wt	1,000			
					Repro	1,000			
Ward et al. 1994									

Table 2-3. Levels of Significant Exposure to Methyl *tert*-Butyl Ether (MTBE) – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
CHRONIC EXPOSURE									
35	Rat (Sprague-Dawley) 60 M, 60 F	104 weeks 4 days/week (GO)	0, 250, 1,000	BW, CS, FI, WI, GN, HP	Death			250 F	20–30% decrease in survival
					Bd wt	1,000			
					Resp	1,000			
					Cardio	1,000			
					Gastro	1,000			
					Musc/skel	1,000			
					Hepatic	1,000			
					Renal	1,000			
					Dermal	1,000			
					Endocr	1,000			
					Immuno	1,000 M	250 F		Dysplastic proliferation of lymphoreticular tissue (possibly preneoplastic) in females
					Neuro	1,000			
					Repro	1,000			
					Cancer			250 F 1,000 M	CEL: Leukemia and lymphoma in females, Leydig cell tumors in males
Belpoggi et al. 1995, 1997									
36	Rat (Wistar) 10 M, 10 F	1 year (W)	M: 0, 29, 166, 384 F: 0, 54, 258, 1,119	BW, FI, WI, CS, UR, OW, HP	Bd wt	1,119 F 384 M			
					Resp	1,119 F 384 M			
					Cardio	1,119 F 384 M			
					Gastro	1,119 F 384 M			
					Musc/skel	1,119 F 384 M			
					Hepatic	1,119 F 384 M			

Table 2-3. Levels of Significant Exposure to Methyl *tert*-Butyl Ether (MTBE) – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Renal	1,119 F	29 M		9–19% increase in relative kidney weights, increased incidence and severity of chronic progressive nephropathy in males
					Ocular	1,119 F 384 M			
					Endocr	1,119 F 384 M			
					Immuno	1,119 F 384 M			
					Neuro	1,119 F 384 M			
					Repro	1,119 F 384 M			
Bermudez et al. 2012									
37	Rat (Wistar) 50 M, 50 F	2 years (W)	M: 0, 25, 140, 330 F: 0, 49, 232, 1,042	BW, CS, FI, GN, HP, OW, WI	Bd wt	1,042 F 330 M			
					Resp	1,042 F 330 M			
					Cardio	1,042 F 330 M			
					Gastro	1,042 F 330 M			
					Musc/skel	1,042 F 330 M			
					Hepatic	1,042 F 330 M			
					Renal	232 F 140 M	1,042 F 330 M		>10% increase in relative kidney weights and increased severity of chronic progressive nephropathy
					Ocular	1,042 F 330 M			
					Endocr	1,042 F 330 M			

Table 2-3. Levels of Significant Exposure to Methyl *tert*-Butyl Ether (MTBE) – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Immuno	1,042 F 330 M			
					Neuro	1,042 F 330 M			
					Repro	1,042 F 330 M			
					Cancer				No exposure-related increases in tumor incidence

Dodd et al. 2013

[a]The number corresponds to entries in Figure 2-3; differences in levels of health effects and cancer effects between male and females are not indicated in Figure 2-3. Where such differences exist, only the levels of effect for the most sensitive sex are presented.
[b]Used to derive a provisional intermediate oral MRL of 0.6 mg/kg/day for MTBE. The NOAEL of 90 mg/kg/day was adjusted for intermittent exposure (5 days/week) and divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability); see Appendix A for more detailed information regarding the provisional MRL.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BC = blood chemistry; Bd wt or BW = body weight; BI = biochemical changes; Cardio = cardiovascular; CEL = cancer effect level; CNS = central nervous system; CS = clinical signs; Develop = developmental; DX = developmental effects; Endocr = endocrine; F = female(s); FI = food intake; FSH = follicle-stimulating hormone; (G) = gavage; (GO) = gavage in oil; (GW) = gavage in water; Gastro = gastrointestinal; GN = gross necropsy; HE = hematology; Hemato = hematological; HP = histopathology; Immuno = immunological; LD_{50} = dose producing 50% death; LDH = lactate dehydrogenase; LE = lethality; LH = luteinizing hormone; LOAEL = lowest-observed-adverse-effect level; M = male(s); MRL = Minimal Risk Level; Musc/skel = muscular/skeletal; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; NX = neurological function; OF = organ function; OW = organ weight; PND = postnatal day; Repro = reproductive; Resp = respiratory; TWA = time-weighted average; UR = urinalysis; (W) = water; WBC = white blood cell; WI = water intake

Figure 2-3. Levels of Significant Exposure to Methyl *tert*-Butyl Ether (MTBE) – Oral

Acute (≤14 days)

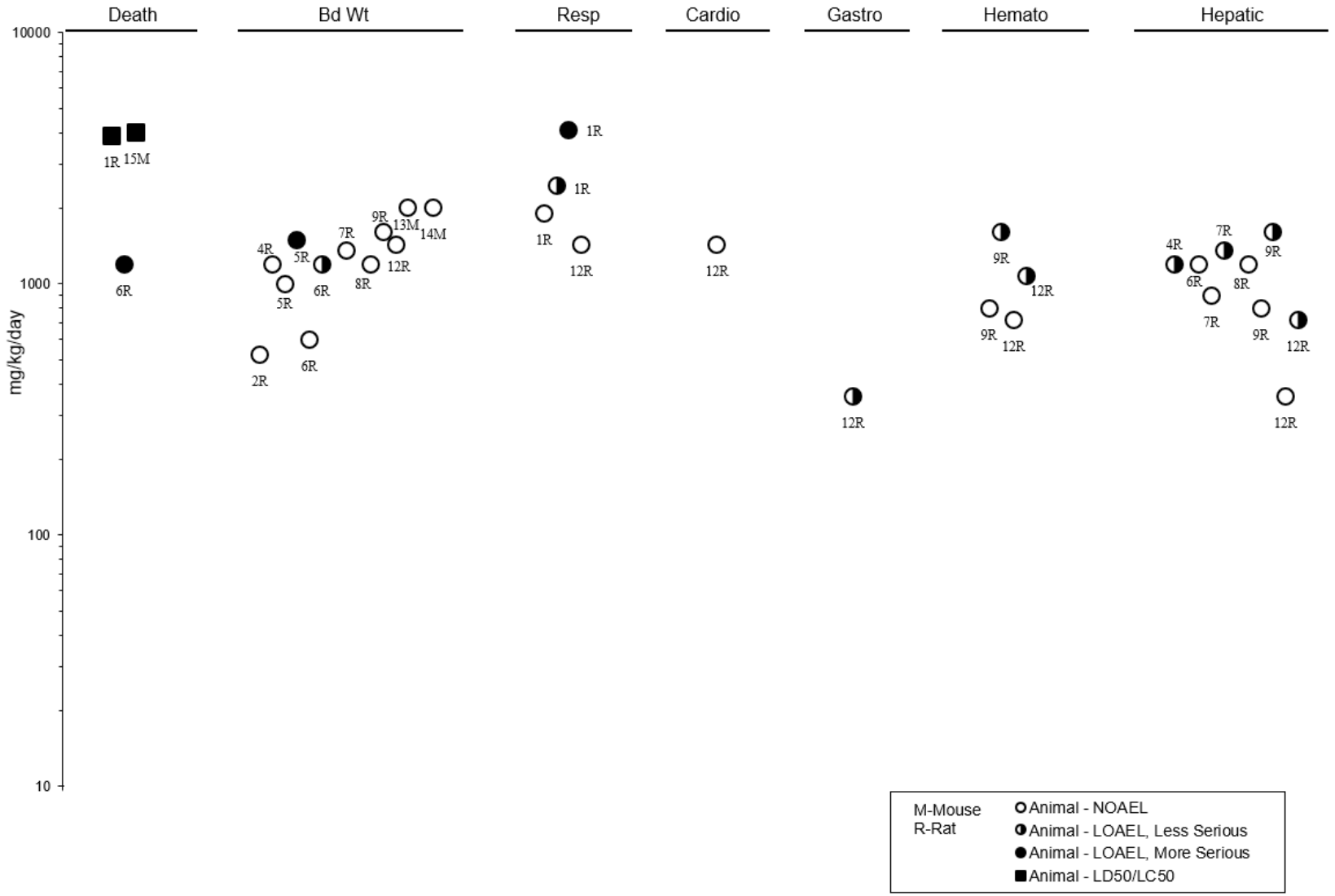


Figure 2-3. Levels of Significant Exposure to Methyl *tert*-Butyl Ether (MTBE) – Oral

Acute (≤14 days)

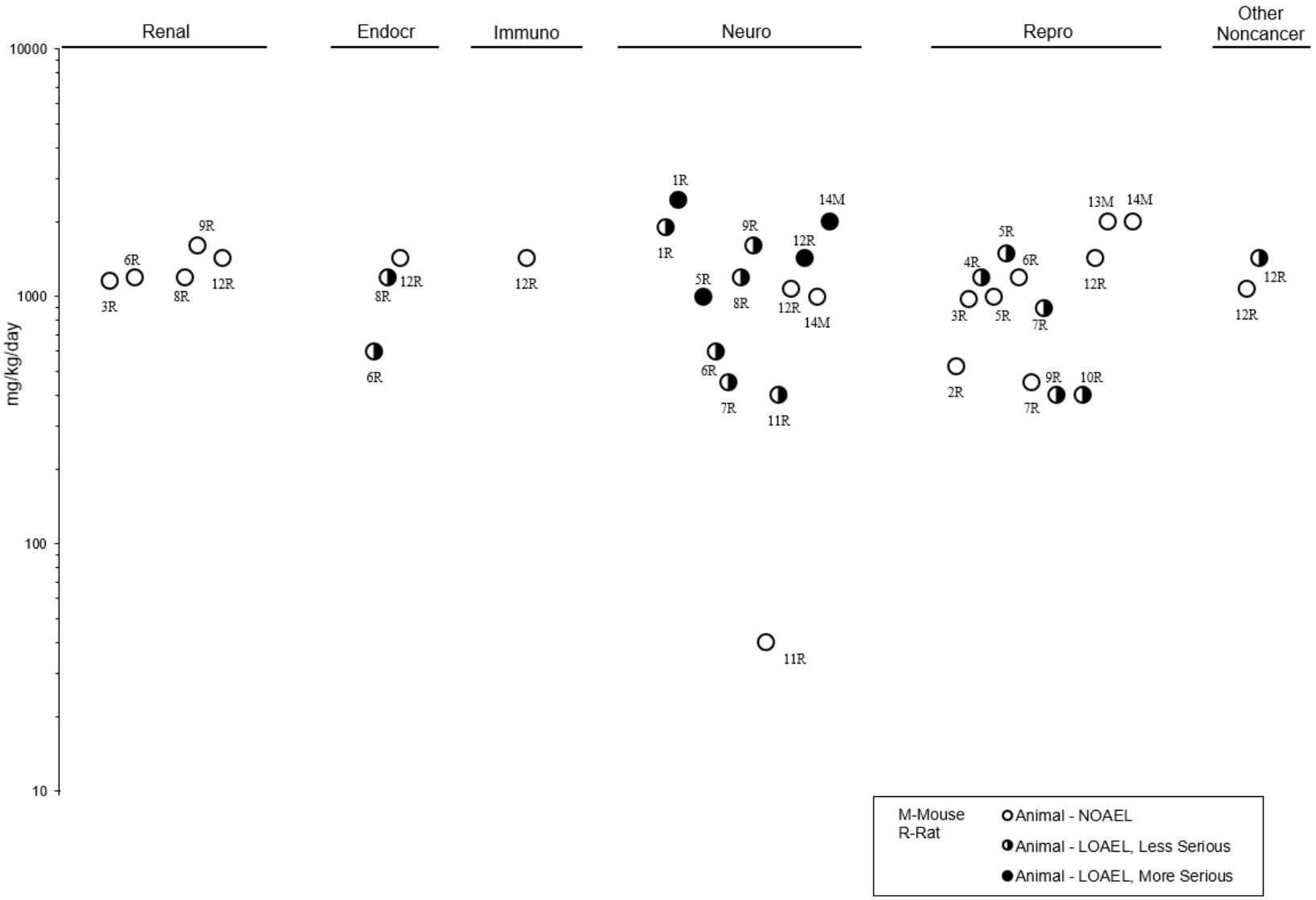


Figure 2-3. Levels of Significant Exposure to Methyl *tert*-Butyl Ether (MTBE) – Oral

Intermediate (15-364 days)

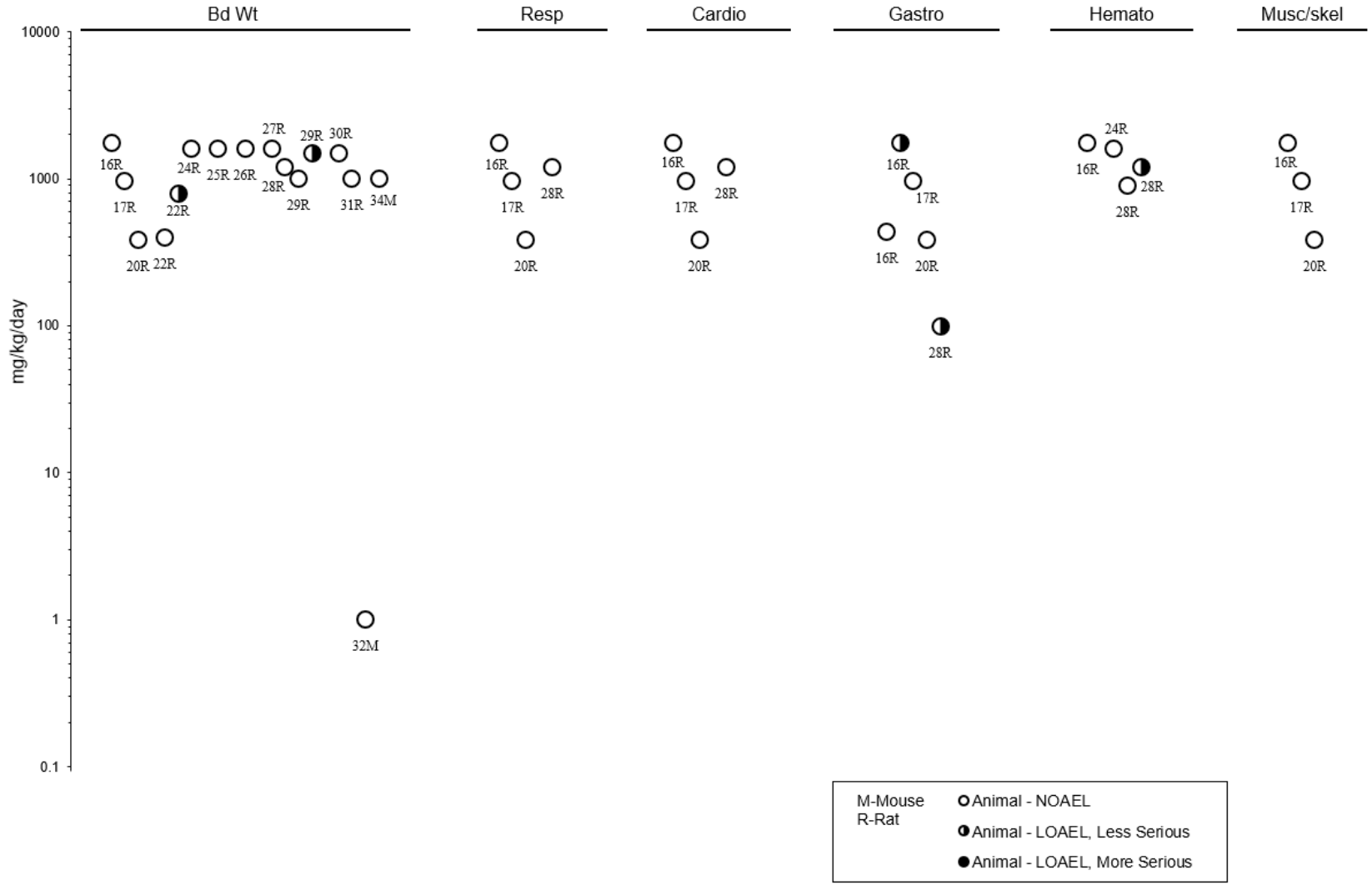


Figure 2-3. Levels of Significant Exposure to Methyl *tert*-Butyl Ether (MTBE) – Oral

Intermediate (15-364 days)

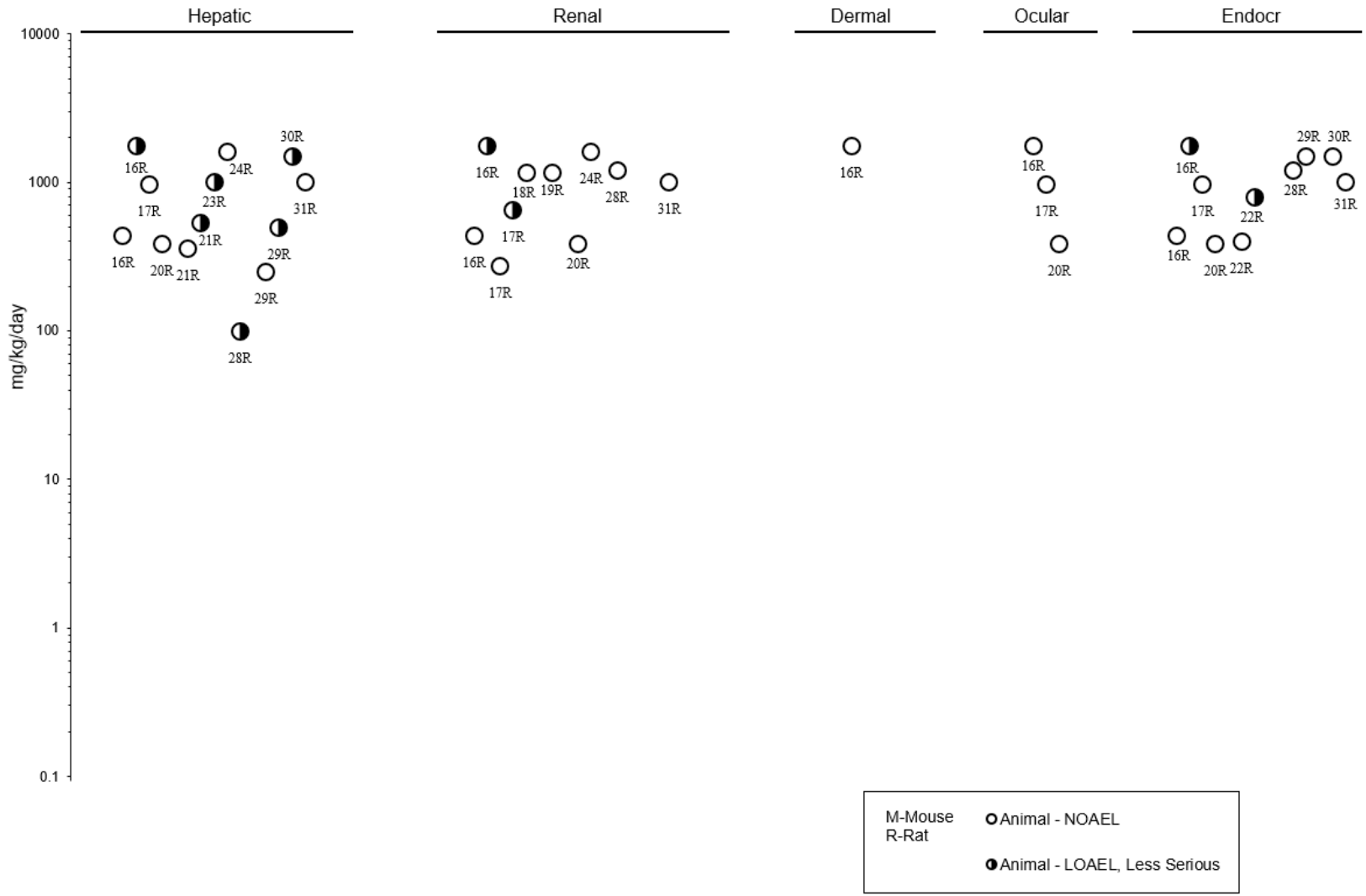


Figure 2-3. Levels of Significant Exposure to Methyl *tert*-Butyl Ether (MTBE) – Oral

Intermediate (15-364 days)

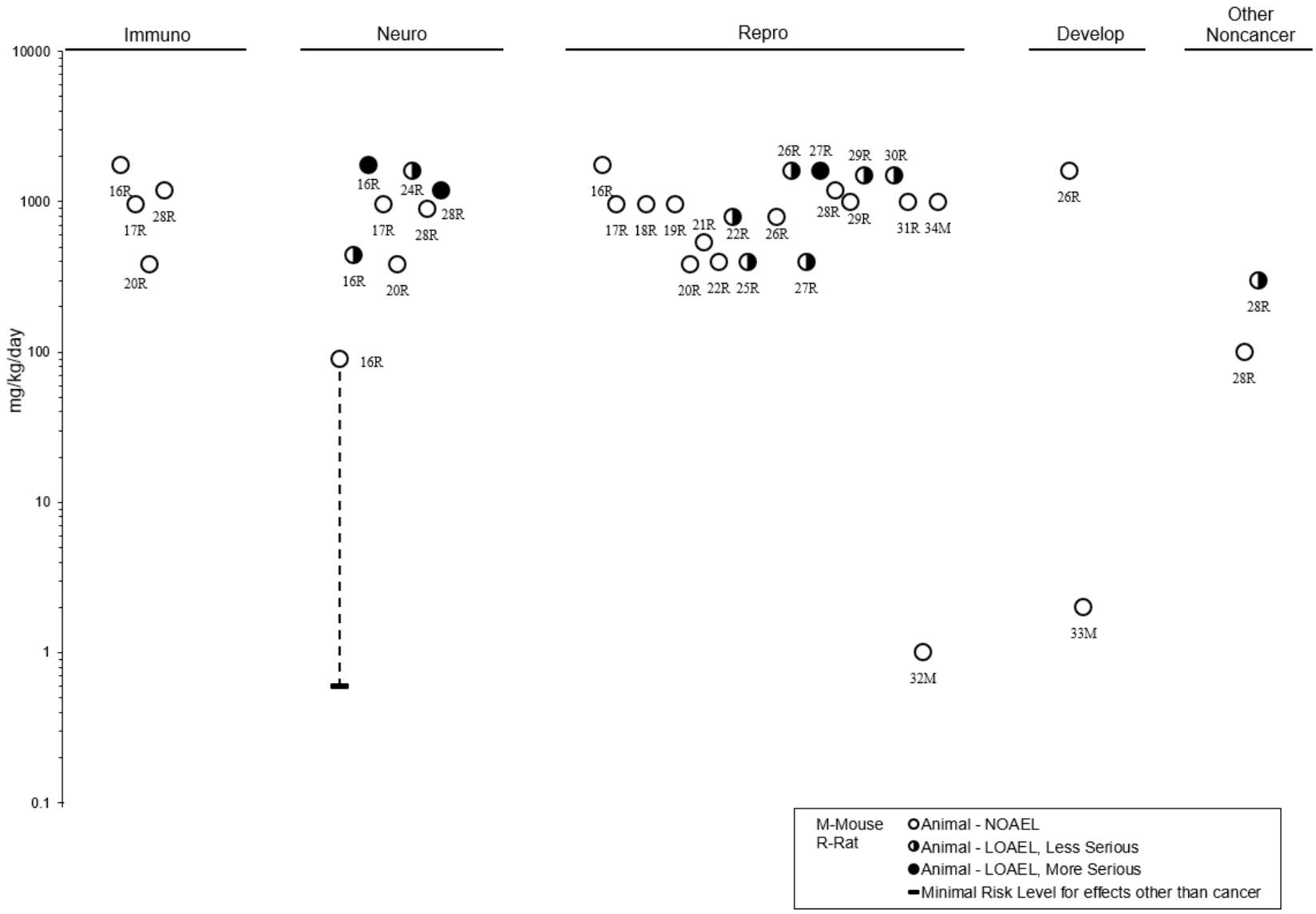


Figure 2-3. Levels of Significant Exposure to Methyl *tert*-Butyl Ether (MTBE) – Oral

Chronic (≥365 days)

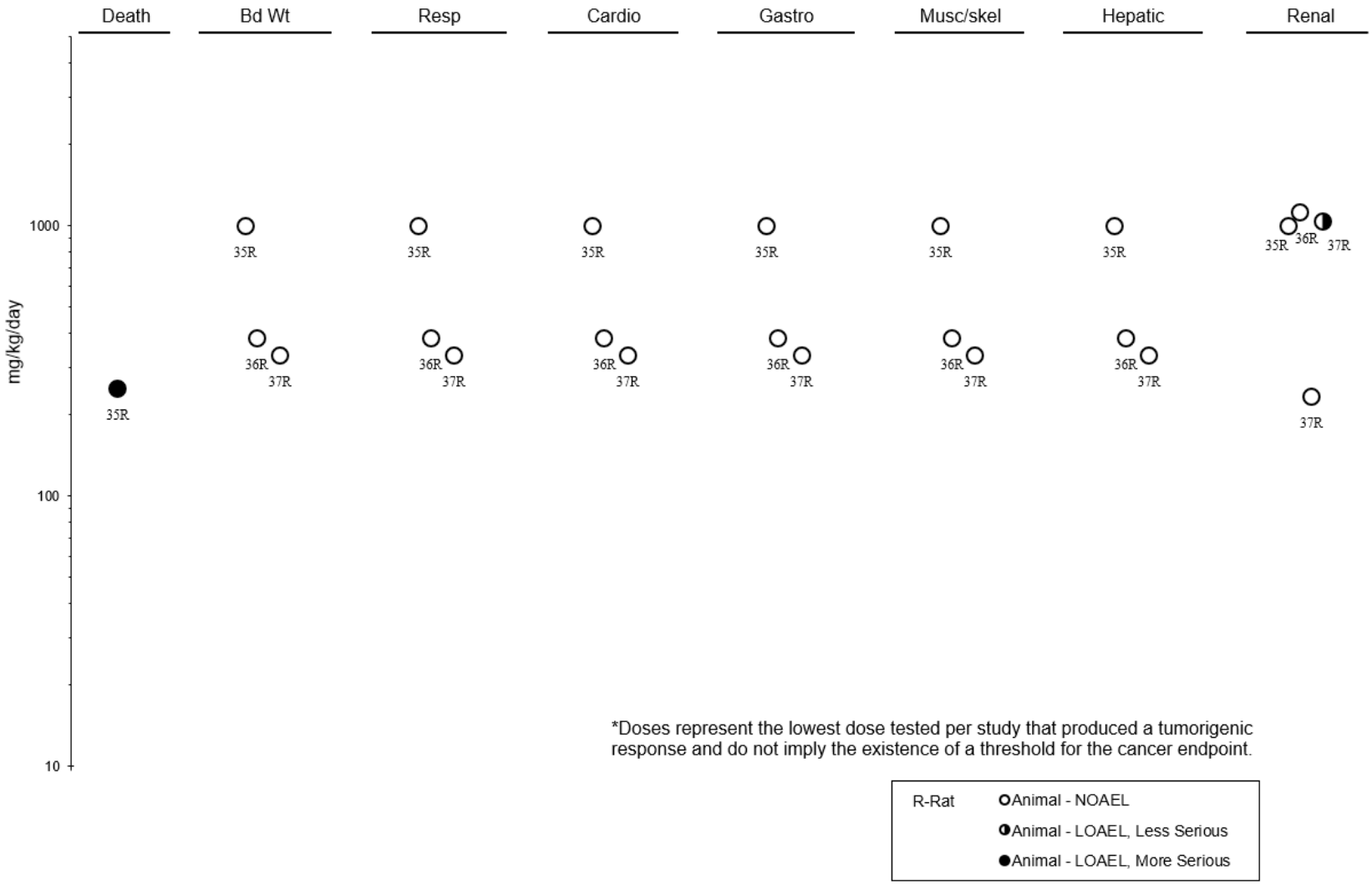


Figure 2-3. Levels of Significant Exposure to Methyl *tert*-Butyl Ether (MTBE) – Oral

Chronic (≥365 days)

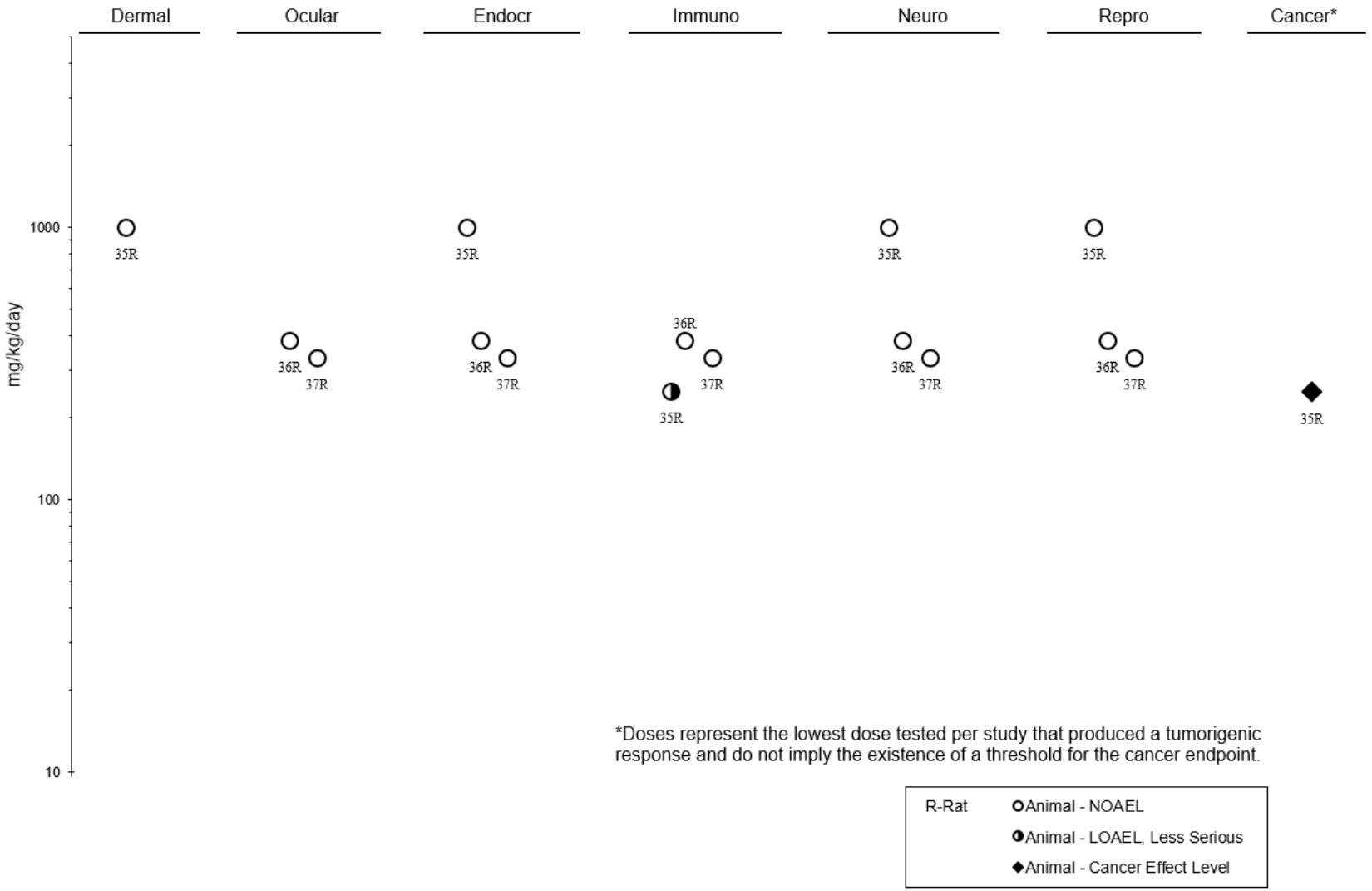


Table 2-4. Levels of Significant Exposure to Methyl *tert*-Butyl Ether (MTBE) – Dermal

Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
ACUTE EXPOSURE								
Human 22 M, 21 F	1 hour	0, 1.7 ppm	CS, NX, OP	Dermal	1.7			
				Ocular	1.7			
				Immuno	1.7			
Cain et al. 1996 (data also available in unpublished report by Cain et al. 1994; exposure via MTBE in air; immune cell composition measured in tear fluid and nasal lavage)								
Human 10 M	2 hours	5, 25, 50 ppm	CS	Ocular	50 M			
				Immuno	50 M			
Johanson et al. 1995; Nihlén et al. 1998a (exposure via MTBE in air; immune cell composition and inflammatory markers measured in nasal lavage)								
Human 19 M, 18 F	1 hour	0, 1.39 ppm	CS, NX, BI	Dermal	1.39			
				Ocular	1.39			
				Immuno	1.39			
Prah et al. 1994 (exposure via MTBE in air; inflammatory markers measured in nasal lavage)								
Rat (NS) NS	4 hours	18,892, 34,127, 386,57, 41,860, 63,953 ppm	CS	Ocular		18,892		Eye discharge, irritation
ARCO 1980 (exposure to commercial MTBE [99.1% purity] via air)								
Rat (NS) (NS)	4 hours	19,621, 29,681, 39,406, 55,784 ppm	CS	Ocular		19,621		Irritation, lacrimation
ARCO 1980 (exposure to ARCO MTBE (96.2% purity) via air)								
Rat Sprague-Dawley 20 M, 20 F	9 days 5 days/week 6 hours/day	0, 100, 300, 1,000, 3,000 ppm	CS	Ocular		100		Lacrimation, conjunctival swelling
Texaco Inc. 1981 (exposure via MTBE in air)								

Table 2-4. Levels of Significant Exposure to Methyl *tert*-Butyl Ether (MTBE) – Dermal

Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Rat (Fischer-344) 22 M, 22 F	6 hours	0, 800, 4,000, 8,000 ppm	CS	Ocular	4,000	8,000		Lacrimation
Daughtrey et al. 1997 (data also available in unpublished report by Gill 1989; exposure via MTBE in air)								
Rat (Fischer 344) 5 M, 5 F	13 days 6 hours/day	0, 2,000, 4,000, 8,000 ppm	GN, CS	Dermal Ocular	8,000 8,000			
Dodd and Kintigh 1989 (exposure via MTBE in air)								
Mouse (CD-1) 30 F	10 days (GDs 6–15) 6 hours/day	0, 1,000, 4,000, 8,000 ppm	CS	Ocular	4,000 F	8,000 F		Lacrimation, periocular encrustation
Bevan et al. 1997a (data also available in unpublished report by Tyl and Neeper-Bradley 1989; exposure via MTBE in air)								
Mouse (CD-1) 30 F	10 days GDs 6–15 6 hours/day	0, 250, 1,000, 2,500 ppm	CS	Ocular		250 F		Slightly increased lacrimation
Conaway et al. 1985 (exposure via MTBE in air)								
Rabbit (New Zealand) 6 NS	24 hours	0.5 mL	HP, CS	Dermal		0.5		Slight to severe erythema, acanthosis, focal necrosis
ARCO 1980								
Rabbit (New Zealand) 5 NS	24 hours	10,000 mg/kg	GN, HP, CS, BW, LE	Dermal		10,000		Erythema, skin thickening, edema, blanching
ARCO 1980								

Table 2-4. Levels of Significant Exposure to Methyl *tert*-Butyl Ether (MTBE) – Dermal

Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Rabbit (New Zealand) 9 NS	Once	0.1 mL	CS	Ocular		0.1		Corneal opacities, chemosis, conjunctival redness, discharge
ARCO 1980								
Rabbit (NS) NS B	Once	0.05 mL	CS	Ocular		0.05 M		Congestion of conjunctival, palpebral thickening, and hypersecretion
Snamprogetti 1980								
INTERMEDIATE EXPOSURE								
Rat (Sprague-Dawley) 25 M, 25 F	14–19 weeks 5 days/week 6 hours/day	0, 400, 3,000, 8,000 ppm	CS	Ocular	3,000	8,000		Periocular encrustation and ocular discharge
Bevan et al. 1997b (data also available in unpublished report by Neeper-Bradley 1991; exposure to MTBE via air)								
Rat (Sprague-Dawley) 15 M, 30 F	16–28 weeks 5–7 days/week 6 hours/day	0, 250, 1,000, 2,500 ppm	BW, OW, GN, HP, CS, DX, LE	Dermal Ocular	2,500 2,500			
Biles et al. 1987 (exposure via MTBE in air)								
Rat Sprague-Dawley 10 M, 10 F	13 weeks 5 days/week 6 hours/day	0, 250, 500, 1,000 ppm	CS, GN, HP, OP	Dermal Ocular	1,000 1,000			
Greenough et al. 1980 (exposure via MTBE in air)								
Rat (Fischer-344) 25 M, 25 F	13 weeks 5 days/week 6 hours/day	0, 800, 4,000, 8,000 ppm	CS, HP	Dermal Ocular	8,000 8,000			
Lington et al. 1997 (data also available in unpublished report by Dodd and Kintigh 1989; exposure via MTBE in air)								
Guinea pig (Hartley) 10 M	3 weeks every other day	0.5 mL of 1% solution initially, then 0.1 mL	CS	Dermal Immuno	 0.5 M	0.5 M		Local irritation and increased erythema
ARCO 1980								

Table 2-4. Levels of Significant Exposure to Methyl *tert*-Butyl Ether (MTBE) – Dermal

Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
CHRONIC EXPOSURE								
Rat (Fischer-344) 50 M, 50 F	24 months 5 days/week 6 hours/day	0, 400, 3,000, 8,000 ppm	CS, HP	Dermal	8,000			
				Ocular	8,000 F 400 M	3,000 M		Swollen periocular tissue
Bird et al. 1997 (data also available in unpublished report by Chun et al. 1992; exposure via MTBE in air)								
Mouse (CD-1) 50 M, 50 F	18 months 5 days/week 6 hours/day	0, 400, 3,000, 8,000 ppm	CS	Dermal	8,000			
				Ocular	8,000			
Bird et al. 1997 (data also available in unpublished report by Burleigh-Flayer et al. 1992; exposure via MTBE in air)								

BI = biochemical changes; BW = body weight; CS = clinical signs; DX = developmental toxicity; F = female(s); GD = gestation day; GN = gross necropsy; HP = histopathology; Immuno = immunological; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); NOAEL = no-observed-adverse-effect level; NS = not specified; NX = neurological function; OP = ophthalmology; OW = organ weight

2.2 DEATH

No studies were located regarding death in humans following exposure to MTBE. Exposure-related deaths have been reported in laboratory animals following acute and chronic inhalation and oral exposures.

Information regarding death in animals following inhalation exposure was located for rats, mice, and rabbits. Acute inhalation 4-hour LC_{50} (lethal concentration, 50% kill) values in rats for two grades of MTBE were determined to be 39,395 ppm for ARCO MTBE (96.2% MTBE) and 33,370 ppm for commercial MTBE (99.1% MTBE) (ARCO 1980). An acute LC_{50} in mice following inhalation of MTBE for 10 minutes was determined to be 180,000 ppm; the LT_{50} (time at which death occurs in 50% of exposed animals) in mice exposed to 209,300 ppm was 5.6 minutes (Snamprogetti 1980). Repeated brief exposures to high inhalation concentrations of MTBE (5–10 minutes/day, 5 days/week for 30 days) did not result in mortalities in rats at up to 80,000 ppm (Snamprogetti 1980) or mice at 50,000 ppm; 1/30 mice died at 80,000 ppm. No deaths occurred in rats or mice exposed to concentrations up to 8,000 ppm for acute durations (Bevan et al. 1997a; Bird et al. 1997; Conaway et al. 1985; Daughtrey et al. 1997; Dodd and Kintigh 1989; Moser et al. 1996; MTBE Committee 1990a; Prescott-Mathews et al. 1997; Texaco Inc. 1981; Vergnes and Chun 1994; Vergnes and Kintigh 1993; Vergnes and Morabit 1989) or intermediate durations (Bevan et al. 1997b; Biles et al. 1987; Bird et al. 1997; Daughtrey et al. 1997; Greenough et al. 1980; Lington et al. 1997; Moser et al. 1996, 1998). In a 24-month inhalation study, increased mortality and decreased mean survival time occurred in male rats exposed to ≥3,000 ppm (Bird et al. 1997). Slight, but not statistically significant, increases in mortality and decreases in mean survival time also occurred in the male rats exposed to 400 ppm (lowest concentration tested) and females exposed to ≥3,000 ppm. The early mortality was attributed to chronic progressive nephropathy in both males and females. In an 18-month inhalation study, increased mortality and decreased mean survival time were observed in male mice at 8,000 ppm; female survival was comparable to controls (Bird et al. 1997). The early mortality in male mice was attributed to obstructive uropathy.

Oral LD_{50} (lethal dose, 50% kill) values for rats and mice were determined to be 3,866 mg/kg and 4,000 mg/kg, respectively (ARCO 1980; Little et al. 1979). In a series of 2-week experiments, 3/10 rats died following exposure to 1,200 mg/kg/day via gavage in the first experiment (6–7 days/week), but not in three additional experiments by the same study authors at doses ranging from 1,200 to 1,500 mg/kg/day for 12–14 days (de Peyster et al. 2003, 2014). No treatment-related deaths were observed in rats or mice orally exposed to MTBE via gavage at doses up to 2,000 mg/kg for acute (Billitti

et al. 2005; de Peyster et al. 2008; Dong-mei et al. 2009; Li et al. 2008; MTBE Committee 1990c; Robinson et al. 1990) or intermediate (de Peyster et al. 2003, 2008; Dong-mei et al. 2009; Gholami et al. 2015; Amoco 1992; Khalili et al. 2015; Li et al. 2008; Robinson et al. 1990; Ward et al. 1994; Williams et al. 2000) durations. Similarly, no deaths were observed in rats or mice exposed via drinking water to doses as high as 1,153 mg/kg/day in acute (Berger and Horner 2003; Bermudez et al. 2012) or intermediate (Bermudez et al. 2012) studies. Dose-related decrease in survival was observed in female rats beginning at week 16 following exposure to gavage doses of ≥250 mg/kg/day, 4 days/week, for 104 weeks; male survival was comparable to controls at doses up to 1,000 mg/kg/day (Belpoggi et al. 1995, 1997). Chronic exposure via drinking water did not result in treatment-related mortalities in rats at doses up to 384 mg/kg/day in males or 1,119 mg/kg/day in females (Bermudez et al. 2012; Dodd et al. 2013).

No deaths occurred in rats dermally exposed to doses up to 400 mg/kg for 6 hours (MTBE Committee 1990b) or in rabbits dermally exposed to 10,000 mg/kg for 24 hours (ARCO 1980).

Significant numbers of rats died after a dose of 148 mg/kg was administered intravenously or intrahepatically, but no rats died after the same dose was administered intraperitoneally (Akimoto et al. 1992). In other intraperitoneal studies, one study determined intraperitoneal LD_{50} values of 1,249 mg/kg in rats and 1,010 mg/kg in mice (Snamprogetti 1980), while another study reported death in two of five rats after dosing with 3,705 mg/kg (Brady et al. 1990). The intravenous LD_{50} in rats was 415 mg/kg; subcutaneous LD_{50} values were much higher (4,946 mg/kg for rats and 2,646 mg/kg for mice). Two of six rabbits that received 1,782 mg/kg through the bile duct died (Adam et al. 1990).

2.3 BODY WEIGHT

No studies were located regarding body weight effects in humans following exposure to MTBE. Decreased body weight following exposure to MTBE has been reported in laboratory animals following acute-, intermediate-, and chronic-duration inhalation exposures and inconsistently reported in acute- and intermediate-duration oral exposure studies.

Body weight effects following acute inhalation exposure were only observed at high concentrations (≥4,000 ppm). Single exposures up to 8,000 ppm for 6 hours had no effect on body weight in rats (Daughtrey et al. 1997). However, exposure to 8,000 ppm for 5 days (6 hours/day) resulted in a significant 12% decrease in terminal body weights associated with a 3% weight loss over the treatment

period (compared to an 8% body weight gain in controls) (Vergnes and Morabit 1989). At lower exposure levels (800 and 4,000 ppm), terminal body weights in males at these two levels did not significantly differ from controls despite significant decreases in body weight gain of ~20% compared to control. In the same study, female body weight effects were only observed at 8,000 ppm, with a 73% decrease in body weight gain compared to controls in female rats. Similarly, a decrease in body weight gain of 65–66% occurred in male rats during the first 1–3 and 1–14 days of exposure to 4,000 and 8,000 ppm, respectively, and a 36% decrease in body weight gain occurred in female rats during the first 1–7 days of exposure to 8,000 ppm in a preliminary 13-day range-finding study for a 13-week study (Dodd and Kintigh 1989). In other acute studies, no body weight effects were noted in rats following intermittent acute exposure to concentrations up to 3,000 ppm for 9–14 days (Prescott-Mathews et al. 1997; Savolainen et al. 1985; Texaco Inc. 1981) or in mice following intermittent acute exposure to concentrations up to 8,000 ppm for 1–13 days (Dodd and Kintigh 1989; Moser et al. 1996; Vergnes and Kintigh 1993).

In longer-duration inhalation studies, body weight effects were inconsistently observed at 8,000 ppm; no body weight effects were noted at lower doses. In a 4–5-week study in rats, a 2% loss of body weight was observed in male rats intermittently exposed to 8,000 ppm during the first week, and body weight gain across the exposure period was decreased by 24–35%, compared with controls (Bird et al. 1997). In similarly exposed females, a transient 24% decrease in body weight gain was observed at 8,000 ppm during the first 2 weeks of exposure. Decreased body weight and/or body weight gain were reported at 8,000 ppm in several other studies with longer exposure durations, including 2-generation and 24-month studies in rats (Bevan et al. 1997b; Bird et al. 1997) and 16-week, 32-week, and 18-month studies in mice (Bird et al. 1997; Moser et al. 1996, 1998). In other intermediate-duration studies, no exposure-related body weight effects were noted at concentrations up to 8,000 ppm in rats and mice exposed for 3–13 weeks (Bird et al. 1997; Daughtrey et al. 1997; Greenough et al. 1980; Lington et al. 1997; Moser et al. 1996), up to 2,500 ppm in rats exposed for 16–28 weeks (Biles et al. 1987), or up to 300 ppm in rats exposed for 6–5 weeks (Savolainen et al. 1985).

In pregnant mice, a >10% reduction in maternal weight and a >25% reduction in maternal body weight gain were observed both during and after exposure to 8,000 ppm on gestational days (GDs) 6–15 (Bevan et al. 1997a). Body weight effects were accompanied by an approximate 30% reduction in food consumption during exposure only, which may be secondary to observed hypoactivity in exposed dams. In other gestational exposure studies, no maternal body weight effects were noted in rats or mice exposed to concentrations up to 2,500 ppm (Conaway et al. 1985) or in rabbits exposed to concentrations up to

8,000 ppm (Bevan et al. 1997a). In a 2-generation study, no maternal body weight effects were noted in F0 or F1 rat dams intermittently exposed to concentrations up to 8,000 ppm (Bevan et al. 1997b).

Body weight effects following acute oral exposure were only observed at high doses and were likely due to decreased food intake secondary to sedative effects of MTBE at high doses (see Section 2.15). Daily gavage exposure to MTBE for 14 days caused significant decreases in body weight gains of male and female rats at doses ≥714 and ≥1,071 mg/kg/day, respectively (magnitude not specified); however, final body weights remained within 10% of controls at doses up to 1,428 mg/kg/day (highest dose tested) (Robinson et al. 1990). Observed changes in body weight gain are likely secondary to the significant decrease in food intake in treated rats, which may be due to the hypoactivity induced by MTBE. In a series of 2-week experiments, a 10% decrease in body weight was observed in male rats exposed to 1,200 mg/kg/day via gavage in the first experiment (6–7 days/week), but not in three additional experiments by the same study authors at doses ranging from 1,200 to 1,500 mg/kg/day (de Peyster et al. 2014). In a similar experiment, body weight loss was observed in male rats exposed to 1,500 mg/kg/day via gavage every other day for 12 days (de Peyster et al. 2003). Food consumption was not reported in the studies by de Peyster et al. (2003, 2014); however, doses associated with decreased body weight reportedly caused lethargy, which may have decreased food intake. Another 2-week gavage study reported no significant changes in body weights or food consumption in male rats exposed daily to doses up to 1,600 mg/kg/day (Dong-mei et al. 2009). In an acute drinking water study in rats, no body weight effects were noted in females exposed to 520 mg/kg/day for 2 weeks (Berger and Horner 2003). No body weight effects were observed in mice exposed to gavage doses up to 2,000 mg/kg/day for 3 days (Billitti et al. 2005; de Peyster et al. 2008).

There is no consistent evidence for body weight effects in intermediate-duration oral studies in rats and mice, or chronic-duration oral studies in rats. In 28-day gavage studies, male rats showed an 11% decrease in body weight following daily exposure to 800 mg/kg/day (de Peyster et al. 2003), and a 7–12% decrease in body weight from day 15 to 28 following daily exposure to 1,500 mg/kg/day, but not at doses ≤1,000 mg/kg/day (Williams et al. 2000). In contrast, no body weight effects were noted in rats in other intermediate-duration studies at daily gavage doses of up to 1,500 mg/kg/day for 15 days (Williams et al. 2000), 1,750 mg/kg/day for 28–30 days (Amoco 1992; Dong-mei et al. 2009; Gholami et al. 2015; Khalili et al. 2015; Li et al. 2008), or 1,200 mg/kg/day for 90 days (Robinson et al. 1990). Similarly, no body weight effects were noted following chronic exposure to gavage doses up to 1,000 mg/kg/day (Belpoggi et al. 1995, 1997). In drinking water studies, no body weight effects were reported in rats following intermediate-duration exposure to doses ≤1,153 mg/kg/day (Bermudez et al. 2012), or chronic doses

≤1,119 mg/kg/day (Bermudez et al. 2012; Dodd et al. 2013). In addition, no changes in body weight were found in mice exposed to gavage doses up to 1,000 mg/kg/day for 3 weeks (Ward et al. 1994), or drinking water doses up to 1 mg/kg/day for 28 days (de Peyster et al. 2008).

2.4 RESPIRATORY

There is some evidence that workers exposed to fuel containing MTBE during the oxyfuel program in the early 1990s experienced increased respiratory symptoms (e.g., irritation, coughing) compared to workers exposed to fuels that did not contain MTBE; however, clear conclusions cannot be drawn due to confounding factors and study limitations. In controlled exposure studies, self-reported respiratory symptoms were not increased in healthy volunteers exposed to MTBE at concentrations up to 50 ppm. In animal studies, evidence of respiratory irritation was observed at high exposure levels in both inhalation and oral studies.

Following several anecdotal reports of respiratory symptoms associated with introduction of MTBE into gasoline during the oxyfuel program in the United States during the early 1990s, the Centers for Disease Control and Prevention (CDC) conducted several studies evaluating potential associations between MTBE exposure and respiratory symptoms (see Table 2-1). Several of these studies reported an increase in self-reported respiratory symptoms (burning sensation in the nose, mouth, or throat or cough) in Alaskan workers during the oxyfuel program following occupational exposure to gasoline containing MTBE (e.g., taxi drivers or health-care workers that travelled routinely in cars), compared either with individuals with low exposure (e.g., noncommuter students) or with workers exposed to gasoline that did not contain MTBE (Alaska DHSS 1992a, 1992b; Moolenaar et al. 1994). However, these studies only provide suggestive evidence due to several limitations, including lack of a referent group (Alaska DHSS 1992b only), small to modest subject numbers, lack of statistical analysis of incidence data, potential influence of widespread media coverage and public opposition to the oxyfuel program, and/or lack of consideration for other confounding factors (e.g., other exposures, including potential combustion products of MTBE). No evidence of increased respiratory symptoms was observed in occupationally exposed workers, compared with unexposed referents, in similar studies during the oxyfuel program conducted in New York (CDC 1993a), Connecticut (CDC 1993b; White et al. 1995), or New Jersey (Mohr et al. 1994).

Results from population-based studies evaluating the potential association between respiratory symptoms and MTBE exposure due to the oxyfuel program are mixed (see Table 2-1). In a population-based

telephone survey, a statistically significant increased risk of respiratory symptoms (throat irritation, sinus congestion) was observed in residents of metropolitan Milwaukee, Wisconsin, in which oxyfuel was used, compared to residents of non-metropolitan Wisconsin (MTBE-free gasoline); however, the risk was not increased for any respiratory symptom for residents of metropolitan Chicago, Illinois (oxyfuel) compared to non-metropolitan Wisconsin (Wisconsin DHSS 1995). The results in Milwaukee may have been biased by knowledge of the oxyfuel program and potential health effects due to increased media coverage in Milwaukee because, in the telephone survey, familiarity with MTBE as a reformulated gasoline additive was reported by 54% of the Milwaukee residents, 23% of Chicago residents, and 40% of the Wisconsin residents. Additionally, non-metropolitan Wisconsin may not have been an appropriate referent group for the Chicago residents. One ecological study also reported a statistically significant increase in doctor's visits with diagnostic codes pertaining to respiratory symptoms, including burning throat, burning nose, cough, wheezing, and upper respiratory infection, in Philadelphia, Pennsylvania during 1997 (during the 6th year of the oxyfuel program), compared to 1992 (at the initiation of the oxyfuel program) based on medical record review (Joseph and Weiner 2002). The study authors concluded that "some environmental factor" in the mid-1990s was associated with immune system findings and suggested that this factor is MTBE. However, this study has several major limitations, primarily a study design that does not allow for control for confounders (other chemical exposures, occupation, concomitant diseases, sex, age, race, etc.), that preclude meaningful conclusions. In contrast, another ecological study in Fairbanks and Anchorage, Alaska (Gordian et al. 1995) did not find an increased rate of treatment for respiratory symptoms (based on medical insurance records) over the winter of 1992–1993 (during the oxyfuel program), compared with the number of claims during the two preceding winters (prior to the oxyfuel program). However, this study would miss mild and/or transient respiratory effects associated with MTBE exposure that would not result in seeking medical attention.

In controlled human inhalation experiments, no increases in self-reported respiratory symptoms (nose or throat irritation, dry or sore throat, stuffy or runny nose, sinus congestion, cough, wheezing, chest tightness, and/or shortness of breath) were observed in volunteers during or after exposure to MTBE at 1.39 or 1.7 ppm for 1 hour (Cain et al. 1996; Prah et al. 1994), or 50 ppm for 2 hours during light exercise (Johanson et al. 1995; Nihlén et al. 1998a). The odor threshold was determined to be approximately 0.18 ppm (Prah et al. 1994).

Respiratory effects have been observed in animals following acute inhalation exposure to MTBE. A 4-hour exposure of rats to concentrations ≥19,621 ppm ARCO MTBE (96.2% MTBE) caused hyperpnea, while a 4-hour exposure of rats to ≥18,892 ppm commercial MTBE (99.1% MTBE) caused tachypnea

and nasal discharge, with respiration gradually slowing until the rats died (ARCO 1980). In a mouse study to determine the RD_{50} (the concentration that results in 50% decrease in respiratory rate) for respiratory irritancy of MTBE, a threshold irritant response (13%) in respiratory rate occurred at 83 ppm and a 52% decrease in breathing frequency occurred at 8,321 ppm (Tepper et al. 1994). No pulmonary irritation was observed at concentrations ≤2,774 ppm, but a mixed pattern of irritant response, indicating both sensory and pulmonary irritation, occurred at 8,321 ppm. The RD_{50}, indicative of sensory irritation, was determined to be 4,604 ppm. Intermittent exposure of rats for 9 days to concentrations of 1,000 or 3,000 ppm resulted in high incidence and increased severity of inflammation of the nasal mucosa and trachea (Texaco Inc. 1981). In contrast, no clinical signs of respiratory irritation or gross or microscopic lesions of the respiratory tract were observed in rats intermittently exposed to concentrations up to 8,000 ppm for 13 days (Dodd and Kintigh 1989).

In pregnant mice, labored breathing was observed in dams exposed via inhalation to 8,000 ppm, but not 4,000 ppm, from GD 6 to 15 (Bevan et al. 1997a). In similarly exposed rabbits, no clinical signs of respiratory irritation were observed (Bevan et al. 1997a). No exposure-related clinical signs of respiratory irritation or histological alterations of the respiratory tract were observed in intermediate- or chronic-duration inhalation studies in rats or mice exposed to concentrations as high as 8,000 ppm (Bevan et al. 1997b; Biles et al. 1987; Bird et al. 1997; Greenough et al. 1980; Lington et al. 1997). Decreases in absolute and relative lung weights were reported in an intermediate-duration inhalation study in rats at 1,000 ppm (Greenough et al. 1980); these changes were not associated with histological alterations and were therefore not considered biologically relevant.

A single high oral dose (≥4,080 mg/kg) of MTBE caused labored respiration in rats, and gross pathological changes consistent with the irritating nature of MTBE were observed at ≥2,450 mg/kg (ARCO 1980). Alterations in absolute and/or relative lung weights were reported in one acute (decreased weight) and one intermediate (increased weight) oral study in rats (Robinson et al. 1990), but not others (Bermudez et al. 2012; Dong-mei et al. 2009); these changes were not associated with histological alterations and were therefore not considered biologically relevant (not included in LSE table). Acute-, intermediate-, and chronic-duration studies have not found histopathological alterations in the lungs or other respiratory tract tissues in rats and mice exposed to doses as high as 1,428 mg/kg/day (Amoco 1992; Belpoggi et al. 1995, 1997; Bermudez et al. 2012; Dodd et al. 2013; Robinson et al. 1990).

A number of studies have been conducted in animals to determine possible side effects of MTBE therapy for gallstone dissolution. Pulmonary hemorrhage was observed in rats given 148 mg/kg MTBE

intrahepatically, intraperitoneally, or intravenously, with intravenous dosing producing the greatest damage (Akimoto et al. 1992). Intravenous injection of rats, rabbits, and cats with $\geq$7.4 mg/kg resulted in increased respiratory rates, which paralleled decreases in blood pressure and bradycardia, and intraperitoneal injection of rats with 185 mg/kg/day for 15 days resulted in pneumonia (Snamprogetti 1980). Transient dyspnea occurred in rabbits injected with 740.5 mg/kg MTBE through a catheter to the cystic duct (Tritapepe et al. 1989), and lung congestion with pneumonia occurred in pigs infused with 4,255 mg/kg MTBE through a catheter to the gallbladder (McGahan et al. 1988). However, no histopathological lung lesions were found in dogs injected with 635 mg/kg MTBE through a catheter to the gallbladder (Allen et al. 1985b).

2.5 CARDIOVASCULAR

Available human studies are too limited to determine if MTBE exposure affects cardiovascular health or function. Based on inhalation and oral studies in animals, MTBE does not appear to have adverse effects on the cardiovascular system.

One ecological study reported a statistically significant increase in doctor's visits with diagnostic codes pertaining to cardiac symptoms (tachycardia, palpitations, murmurs) in medical records from General Medicine Division of the Clinical Practices at the University of Pennsylvania in 1997, 6 years after introduction of oxyfuel containing MTBE to the surrounding Philadelphia region, compared to 1992, the year that the oxyfuel program was initiated (Joseph and Weiner 2002; see Table 2-1). The study authors concluded that "some environmental factor" in the mid-1990s was associated with increased cardiac symptoms and suggested that this factor is MTBE. However, this study has several major limitations, primarily a study design that does not allow for control for confounders (other chemical exposures, occupation, concomitant diseases, sex, age, race, etc.), that preclude meaningful conclusions.

A number of clinical studies of patients receiving MTBE therapy intracystically for the dissolution of gallstones have recorded side effects. Infrequently reported cardiac findings include transient hypertension in 1/10 patients (Murray et al. 1988) and hypotension in 2/29 patients, palpitations in 1/29 patients, and angina in 1/29 patients (Neoptolemos et al. 1990) given MTBE via nasobiliary catheter. Vasovagal reactions were found in 4/24 patients given MTBE via the percutaneous transhepatic route to the gallbladder (Eidsvoll et al. 1993). In another study, a vasovagal reaction was only observed in 1/75 patients given MTBE via percutaneously placed cholecystostomy catheter (Williams et al. 1990).

No treatment-related changes in heart weight or gross or histopathological lesions of the heart were found in rats intermittently exposed to inhalation concentrations up to 3,000 ppm for 9 days (Texaco Inc. 1981) or up to 8,000 ppm for 13 weeks (Greenough et al. 1980; Lington et al. 1997). Similarly, no treatment-related changes in heart weight or gross or histopathological lesions of the heart were observed in rats or mice exposed to concentrations up to 8,000 ppm for 24 or 18 months, respectively (Bird et al. 1997).

Based on histological examination of the heart and aorta of rats, oral exposure to MTBE appears to be without effects on the cardiovascular system. Gavage administration of MTBE did not result in alterations in heart weight or heart or aorta histology of rats at ≤1,428 mg/kg/day for 14 days (Robinson et al. 1990), ≤1,750 for 4 weeks (Amoco 1992), or ≤1,000 mg/kg/day for 104 weeks (Belpoggi et al. 1995, 1997). In drinking water studies, no exposure-related changes in heart weight or histology were observed in rats at doses up 972 mg/kg/day in males or 1,153 mg/kg/day in females for 13 weeks (Bermudez et al. 2012), 384 mg/kg/day in males for 6 months (Bermudez et al. 2012), 1,119 mg/kg/day in females for 1 year (Bermudez et al. 2012), or 330 mg/kg/day in males or 1,042 mg/kg/day in females for 2 years (Dodd et al. 2013). In males exposed to doses ≥29 mg/kg/day via drinking water for 1 year, absolute, but not relative, weight of the heart was significantly less in all treated groups, compared to controls; however, these findings were attributed to observed decreases in male body weights and no histopathological changes were observed in the heart at doses up to 384 mg/kg/day (Bermudez et al. 2012).

Effects noted in animals after administration of MTBE by other routes include decreased blood pressure in rabbits and decreased blood pressure, heart rate changes, and electrocardiographic variations in cats given 7.4 mg/kg intravenously and decreased blood pressure and bradycardia in rats given 7.4 mg/kg intravenously or 370 mg/kg intraperitoneally (Snamprogetti 1980).

2.6 GASTROINTESTINAL

Several epidemiology studies report nausea and/or vomiting with inhalation exposure to gasoline containing MTBE; however, these symptoms are likely related to neurological effects associated with MTBE exposure. Therefore, these studies are discussed in Section 2.15 (Neurological). Other human studies are limited to one occupational study that evaluated self-reported diarrhea and studies in patients receiving MTBE therapy for gallstone dissolution, which reported gastrointestinal side effects. In animals, the gastrointestinal tract only appears to be a target of toxicity following exposure to high gavage

doses. Observed effects in humans and animals are consistent with irritative effects on the gastrointestinal mucosa.

No associations between diarrhea and inhalation exposure to MTBE in gasoline were observed in a cross-sectional occupational study conducted by the CDC in Albany, New York (CDC 1993a; see Table 2-1). A number of clinical studies of patients receiving MTBE therapy for gallstone dissolution have recorded gastrointestinal side effects, indicative of irritation. These include vomiting, nausea, anorexia, emesis, duodenitis, retching, upper abdominal burning sensation during infusion, gas, and duodenal ulcer in patients receiving MTBE via percutaneous intracystic infusion, gallbladder catheter, or nasobiliary catheter (Allen et al. 1985a; Bonardi et al. 1986; Brandon et al. 1988; Di Padova et al. 1986; Eidsvoll et al. 1993; Hellstern et al. 1990; Holl et al. 1991; Janowitz et al. 1993; Kaye et al. 1990; Leuschner et al. 1988, 1991; McNulty et al. 1991; Murray et al. 1988; Neoptolemos et al. 1990; Saraya et al. 1990; Thistle et al. 1989; Tobio-Calo et al. 1992; Uchida et al. 1994; Williams et al. 1990). The irritation occurs due to leakage from the gallbladder into the gastrointestinal tract.

The gastrointestinal tract was not affected in rats exposed to MTBE via inhalation exposure. Intermittent exposure of rats for 9 days to concentrations up to 3,000 ppm caused no gross or histological changes of the stomach, duodenum, jejunum, ileum, colon, or rectum (Texaco Inc. 1981). Similarly, no exposure-related gastrointestinal tract lesions were observed in intermediate-duration studies that exposed rats to MTBE at concentrations up to 8,000 ppm for 13–19 weeks (Bevan et al. 1997b; Greenough et al. 1980; Lington et al. 1997). In chronic-duration inhalation studies, no treatment-related changes in the gastrointestinal tract were observed in rats or mice exposed to concentrations up to 8,000 ppm for 24 or 18 months, respectively (Bird et al. 1997).

MTBE appears to be irritating to the gastrointestinal tract of rats following gavage exposure as evidenced by diarrhea and histological lesions, which may be due to irritative portal-of-entry effects associated with bolus gavage. Rats treated with daily oral doses ≥357 mg/kg/day for 14 days had diarrhea by the third day of dosing, which continued throughout the remaining treatment period (Robinson et al. 1990). Similarly, diarrhea was observed in rats during a 90-day study immediately after daily gavage exposure to doses ≥100 mg/kg/day throughout the entire exposure period (Robinson et al. 1990). Daily oral administration of 1,750 mg/kg/day MTBE via gavage for 4 weeks to rats resulted in submucosal edema in the squamous portion of the stomach; no gross lesions were observed in the duodenum, jejunum, ileum, cecum, colon, rectum, salivary glands, stomach, or tongue (Amoco 1992). In a 104-week study, in which male and female rats were given gavage doses ≤1,000 mg/kg/day, 4 days/week, histological examination

of the oral cavity, salivary glands, tongue, esophagus, stomach (fore and glandular), and intestines (four levels) revealed no treatment-related lesions (Belpoggi et al. 1995, 1997).

In drinking water studies, no exposure-related clinical signs or gross or histopathological changes in the gastrointestinal tract were reported in rats following intermediate-duration exposure to doses ≤1,153 mg/kg/day (Bermudez et al. 2012), or chronic-duration exposure to doses ≤1,119 mg/kg/day (Bermudez et al. 2012; Dodd et al. 2013)

In a pharmacokinetic study, in which MTBE was applied dermally to the dorsal flank of rats via an occluded chamber, some rats developed slight diarrhea at a dermal dose of 40 mg/kg but not 400 mg/kg (MTBE Committee 1990b). Since the dermally applied MTBE was protected by occlusion, it is unlikely that oral uptake via grooming contributed to the absorbed dose. This study is not included in the dermal LSE table due to the lack of controls and dose-response.

Effects noted in animals after administration of MTBE by other routes include light diarrhea in rats injected intravenously (MTBE Committee 1990b), necrosis of the duodenum in rabbits infused intraductally (Adam et al. 1990), and vomiting and/or duodenitis in rabbits (Tritapepe et al. 1989) and pigs (McGahan et al. 1988; Vergunst et al. 1994) treated intraductally, and dogs infused via gallbladder catheter (Allen et al. 1985b).

In a study in which jejunal segments were cannulated in rats, filled with 2–3 mL of MTBE, and perfused with α-aminoisobutyric acid (an actively absorbed nonmetabolizable amino acid) and polyethylene glycol 4000 (a nonabsorbable reference marker), or with mannitol (a passively absorbed hexone) and polyethylene glycol, MTBE caused reduction in active transport, increased passive permeability, and loss of mucosal weight (Zakko et al. 1995).

2.7 HEMATOLOGICAL

No studies were located regarding hematological effects in humans following inhalation, oral, or dermal exposure to MTBE; however, transient hematological effects have been noted as a side effect in some humans treated with MTBE intracystically for the dissolution of gallstones. In laboratory animals, no biologically relevant changes in hematological parameters were noted in inhalation studies, and findings in oral studies were limited to effects in white blood cell parameters at high gavage doses.

A number of clinical studies of patients receiving MTBE therapy have recorded hematological findings. These include a transient leukocytosis (Allen et al. 1985a; Hellstern et al. 1990, 1998; Holl et al. 1991; Janowitz et al. 1993; Leuschner et al. 1991, 1994; Neubrand et al. 1994; Thistle et al. 1989) and decreased hemoglobin levels (Kaye et al. 1990). The transient leukocytosis has been attributed to a slight leakage of bile after removal of the catheter (Thistle et al. 1989). In two studies of 75 patients (Thistle et al. 1989) and 8 patients (Ponchon et al. 1988), hemolysis and/or hematuria occurred in 1 patient in each study. In both cases, excessive overflow of MTBE from the gallbladder occurred, leading to systemic absorption or direct contact of MTBE with the vascular structure. Most clinical studies in which hematological parameters were monitored did not find changes except in a few patients, and some found none at all (Di Padova et al. 1986; Eidsvoll et al. 1993; McNulty et al. 1991; Uchida et al. 1994).

No biologically relevant changes in hematological parameters were reported in animals following exposure to MTBE via inhalation. In the only available acute-duration study evaluating hematological parameters, no exposure-related changes in hematological values were observed in rats exposed intermittently for 9 days at concentrations up to 3,000 ppm (Texaco Inc. 1981). In intermediate-duration inhalation studies in rats, several mild, but statistically significant, changes were observed in exposed rats; however, none of the findings were considered biologically or toxicologically relevant. In one 13-week study in rats, reported hematological findings following intermittent exposure to 1,000 ppm included a slight increase in white blood cell counts in males and females, and a slight increase in hemoglobin levels in males (Greenough et al. 1980). In another 13-week study in rats, most observed effects were ≤5% different from controls, and included decreased red blood cell (RBC) hemoglobin and increased hematocrit, mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), reticulocytes, and leukopenia in males at 4,000 and/or 8,000 ppm and increased hematocrit and segmented neutrophil count in females at 8,000 ppm (Lington et al. 1997). In chronic-duration inhalation studies, no treatment-related changes in hematological parameters were observed in rats or mice exposed to concentrations up to 8,000 ppm for 24 or 18 months, respectively (Bird et al. 1997). In addition, histological examination of the bone marrow revealed no treatment-related lesions.

Oral studies do not provide consistent evidence of adverse hematological effects in rats following gavage exposure to MTBE. The percent of monocytes was significantly increased in male rats exposed to ≥357 mg/kg/day for 14 days or 1,200 mg/kg/day for 90 days via gavage (Robinson et al. 1990). In female rats, a significant 40% decrease in white blood cell (WBC) count was observed after exposure to 1,200 mg/kg/day for 90 days via gavage; no adverse hematological effects were noted at doses up to 1,428 mg/kg/day for 14 days (Robinson et al. 1990). Additional statistically significant findings were

noted in exposed animals, including alterations in the RBC compartment, but findings were small in magnitude (<10%), predominantly in males, and likely secondary to dehydration associated with observed diarrhea (see Section 2.6). Another 2-week gavage study in male rats reported alterations in WBC parameters at 1,600 mg/kg/day, but not ≤800 mg/kg/day, including a 2-fold increase in total WBC count, 2-fold increase in the percentage of lymphocytes, 3-fold increase in the percentage of granulocytes, and 5–fold increase in the percentage of eosinophils (Dong-mei et al. 2009). Males exposed to 1,600 mg/kg/day also showed a small, but significant, 20% reduction in the RBC volume distribution width. When animals were exposed to the same doses for 4 weeks, hematological findings were limited to an 8% increase in hemoglobin at 1,600 mg/kg/day and a 50% reduction in eosinophils at 800 mg/kg/day, but not 1,600 mg/kg/day (Dong-mei et al. 2009). The findings at 4 weeks were not considered biologically relevant due to small magnitude or lack of dose-response. Similarly, no biologically relevant hematological effects were observed in another 4-week study that exposed male or female rats to gavage doses up to 1,750 mg/kg/day (Amoco 1992). Statistically significant changes included increased mean RBC counts in males at 440 mg/kg/day, but not higher doses, and increased mean corpuscular hemoglobin (MCH) in female rats at 90 and 1,750 mg/kg/day only. The toxicological significance of these changes is not certain since they are not dose-related, and no other hematological effects were noted. No pathology was seen in the femur, sternum, or bone marrow.

A number of studies have been conducted in animals to determine possible side effects of MTBE therapy for gallstone dissolution, but only three studies were located that monitored hematological parameters. In these studies, dogs (Allen et al. 1985b; Peine et al. 1990) or pigs (Vergunst et al. 1994) received MTBE via gallbladder catheter, and no hematological effects were found.

2.8 MUSCULOSKELETAL

No studies were located regarding musculoskeletal effects in humans following exposure to MTBE. In animal studies, the only observed musculoskeletal effect was osteodystrophy secondary to chronic progressive nephropathy in male rats chronically exposed to MTBE vapors. No primary musculoskeletal effects were observed following inhalation or oral exposure.

The musculoskeletal system was not directly affected in rats or mice exposed to MTBE via inhalation. Gross and histological examination of bone and skeletal muscle of rats revealed no treatment-related lesions following intermittent exposure to concentrations up to 3,000 ppm for 9 days (Texaco Inc. 1981), or up to 1,000 ppm for 13 weeks (Greenough et al. 1980). Similarly, an intermittent exposure for

13 weeks to concentrations up to 8,000 ppm produced no microscopic lesions in bones of treated rats (Lington et al. 1997). In chronic-duration inhalation studies, no treatment-related changes in gross and histological examination of the gastrocnemius muscle were observed in rats or mice exposed to concentrations up to 8,000 ppm for 24 or 18 months, respectively (Bird et al. 1997). No treatment-related histopathological lesions were found in the bone tissue of mice (Bird et al. 1997); however, fibrous osteodystrophy, which was secondary to chronic progressive nephropathy, was observed in male rats at all concentrations (≥400 ppm) (Bird et al. 1997). As discussed for Renal Effects in Section 2.10, the higher incidence and greater severity of chronic progressive nephropathy at lower exposure concentrations in male rats compared with female rats may be due to the exacerbation of this syndrome by the accumulation of α2u,-globulin or another unknown protein unique to male rats.

In a study evaluating enzyme activities in muscle, intermittent exposure to 300 ppm for 2–15 weeks did not affect muscle succinate dehydrogenase or acetylcholinesterase activities in rats (Savolainen et al. 1985). Muscle creatine kinase activity decreased at 2 weeks, returned to normal levels at week 10, and then significantly increased at 15 weeks in rats exposed to 100 or 300 ppm. These changes in creatine kinase activity were attributed to adaptation at the muscle level to MTBE exposure and were not considered adverse. Musculoskeletal endpoints from this study were considered too limited to establish NOAEL/LOAEL values; therefore, this study was not included in the LSE table.

Based on histological examination of the muscle and skeletal tissues, oral exposure to MTBE appears to be without effects on the musculoskeletal system. Histological examination of the skeletal muscle and sternum of rats given gavage doses up to 1,750 mg/kg/day, 5 days/week, for 4 weeks revealed no treatment-related lesions (Amoco 1992). In drinking water studies, no pathological lesions were reported in “skeletomuscular tissues” in rats in intermediate-duration studies at doses up to 1,153 mg/kg/day (Bermudez et al. 2012), or chronic-duration studies at doses up to 1,119 mg/kg/day (Bermudez et al. 2012; Dodd et al. 2013). In another chronic rat study, histological examination of the cranium (five levels) revealed no treatment-related lesions at gavage doses up to 1,000 ppm, 4 days/week, for 104 weeks (Belpoggi et al. 1995, 1997).

2.9 HEPATIC

Human occupational studies evaluating potential effects of MTBE exposure on hepatic endpoints are limited to a single cross-sectional study reporting no association between non-alcoholic fatty liver disease (NAFLD) and low MTBE exposures in Chinese gas station workers. Additional human studies have

reported hepatic side effects in patients treated with MTBE intracystically for the dissolution of gallstones. Inhalation and oral exposure studies in rats, mice, and rabbits provide suggestive evidence that the liver is a target following acute-, intermediate-, or chronic-duration exposure.

Potential associations between MTBE exposure and NAFLD were evaluated in a cross-sectional study of gas station attendants employed in Southern China (Yang et al. 2016). Among the study participants, 11/71 were diagnosed with NAFLD (10/41 males, 1/30 females). The average MTBE exposure did not differ significantly between workers diagnosed with NAFLD and workers without NAFLD; the average exposure concentration was 0.081 ppm in workers with NAFLD and 0.079 ppm in workers without NAFLD. No associations between the prevalence of NAFLD and MTBE exposure were found (see Table 2-1 for odds ratios). Limitations of this study are the relatively low exposure levels (did not exceed the American Conference of Governmental Industrial Hygienists [ACGIH] Threshold Limit Value [TLV] of 50 ppm), small sample size, and cross-sectional design.

A number of clinical studies of patients receiving MTBE therapy have recorded side effects in liver, bile duct, and gallbladder, due perhaps to leakage or overflow of MTBE. For example, clinical studies reported transient or slight elevations of serum aminotransaminases, hematobilia, or increases in serum bilirubin (Allen et al. 1985a, Bonardi et al. 1986; Holl et al. 1991; Janowitz et al. 1993; Kaye et al. 1990; Leuschner et al. 1991, 1994; Neubrand et al. 1994; Thistle et al. 1989; Uchida et al. 1994). Other effects reported in patients exposed to MTBE by these procedures include cholangitis in patients with elevated serum aminotransaminase levels (Hellstern et al. 1998; Kaye et al. 1990), cholecystitis and pericholecystitis (Schumacher et al. 1990), persistent dilatation of the common bile duct (Tritapepe et al. 1989), transient, reversible edema and inflammation of the gallbladder mucosa (Eidsvoll et al. 1993; Uchida et al. 1994; van Sonnenberg et al. 1991), and bile leak after therapy (Hellstern et al. 1998).

The liver effects observed in laboratory animals include increases in liver weight, alterations in serum clinical chemistry parameters, and histological alterations. In general, the liver effects are minimal to mild in severity and have not been consistently found across studies.

Increases in liver weight have been observed in rats, mice, and rabbits following inhalation and oral exposure to MTBE. Acute inhalation exposure resulted in relative liver weight increases of ≥10% in rats exposed ≥4,000 ppm for 13 days (Dodd and Kintigh 1989), mice exposed to 8,000 ppm for 3 days (Moser et al. 1996), mice exposed to ≥2,000 ppm for 13 days (Dodd and Kintigh 1989), and rabbits exposed to 8,000 ppm on GDs 6–15 (Bevan et al. 1997a). No biologically relevant alterations in liver weight were

observed in rats exposed to MTBE via inhalation at concentrations up to 3,000 ppm for 9–10 days (Conaway et al. 1985; Texaco Inc. 1981), or in mice exposed to concentrations up to 8,000 ppm on GDs 6–15 (Bevan et al. 1997a; Conaway et al. 1985). Intermediate- and chronic-duration inhalation exposures resulted in an 8–45% increase in relative liver weight in rats exposed to 800–8,000 ppm for ≥4 weeks (Bevan et al. 1997b; Bird et al. 1997; Lington et al. 1997); however, no liver weight alterations were observed in rats after 13 weeks of exposure to 1,000 ppm MTBE (Greenough et al. 1980). Several mouse studies conducted by Moser et al. (1996) reported >10% increases in relative liver weight resulting from exposure to 8,000 ppm MTBE for 3–32 weeks. A 9–13% increase in relative liver weight was observed in mice exposed to ≥3,000 ppm for 28 days, and a 39% increase in relative liver weight was observed in mice exposed to 8,000 ppm for 18 months (Bird et al. 1997).

Several acute-duration oral studies in rats reported alterations in liver weight. A small, but statistically significant, 7% increase in relative liver weight was observed in male rats following gavage exposure to 1,428 mg/kg/day for 14 days; no exposure-related liver weight changes were observed in females (Robinson et al. 1990). In other 14-day gavage studies in male rats, significant 13–18% increases in relative liver weight were observed following exposure to ≥1,200 mg/kg/day (Dong-mei et al. 2009; de Peyster et al. 2003, 2014). However, two additional 14-day studies in rats reported no effect on liver weight at doses up to 1,200 mg/kg/day (de Peyster et al. 2014). Longer-term studies have reported increases in liver weight when the MTBE was administered via gavage but not following drinking water exposure. In 28-day studies, reported LOAELs for elevated relative liver weights in rats following daily gavage exposure range from 1,000 mg/kg/day (de Peyster et al. 2003; Williams et al. 2000) to 1,750 mg/kg/day (Amoco 1992); relative liver weights were also significantly increased by 13–15% in rats administered ≥900 mg/kg/day for 90 days (Robinson et al. 1990). In drinking water studies, no changes in liver weight were reported in rats at doses up to 1,153 mg/kg/day for 13 weeks (Bermudez et al. 2012), 384 mg/kg/day for 6 months (Bermudez et al. 2012), 1,119 mg/kg/day for 1 year (Bermudez et al. 2012), or 1,042 mg/kg/day for 2 years (Dodd et al. 2013).

Acute- and intermediate-duration inhalation studies have not found biologically relevant alterations in serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), alkaline phosphatase (ALP), and/or bilirubin levels at concentrations of 3,000 ppm for 9 days (Texaco Inc. 1981), or up to 8,000 ppm for 4–13 weeks (Bird et al. 1997; Lington et al. 1997; Greenough et al. 1980). Oral exposure studies have reported some alterations in serum clinical chemistry parameters. The observed alterations included increased serum AST and LDH levels in male rats administered via gavage ≥1,071 mg/kg/day for 14 days (Robinson et al. 1990), increased serum AST and ALT in rats administered

via gavage 1,000 mg/kg/day for 28 days (de Peyster et al. 2003), and increased serum AST levels in males administered ≥ 300 mg/kg/day via gavage for 90 days (Robinson et al. 1990). No adverse alterations in these serum clinical chemistry parameters were observed after exposure to doses up to 1,600 mg/kg/day for 2 weeks or 1,750 mg/kg/day for 2 or 4 weeks (Amoco 1992; Dong-mei et al. 2009; Williams et al. 2000). Several oral exposure studies reported increases in serum cholesterol levels in rats. Significant increases in serum cholesterol were observed in male rats exposed to 1,428 mg/kg/day and in female rats exposed to 714 or 1,071 mg/kg/day for 14 days, but not 1,428 mg/kg/day (Robinson et al. 1990); in male rats exposed to 1,600 mg/kg/day for 2 weeks (Dong-mei et al. 2009); and in females rats exposed to ≥100 mg/kg/day and male rats at 900 mg/kg/day, but not at 1,200 mg/kg/day, for 90 days (Robinson et al. 1990). In a 4-week study, several measures of cholesterol were significantly altered at doses from 400 to 1,600 mg/kg/day, but no clear pattern was observed (Dong-mei et al. 2009). One 4-week study reported a decrease in serum cholesterol at 1,750 mg/kg/day in male and female rats (Amoco 1992). Another study in rats evaluated serum cholesterol and triglycerides following a 3-month exposure to very low doses of MTBE (0.006, 0.03, or 0.15 mg/kg/day) (Saeedi et al. 2017). Serum triglycerides and cholesterol were decreased at all tested doses, serum high density lipoprotein (HDL) cholesterol was decreased at all tested doses, serum low density lipoprotein (LDL) cholesterol was increased at ≥0.03 mg/kg/day; however, findings were not clearly dose related. Due to lack of clear dose-response and limited endpoints evaluated in this low-dose study, a NOAEL/LOAEL determination was not made based on alterations in serum cholesterol.

Hepatocellular hypertrophy has been reported in rats following oral exposure and in mice following inhalation and oral exposure. Mild hepatocellular hypertrophy was observed in mice exposed to 8,000 ppm for acute-, intermediate-, or chronic-durations (Bird et al. 1997; Moser et al. 1996). In contrast, no histological alterations were observed in the livers of rats following inhalation exposure to 1,000 ppm for 13 weeks (Greenough et al. 1980), or 8,000 ppm for 28 days (Bird et al. 1997), 13 weeks (Lington et al. 1997), 14–19 weeks (Bevan et al. 1997b), or 24 months (Bird et al. 1997). Most oral studies did not report exposure-related hepatic lesions; however, Williams et al. (2000) reported centrilobular hypertrophy in rats exposed to gavage doses ≥500 mg/kg/day for 28 days or 1,500 mg/kg/day for 15 days. In other gavage studies, no exposure-related hepatic lesions were observed in rats at doses up to 1,428 mg/kg/day for 14 days (Robinson et al. 1990), 1,200 mg/kg/day for 90 days (Robinson et al. 1990), or 1,000 mg/kg/day for 104 weeks (Belpoggi et al. 1995, 1997). In drinking water studies, no changes in liver histopathology were reported in rats at doses up to 1,153 mg/kg/day for 13 weeks (Bermudez et al. 2012), 384 mg/kg/day for 6 months (Bermudez et al. 2012), 1,119 mg/kg/day for 1 year (Bermudez et al. 2012), or 1,042 mg/kg/day for 2 years (Dodd et al. 2013).

A number of studies have been conducted in animals to determine possible hepatic side effects of MTBE therapy for gallstone dissolution. These treatments of animals have also resulted in increases in serum levels of liver enzymes, such as serum ALP in dogs (Allen et al. 1985b) and increased serum ALP, ALT, and AST in rabbits (Tritapepe et al. 1989). Lobular necrosis of hepatocytes and mild portal inflammation in the liver was found in pigs given MTBE via the percutaneous transhepatic route to the gallbladder (Chen et al. 1995). Effects on the gallbladder after administration of MTBE via catheter to the gallbladder or the liver include necrosis of the gallbladder and bile ducts, fibrosis of the gallbladder, hyperplastic cholecystitis, inflammation and focal ulceration of the gallbladder mucosa, and edema in rabbits and pigs (Adam et al. 1990; Chen et al. 1995; Dai et al. 1989; Esch et al. 1992; Griffith et al. 1990; McGahan et al. 1988; Vergunst et al. 1994). That these effects were not due to the surgical procedure was demonstrated using sham-treated saline controls or solvent controls.

Mechanisms of Hepatotoxicity. Observed findings of increased liver weight and centrilobular hypertrophy in mice are likely due to an initial increase in metabolic demand on liver cells with exposure to MTBE, resulting in a compensatory increase in hepatocellular proliferation that progresses to hepatocellular proliferation with repeated exposure (Chun and Kintigh 1993; Clary 1997; McGregor 2006). Intraperitoneal injection of rats with MTBE resulted in a 47-fold induction of pentoxyresorufin O-dealkylase activity, an activity associated with cytochrome P4502B1 (Brady et al. 1990). Cytochrome P4502B1 is also involved in the demethylation of MTBE; thus, MTBE appears to induce its own metabolism. In support, liver enzyme induction in female mice intermittently exposed to MTBE at air concentrations of 8,000 ppm for 3 days, 3 weeks, 16 weeks, or 32 weeks was accompanied by increased hepatic deoxyribonucleic acid (DNA) syntheses and/or hepatic hypertrophy (Moser et al. 1996). In a special experiment for cell proliferation evaluations of hepatocytes, male and female mice were exposed to 0, 400, 3,000, or 8,000 for 5 or 23 exposures (Bird et al. 1997). Significantly increased uptake of 5-bromo-2'-deoxyuridine in the nuclei of hepatocytes of female mice, but not male mice, was found at an exposure level of 8,000 ppm, but not $\leq$3,000 ppm, for 5 days. No increase in hepatocellular proliferation was found when mice were similarly exposed for 23 exposures.

In a 4-week gavage study in rats, liver cytochrome P450 enzyme levels were significantly elevated by ~1.5-fold following exposure to 1,500 mg/kg/day from days 1 to 12 (every other day) and 750 mg/kg/day from days 13 to 28 (every other day); time-weighted average (TWA) dose was calculated to be 536 mg/kg/day (de Peyster et al. 2003). Another 2-week study in rats reported dose-related increases in liver microsomal uridine diphosphate glucuronosyl transferase (UDPGT) activity following intermittent

exposure to 50, 100, and 300 ppm for 2 weeks, but not at 6, 10, or 15 weeks (Savolainen et al. 1985). The biological significance of this finding is not clear. Exposure to these levels for up to 15 weeks did not affect rat liver microsomal cytochrome P450 content or the enzymatic activities of NADP-cytochrome c reductase or 7-ethoxycoumarin 0-deethylase. Although induction of liver microsomal enzymes may be potentially adverse, other studies in rats (Bevan et al. 1997b; Bird et al. 1997; Dodd and Kintigh 1989; Lington et al. 1997; Texaco Inc. 1981) indicate that hepatic effects associated with enzyme induction (e.g., increased liver weight) occur in rats only at much higher exposure levels.

Mechanisms for elevated serum cholesterol noted in some oral studies are unknown, and the adversity of this finding is unclear due to the lack of associated hepatic lesions (e.g., fatty liver).

2.10 RENAL

No studies were located regarding renal effects in humans following inhalation, oral, or dermal exposure to MTBE. Data from patients treated with MTBE intracystically for the dissolution of gallstones do not consistently report renal side effects. Based on inhalation and oral studies in animals, the male rat, and to a lesser extent the female rat, are susceptible to kidney damage following exposure to MTBE. Findings in male rats are likely due, in part, to α2u-globulin accumulation, which is not relevant to human health.

A number of clinical studies of patients receiving MTBE therapy have recorded side effects. In two such studies, urinalysis in 1 patient suggested that MTBE did not cause abnormal renal function (Allen et al. 1985a), and no renal failure was found in 12 patients (Uchida et al. 1994). Renal failure and anuria, however, were reported in a patient who experienced severe complications due to extravasation of MTBE from the gallbladder lumen (Ponchon et al. 1988).

Studies in rats have identified sex-related differences in the renal toxicity of MTBE. In male rats, renal alterations have been reported following acute, intermediate, and chronic inhalation and oral exposure. The observed effects include alterations in kidney weight and histopathology.

Increases in absolute and/or relative kidney weights have been inconsistently reported in male rats. Increases in kidney weight were observed following inhalation exposure to 8,000 ppm for 28 days (Bird et al. 1997), inhalation exposure to ≥800 ppm for 13 weeks (Lington et al. 1997), oral exposure to a TWA gavage dose of 1,350 mg/kg/day for 2 weeks (de Peyster et al. 2014), gavage doses of 1,500 mg/kg/day for 15 days or ≥250 mg/kg/day for 28 days (Williams et al. 2000), gavage doses of 1,750 mg/kg/day for

4 weeks (Amoco 1992), gavage doses ≥900 mg/kg/day for 90 days (Robinson et al. 1990), drinking water doses of ≥514 mg/kg/day for 13 weeks or 29 mg/kg/day for 1 year (Bermudez et al. 2012), and drinking water doses of 330 mg/kg/day for 2 years (Dodd et al. 2013). However, other studies have not found alterations in male rat kidney weight following acute or chronic inhalation exposure to concentrations as high as 8,000 ppm (Bird et al. 1997; Dodd and Kintigh 1989), oral acute or intermediate exposure to gavage doses as high as 1,600 mg/kg/day (de Peyster et al. 2014; Dong-mei et al. 2009; Robinson et al. 1990), or chronic exposure to drinking water doses as high as 384 mg/kg/day (Bermudez et al. 2012).

Two studies found increases in serum blood urea nitrogen (BUN) in male rats exposed via inhalation to 1,000 ppm for 13 weeks (Greenough et al. 1980), or via gavage to 1,428 mg/kg/day for 14 days (Robinson et al. 1990). However, most studies did not find biologically relevant alterations in BUN and/or creatinine following acute or intermediate inhalation exposure to up to 8,000 ppm (Bird et al. 1997; Lington et al. 1997; Texaco Inc. 1981), or oral exposure to up to 1,750 mg/kg/day (Amoco 1992; de Peyster et al. 2014; Dong-mei et al. 2009; Robinson et al. 1990). Bird et al. (1997) reported increased urine volume and decreased urinary pH in male rats exposed to 8,000 ppm for 28 days, but there was no other indication of renal damage in serum clinical chemistry or urinalysis measures.

Histological alterations have been observed in the kidney of male rats following inhalation and oral exposure to MTBE. In male rats, increased cell proliferation in the epithelial cells of the renal proximal convoluted tubules were observed in male rats following inhalation exposures to ≥1,500 ppm for 10 days (Prescott-Matthews et al. 1997), with increased cell proliferation following inhalation exposure to ≥3,000 ppm for 5–10 days (Bird et al. 1997; Prescott-Matthews et al. 1997) or 28 days (Bird et al. 1997). Several studies have reported hyaline droplets in the renal proximal convoluted tubules of male rats following inhalation exposure to 8,000 ppm for 13 weeks (Lington et al. 1997), acute oral exposure to ≥972 mg/kg/day (Bermudez et al. 2012; Robinson et al. 1990), and intermediate-duration oral exposure to ≥250 mg/kg/day (Amoco 1992; Bermudez et al. 2012; Robinson et al. 1990; Williams et al. 2000). Chronic-duration exposure resulted in increases in the incidence and severity of chronic progressive nephropathy in male rats following inhalation exposure to ≥400 ppm for 24 months (Bird et al. 1997), oral exposure to ≥29 mg/kg/day for 1 year (Bermudez et al. 2012), or oral exposure to 330 mg/kg/day for 2 years (Dodd et al. 2013). No histological alterations were observed in the kidneys of male rats following inhalation exposure to 3,000 ppm for 9 days (Texaco Inc. 1981) or 1,000 ppm for 13 weeks (Greenough et al. 1980), or following oral exposure to 384 mg/kg/day for 6 months (Bermudez et al. 2012) or 1,000 mg/kg/day for 2 years (Belpoggi et al. 1995, 1997).

In contrast to the findings in male rats, renal effects in female rats have been limited to alterations in kidney weight following acute-, intermediate-, and chronic-duration exposure and histological alterations after chronic exposure. Although some acute- and intermediate-duration studies reported increases in absolute and/or relative kidney weights in female rats (Bermudez et al. 2012; Dodd and Kintigh 1989; Lington et al. 1997; Robinson et al. 1990), these increases were not associated with histological alterations and were not considered biologically relevant. Inhalation or oral exposure to MTBE for ≤1 year did not result in histological alterations in female rats. The highest NOAEL values for each exposure duration were 3,000 ppm for acute inhalation exposure (Texaco Inc. 1981), 8,000 ppm for intermediate inhalation exposure (Bird et al. 1997; Greenough et al. 1980; Lington et al. 1997), 1,428 mg/kg/day acute oral exposure (Bermudez et al. 2012; Robinson et al. 1990), 1,750 mg/kg/day for intermediate oral exposure (Amoco 1992; Bermudez et al. 2012: Robinson et al. 1990), and 1,119 mg/kg/day for a 1-year oral exposure (Bermudez et al. 2012). In chronic-duration studies, elevated kidney weight observed in female rats exposed to ≥3,000 ppm via inhalation and 1,042 mg/kg/day via drinking water for 2 years was considered relevant, as it was accompanied by increased incidence and severity of chronic progressive nephropathy (Bird et al. 1997; Dodd et al. 2013). A third 2-year study did not find altered renal weights or histological alterations at a gavage dose of 1,000 mg/kg/day (Belpoggi et al. 1995, 1997).

Data on renal effects in mice are limited to one intermediate and one chronic inhalation study. No exposure-related changes in renal weight or histology were observed in mice exposed to concentrations up to 8,000 ppm for 28 days (Bird et al. 1997). Following inhalation exposure for 18 months, elevated kidney weights were observed in male mice at ≥400 ppm and female mice at 8,000 ppm (Bird et al. 1997). A slight increase in the pH of the urine was observed in males and females exposed to 8,000 ppm; a slight increase in the gamma globulin fraction was also observed in males at 8,000 ppm. Male mice exposed to 8,000 ppm were reported to have increased mortality and decreased mean survival time due to a slight, but not statistically significant, increase in incidence of obstructive uropathy, which may be related to the increases in pH and gamma globulin fraction.

The urinary bladder does not appear to be affected by MTBE as evidenced by the lack of histological alterations in rats exposed by inhalation to 3,000 ppm for 9 days (Texaco Inc. 1981) or 1,000 ppm for 13 weeks (Greenough et al. 1980), or by oral exposure to 1,000 ppm for 2 years (Belpoggi et al. 1995, 1997).

In one study conducted in rabbits to determine possible side effects of MTBE therapy for gallstone dissolution, histological examination revealed no renal damage (Dai et al. 1989).

Mechanisms of Renal Toxicity. Male rats appear more sensitive to renal toxicity following exposure to MTBE than female rats. The histological findings of protein accumulation and large hyaline droplets in the renal tubules of male rats exposed via inhalation (Bird et al. 1997; Lington et a. 1997) or oral exposure (Bermudez et al. 2012) suggest the involvement of α2u-globulin accumulation. α2u-Globulin is a low molecular weight protein synthesized in large quantities in the male rat liver, secreted into the blood under the influence of testosterone (Alden 1986), and filtered through the glomerulus. Renal tubule cells reabsorb α2u-globulin and sequester it into lysosomes, where it is catabolized into amino acids and peptides. In the normal rat kidney, the rate of catabolism of α2u-globulin is relatively slow compared with other proteins (Swenberg et al. 1989). Chemicals that bind to α2u-globulin yield a complex that is more resistant to the proteolytic enzymes in the lysosomes, which leads to the accumulation of the complex in the tubule cells. Accumulation of the chemical α2u-globulin complex causes lysosomal overload and necrosis of the tubule cells, with subsequent proliferative regeneration. If exposure to the chemical is chronic, then accumulation, necrosis, and subsequent cellular proliferation continues, and can lead to a carcinogenic response. α2u-Globulin nephropathy is a condition specific to male rats; that is, it has not been found in female rats or males or females of any other species, including humans (Ahmed 2001; Bogen and Heilman 2015; McGregor 2006; Phillips et al. 2008).

A 10-day inhalation study by Prescott-Mathews et al. (1997) specifically reported α2u-globulin droplet accumulation in association with proximal tubule necrosis and cell proliferation in male rats following intermittent exposure to ≥1,500 ppm MTBE (Prescott-Mathews et al. 1997). Similarly, hyaline droplets were associated with α2u-globulin accumulation in male rats exposed to 972 mg/kg/day via drinking water for 1 or 4 weeks (Bermudez et al. 2012). However, α2u-globulin levels were not significantly elevated in kidneys of male rats exposed to 972 mg/kg/day via drinking water for 13 weeks (Bermudez et al. 2012). Additionally, while Bird et al. (1997) reported evidence of protein accumulation in association with increased cell proliferation in the epithelial cells of the proximal convoluted tubules at ≥3,000 ppm in male rats exposed for 28 days, immunostaining for α2u-globulin accumulation was negative. This suggests that a mechanism other than a α2u-globulin accumulation (perhaps the accumulation of another protein unique to male rats) may be responsible for the observed increased cell proliferation. Similarly, while male rats exposed to ≥800 ppm for 13 weeks showed a treatment-related increase in area and intensity of α2u -globulin positive staining, the α2u-globulin positive staining was not dose-related and α2u-globulin positive proteinaceous casts were not observed at the junction of the proximal tubules and

thin limb of Henle, which are the classical lesions of other α2u-globulin inducing agents (Swenberg and Dietrich 1991). Taken together, available data suggest that while α2u-globulin induction may contribute to renal effects observed in male rats, other mechanisms (potentially another protein specific to male rats) may also play a role in renal pathogenesis following exposure to MTBE. Furthermore, an additional unknown mechanism may also be involved in the enhancement of chronic progressive nephropathy by MTBE due to observed effects, albeit to a lesser degree, in female rats (Bird et al. 1997).

Metabolism of MTBE to *tert*-butanol (Section 3.1.1) likely underlies, or at least contributes to, any α2u-globulin-mediated effects, as α2u-globulin accumulation, protein droplet accumulation, and renal cell proliferation have been reported in male rats exposed to *tert*-butanol at roughly the same potency as MTBE (Ahmed 2001; Bogen and Heilman 2015; McGregor 2006), although modeling predicts that MTBE has a greater binding affinity for α2u-globulin than *tert*-butanol (Leavens and Borghoff 2009).

The effect of intermittent inhalation exposure to 50–300 ppm for 2–15 weeks on rat kidney microsomal enzymes has been studied (Savolainen et al. 1985). Cytochrome P450 content was reported to be significantly increased only after 15 weeks of exposure to 100–300 ppm, while UDPGT and NADP-cytochrome c reductase activities were significantly increased only after 2 weeks of exposure. The enzymatic activity of 2-ethoxycoumarin 0-deethylase was not affected. Although induction of kidney microsomal enzymes may be potentially adverse, other studies (Bird et al. 1997; Greenough et al. 1980; Lington et al. 1997; Texaco Inc. 1981) indicate that microscopic renal lesions and increased kidney weight due to enzyme induction occur in animals only at much higher exposure levels.

2.11 DERMAL

Skin exposure to MTBE vapors in inhalation studies did not result in dermal effects in humans or animals. However, direct exposure to liquid MTBE resulted in skin irritation and damage in rabbits and guinea pigs. No adverse dermal effects were noted in oral studies in animals.

No associations between skin irritation or rash and exposure to MTBE in gasoline were observed in cross-sectional occupational (CDC 1993a) or population-based studies (Wisconsin DHSS 1995) (see Table 2-1). In controlled human inhalation experiments, no differences in incidence of skin rash or dry skin were observed in volunteers during or after exposure to MTBE at ≤1.7 ppm for 1 hour (Cain et al. 1996; Prah et al. 1994). Because any observed changes would likely be attributed to direct vapor contact, dermal endpoints from these studies are included in the dermal LSE table (Table 2-4).

No gross or histopathological lesions were found on the skin of rats exposed to gavage doses up to 1,750 mg/kg/day, 5 days/week, for 4 weeks (Amoco 1992). Similarly, no gross or histopathological lesions of the skin or subcutaneous tissues were observed in rats exposed to gavage doses up to 1,000 mg/kg/day, 4 days/week, for 104 weeks (Belpoggi et al. 1995, 1997).

Direct exposure of the skin to MTBE vapors in air during inhalation studies did not result in dermal effects. No irritation or treatment-related skin lesions were observed during clinical, gross, and/or histological examination in rats exposed to airborne MTBE at concentrations up to 8,000 ppm for 13 days (Dodd and Kintigh 1989) or 13 weeks (Greenough et al. 1980; Lington et al. 1997). Alopecia was commonly observed in rats exposed to 250, 1,000 or 2,500 ppm for 16–28 weeks, but it was not considered to be related to MTBE exposure because the incidence was similar in the exposed and control groups (Biles et al. 1987). In chronic-duration studies, histological examination of the skin revealed no treatment-related lesions in rats or mice exposed to airborne MTBE at concentrations up to 8,000 ppm for 24 or 18 months, respectively (Bird et al. 1997). Because inhalation exposure to chemicals may result in dermal effects due to direct contact of the vapor on the skin, skin irritation effects in animals following inhalation exposure are included in the dermal LSE table (Table 2-4).

Application of 0.5 mL or 10,000 mg/kg ARCO MTBE (96.2% MTBE) or commercial MTBE (99.1% MTBE) to the intact or abraded skin of rabbits resulted in slight to severe erythema, blanching, epidermal thickening, acanthosis, or focal necrosis (ARCO 1980). In a dermal sensitization test in guinea pigs (see Section 2.14), local irritation and increased erythema developed at the site after the initial intradermal injection of 0.5 mL of a 1% MTBE solution (ARCO 1980).

2.12 OCULAR

Eye irritation has been noted in workers and motorists exposed to fumes from gasoline containing MTBE. However, eye irritation has not been reported in healthy volunteers exposed to pure MTBE at concentrations up to 50 ppm. In laboratory animals, eye irritation has also been observed in animals following exposure to high MTBE concentrations during inhalation studies. Direct exposure to liquid MTBE resulted in eye irritation and damage in rabbits. No adverse ocular effects were noted in oral studies in animals.

Several occupational studies evaluated potential associations between eye irritation and MTBE exposure following the introduction of MTBE into gasoline during the oxyfuel program in United States during the 1990s (see Table 2-1). Several of these studies report an increase in self-reported eye irritation during the oxyfuel program in Alaskan workers with occupational exposure to gasoline containing MTBE (e.g., taxi drivers or health-care workers who travelled routinely in cars), compared either with individuals with low exposure (e.g., noncommuter students) or workers exposed to gasoline that did not contain MTBE (Alaska DHSS 1992a, 1992b; Moolenaar et al. 1994). However, these studies only provide suggestive evidence due to several limitations, including lack of a referent group (Alaska DHSS 1992b only), small to modest subject numbers, lack of statistical analysis of incidence data, potential influence of widespread media coverage and public opposition to the oxyfuel program, and/or lack of consideration for other confounding factors (e.g., other exposures, including potential combustion products of MTBE). No clear evidence of increased eye irritation was observed in occupationally exposed workers, compared with unexposed referents, in similar studies during the oxyfuel program conducted in Connecticut (CDC 1993b; White et al. 1995) or New Jersey (Mohr et al. 1994).

Results from population-based studies evaluating the potential association between eye irritation and MTBE exposure due to the oxyfuel program are mixed (see Table 2-1). In a population-based telephone survey, a statistically significant increase in risk of eye irritation was observed in residents of metropolitan Milwaukee, Wisconsin, in which oxyfuel was used, compared to residents of non-metropolitan Wisconsin (MTBE-free gasoline); however, the risk for eye irritation was not increased for residents of metropolitan Chicago, Illinois (oxyfuel) compared to non-metropolitan Wisconsin (Wisconsin DHSS 1995). The results in Milwaukee may have been biased by knowledge of the oxyfuel program and potential health effects due to increased media coverage in Milwaukee because, in the telephone survey, familiarity with MTBE as a reformulated gasoline additive was reported by 54% of the Milwaukee residents, 23% of Chicago residents, and 40% of the Wisconsin residents. Additionally, non-metropolitan Wisconsin may not have been an appropriate referent group for the Chicago residents. One ecological study also reported a statistically significant increase in doctor's visits with diagnostic codes pertaining to eye irritation in Philadelphia, Pennsylvania in 1997 (during the sixth year of the oxyfuel program), compared to 1992 (at the initiation of the oxyfuel program) based on medical record review (Joseph and Weiner 2002). The study authors concluded that "some environmental factor" in the mid-1990s was associated with immune system findings and suggested that this factor is MTBE. However, this study has several major limitations, primarily a study design that does not allow for control for confounders (other chemical exposures, occupation, concomitant diseases, sex, age, race, etc.), that preclude meaningful conclusions.

In controlled human inhalation experiments, no differences in self-reported symptoms of eye irritation (e.g., dry, itching, or irritated eyes; tired or strained eyes; burning eyes) were observed in volunteers during or after exposure to MTBE at air levels ≤1.7 ppm for 1 hour (Cain et al. 1996; Prah et al. 1994), or ≤50 ppm for 2 hours (Johanson et al. 1995; Nihlén et al. 1998a). Additionally, no exposure-related effects were observed in quantitative measures of ocular irritation (blinking frequency, eye redness score, tear film break-up time, or conjunctival epithelial damage) in subjects exposed to ≤50 ppm for 2 hours (Johanson et al. 1995; Nihlén et al. 1998a). Because any observed changes would likely be attributed to direct vapor contact, ocular endpoints from these studies are included in the dermal LSE table (Table 2-4).

No gross lesions were found in the eyes, exorbital lacrimal glands, or Harderian glands and no histopathological lesions were found in the eyes (glands not examined microscopically) in rats exposed to gavage doses up to 1,750 mg/kg/day MTBE for 4 weeks (Amoco 1992). In drinking water studies, no gross or histopathological lesions of the eye were reported in rats in intermediate-duration studies at doses up to 1,153 mg/kg/day (Bermudez et al. 2012), or chronic-duration studies at doses up to 1,119 mg/kg/day (Bermudez et al. 2012; Dodd et al. 2013).

Direct instillation of ARCO MTBE (96.2% MTBE) or commercial MTBE (99.1% MTBE) into the eyes of rabbits resulted in ocular irritation regardless of whether or not the eyes were washed after exposure; however, ARCO MTBE was more irritating than commercial MTBE (ARCO 1980). ARCO MTBE induced corneal opacities, chemosis, and conjunctival redness, while commercial MTBE caused slight conjunctival redness and some discharge, but no corneal opacities. In a similar study, delayed and reversible congestion of the conjunctivae, palpebral thickening, and hypersecretion were observed in the eyes of rabbits following direct instillation of MTBE (Snamprogetti 1980).

Direct exposure of the eyes to MTBE vapors during inhalation exposure has also resulted in ocular effects in animals. Single 4–6-hour exposures to MTBE vapors resulted in lacrimation at air levels ≥8,000 ppm, with irritation and ocular discharge at concentrations ≥18,892 ppm (ARCO 1980; Daughtrey et al. 1997). Inhalation exposure for 9 days to concentrations ≥100 ppm caused higher incidences of lacrimation and conjunctival swelling in exposed rats than in controls; however, gross and histological examination of the eyes revealed no lesions (Texaco Inc. 1981). Pregnant mice exposed to 250–2,500 ppm on GDs 6–15 had a slight increase in the incidence of lacrimation during exposure (Conaway et al. 1985). In another inhalation developmental study in mice, lacrimation with periocular encrustations was observed in mouse dams at 8,000 ppm (Bevan et al. 1997a). Similarly, in a 2-generation study in rats, ocular discharges and

periorbital encrustation were observed in F1 adults exposed to 8,000 ppm for 10 weeks before breeding and throughout mating and gestation (Bevan et al. 1997b). However, eye irritation and other ocular effects, as determined histologically or by ophthalmoscopy, were not found in rats exposed to concentrations up to 8,000 ppm for 13 days (Dodd and Kintigh 1989) or for 13 weeks (Greenough et al. 1980; Lington et al. 1997). No exposure-related clinical signs of eye irritation were noted in rats exposed to concentrations up to 2,500 ppm for 16–28 weeks; lacrimation was among the most common effects observed, but incidences were similar between controls and exposed animals (Biles et al. 1987). In chronic-duration inhalation studies, swollen periocular tissue was observed in male rats intermittently exposed to concentrations ≥3,000 ppm for up to 24 months (Bird et al. 1997); however, no exposure-related lesions were observed in the eye. No treatment-related clinical signs of irritation or ocular lesions were observed in mice exposed to concentrations up to 8,000 ppm for 18 months (Bird et al. 1997). Because inhalation exposure to chemicals may result in ocular effects due to direct eye contact with vapor in the air, eye irritation effects in animals following inhalation exposure are included in the dermal LSE table (Table 2-4).

Blepharospasm was also reported in F0 rats from the 2-generation study and rats and mice from chronic inhalation studies at concentrations ≥3,000 ppm (Bevan et al. 1997b; Bird et al. 1997); however, this is likely a neurological effect associated with inhalation of MTBE rather than evidence of eye irritation from direct vapor exposure.

2.13 ENDOCRINE

No studies were located regarding endocrine effects in humans following inhalation, oral, or dermal exposure to MTBE. Studies in patients treated with MTBE intracystically for the dissolution of gallstones do not indicate pancreatic damage following treatment. Based on inhalation and oral studies in laboratory animals, the adrenal gland may be a target of toxicity following exposure to high levels of MTBE. There is no clear evidence of toxic effects on other non-reproductive endocrine organs/systems following MTBE exposure in animals. Effects to reproductive endocrine glands and hormones are discussed in Section 2.16 (Reproductive).

A number of clinical studies of patients receiving MTBE therapy have investigated effects on the pancreas. In one study of 75 patients administered MTBE via percutaneous intracystic infusion, follow-up examination 6–42 months after therapy revealed that none had pancreatitis (Thistle et al. 1989).

Furthermore, pancreatic function tests administered to eight patients 1 year after intraductal administration of MTBE revealed no pancreatic abnormalities (Tritapepe et al. 1989).

Inhalation and oral exposure studies in laboratory animals have not found alterations in organ weight or histology of the pancreas. No pancreatic alterations were observed in rats following inhalation exposure to ≤3,000 ppm (Texaco Inc. 1981), ≤8,000 ppm (Bevan et al. 1997b; Greenough et al. 1980; Lington et al. 1997), or ≤8,000 ppm (Bird et al. 1997) for acute, intermediate, or chronic durations, respectively, or in mice exposed to ≤8,000 ppm for a chronic duration (Bird et al. 1997). Similarly, no histopathological alterations were observed in the pancreas of rats following oral exposure ≤1,750 mg/kg/day for an intermediate duration (Amoco 1992), or ≤1,042 mg/kg/day for a chronic duration (Belpoggi et al. 1995, 1997; Dodd et al. 2013). Several studies conducted in animals to determine possible side effects of MTBE therapy for gallstone dissolution have examined the pancreas histologically. No treatment-related histological lesions were found in the pancreas of rabbits (Adam et al. 1990; Dai et al. 1989), dogs (Allen et al. 1985b), or pigs (McGahan et al. 1988; Vergunst et al. 1994).

A number of inhalation and oral exposure studies in rats and mice evaluated the potential of MTBE to affect the adrenal gland. The results of these studies provide some suggestive evidence that the adrenal gland is a target; however, the results are inconsistent and additional data are needed. Increases in absolute and/or relative adrenal weights have been inconsistently found following acute-, intermediate-, or chronic-duration exposure. Increases in adrenal weight were reported in rats following acute inhalation exposure to 8,000 ppm (Dodd and Kintigh 1989), intermediate-duration inhalation exposure to ≥3,000 ppm (Bird et al. 1997; Lington et al. 1997), acute-duration oral exposure to ≥600 mg/kg/day (de Peyster et al. 2014), and intermediate-duration oral exposure to ≥800 mg/kg/day (de Peyster et al. 2003, 2014; Amoco 1992; Williams et al. 2000). Adrenal weight increases have also been observed in mice following chronic inhalation exposure to 8,000 ppm (Bird et al. 1997). Several inhalation and oral exposure studies have not found significant increases in adrenal weight in rats following acute-duration inhalation exposure to ≤3,000 ppm (Texaco Inc. 1981), chronic inhalation exposure to ≤8,000 ppm (Bird et al. 1997), acute oral exposure to ≤1,428 mg/kg/day (de Peyster et al. 2014; Robinson et al. 1990), intermediate oral exposure to ≤1,500 mg/kg/day (Bermudez et al. 2012; Williams et al. 2000), or chronic oral exposure to ≤1,119 mg/kg/day (Bermudez et al. 2012; Dodd et al. 2013); no alterations in adrenal weight were reported in mice following exposure to 8,000 ppm for 13 days, 4 months, or 8 months (Dodd and Kintigh 1989; Moser et al. 1998). Histological alterations consisting of a loss of zona reticularis tissue was found in mice following inhalation exposure to 8,000 ppm for 4 or 8 months (Moser et al. 1998). Interpretation of this finding is limited by the lack of incidence data and other studies confirming

this finding. No histological alterations were observed in the adrenal gland of rats following inhalation exposure to 3,000 ppm for 9 days (Texaco Inc. 1981), intermediate or chronic inhalation exposure to 8,000 ppm (Bird et al. 1997; Lington et al. 1997), intermediate oral exposure to ≤1,750 mg/kg/day (Amoco 1992; Bermudez et al. 2012; Robinson et al. 1990; Williams et al. 2000), or chronic oral exposure to ≤1,119 mg/kg/day (Belpoggi et al. 1995, 1997; Bermudez et al. 2012; Dodd et al. 2013). Similarly, no histological alterations were observed in the adrenal gland of mice exposed via inhalation to 8,000 ppm for 18 months (Bird et al. 1997).

Altered corticosterone levels have also been reported in rats following inhalation and oral exposure to MTBE. In a 13-week study, a 3-fold increase in corticosterone was observed in male and female rats at 8,000 ppm; no exposure-related changes were observed in aldosterone or adrenocorticotropic hormone levels (Lington et al. 1997). In a 24-month study in which rats were exposed intermittently to 400, 3,000, or 8,000 ppm, decreased levels of corticosterone were found at 81 weeks in male rats exposed to 8,000 ppm (this group was terminated at week 82 because of high mortality from chronic progressive nephropathy) (Bird et al. 1997). However, corticosterone levels were increased in male and female mice after exposure to 8,000 ppm at week 79 of an 18-month study (Bird et al. 1997). In oral studies, a 2-fold increase in serum corticosterone was observed in male rats exposed to gavage doses ≥600 mg/kg/day for 2 weeks (de Peyster et al. 2014), or 800 mg/kg/day for 4 weeks (de Peyster et al. 2003). However, no changes in serum corticosterone were observed in male rats exposed to doses up to 1,500 mg/kg/day every other day for 12 days followed by exposure to doses up to 750 mg/kg/day for an additional 16 days (TWA doses up to 536 mg/kg/day) (de Peyster et al. 2003). The toxicological significance of these transient and inconsistent changes in corticosterone levels in rats and mice is questionable. One potential reason for inconsistent results between studies may be due to time-of-day-dependent variations in corticosterone levels; however, studies did not report at what time of day blood was collected.

Laboratory animal studies examining the thyroid gland have not found alterations in organ weight or histology following inhalation exposure to ≤3,000 ppm for an acute duration (Texaco Inc. 1981), inhalation exposure to ≤8,000 ppm for an intermediate or chronic duration (Bird et al. 1997; Greenough et al. 1980), oral exposure to 1,750 mg/kg/day for an intermediate duration (Amoco 1992; Bermudez et al. 2012), or oral exposure to ≤1,119 mg/kg/day for a chronic duration (Belpoggi et al. 1995, 1997; Bermudez et al. 2012; Dodd et al. 2013).

Special clinical chemistry analysis was conducted in mice intermittently exposed to MTBE for 28 days followed by a 16-day recovery period (Chun and Kintigh 1993). Serum total triiodothyronine (T3), total

thyroxine (T4), and thyroid stimulating hormone (TSH) were evaluated. Total T4 and TSH were significantly elevated by 30 and 26%, respectively, in male mice at 8,000 ppm at the end of the 28-day exposure period. In contrast, no changes were observed in similarly exposed females at the end of the exposure period, but total T4 was significantly decreased after 3 days of recovery. These alterations were not considered to be biologically significant because they were transient and not associated with histopathological thyroid lesions. A second study reported a decrease in serum total T3 in male rats exposed to daily gavage doses of ≥1,000 mg/kg/day for 28 days (Williams et al. 2000). No changes were observed in serum total T3 at doses up to 1,500 mg/kg/day for 15 days or serum total T4 or TSH at doses up to 1,500 mg/kg/day for 15 or 28 days. The thyroid was not examined for weight or histopathological changes in this study. This finding was not considered biologically relevant due to the small magnitude of change (18%) and lack of evidence for thyroid damage from other oral studies.

Evidence for altered weight or histology in other endocrine organs is limited. In a 24-month study in rats, hyperplasia of the parathyroid glands was observed in males at ≥400 ppm; however, this lesion was secondary to chronic progressive nephropathy, which occurred at the same exposure concentrations (Bird et al. 1997). No treatment-related histopathological lesions were found in the pituitary in this study. Other studies have not reported effects on the parathyroid glands following inhalation or oral exposure (Amoco 1992; Belpoggi et al. 1995, 1997; Bird et al. 1997; Dodd et al. 2013; Greenough et al. 1980; Texaco Inc. 1981). In female mice, a 20–44% decrease in absolute and relative pituitary weight was observed following exposure to 8,000 ppm for 4 or 8 months; this finding was accompanied by hyaline droplets containing adrenal corticotrophin hormone (ACTH) in the pars intermedia of the pituitary gland (Moser et al. 1998). In other studies in rats and mice, no histopathological lesions were observed in the pituitary gland (Amoco 1992; Belpoggi et al. 1995, 1997; Bermudez et al. 2012; Bevan et al. 1997b; Bird et al. 1997; Dodd et al. 2013; Greenough et al. 1980; Lington et al. 1997).

2.14 IMMUNOLOGICAL

Human studies are too limited to determine if MTBE exposure alters immune function. Immune function tests in laboratory animals were limited to a negative skin sensitization study. Data from inhalation and oral studies in laboratory animals that evaluated immune organ weight and histology, but not immune function, provide limited evidence of proliferation of lymphoreticular tissues in rats. These lesions may be preneoplastic in nature (see Section 2.19, Cancer).

Two ecological studies evaluated potential associations between exposure to MTBE in gasoline during the oxyfuel program and immune endpoints (see Table 2-1). The rate of treatment for asthma (based on medical insurance records) was not increased in Fairbanks or Anchorage, Alaska over the winter of 1992–1993 (during the oxyfuel program), compared with the number of claims during the two preceding winters (prior to the oxyfuel program) (Gordian et al. 1995). Similarly, asthma diagnosis was not increased in Philadelphia, Pennsylvania in 1997 (during the 6th year of the oxyfuel program) compared with 1992 (at the initiation of the oxyfuel program) based on medical record review, although a diagnosis of wheezing was statistically increased in 1997 compared with 1992 (Joseph and Weiner 2002). Additionally, diagnostic codes pertaining to immune function (upper respiratory infection, middle ear infection) and allergies (wheezing, skin rash, allergic rhinitis, general allergy) were significantly increased in 1997 compared with 1992 (Joseph and Weiner 2002). The study authors concluded that "some environmental factor" in the mid-1990s was associated with immune system findings and suggested that this factor is MTBE. However, this study has several major limitations, primarily a study design that does not allow for control for confounders (other chemical exposures, occupation, concomitant diseases, sex, age, race, etc.), that preclude meaningful conclusions.

A small occupational study in Fairbanks, Alaska did not find any differences in pre- and post-shift plasma interleukin-6 levels in 22 mechanics exposed to automobile emissions derived from oxyfuels containing MTBE; interleukin-1 levels were below the level of detection at both time points (Duffy 1994). In controlled human inhalation experiments, MTBE exposure did not result in increased inflammatory markers in nasal lavage fluid and/or alterations in immune cell counts in tear fluid or nasal lavage fluid at ≤1.7 ppm for 1 hour (Cain et al. 1996; Prah et al. 1994), or at ≤50 ppm for 2 hours (Johanson et al. 1995; Nihlén et al. 1998a). No concentration-related increases in nasal swelling, as determined via blocking index, were observed at concentrations ranging from ≤50 ppm for 2 hours (Johanson et al. 1995; Nihlén et al. 1998a). Because any observed changes would likely be attributed to direct vapor contact, immune endpoints from these studies are included in the dermal LSE table (Table 2-4).

No animal inhalation studies evaluating the function of the immune system were identified. However, several inhalation studies evaluated immune organ weight and/or histology. Acute intermittent exposure of rats for 9 days to concentrations up to 3,000 ppm did not produce gross or histological lesions in bone marrow, lymph nodes, or spleen (Texaco Inc. 1981). Similarly, no gross or histopathological lesions were observed in lymph nodes of rats after exposure to concentrations up to 8,000 ppm for 13 days (Dodd and Kintigh 1989). One intermediate-duration study reported a higher incidence of lymphoid hyperplasia in submandibular lymph nodes in male rats exposed to 8,000 ppm for 13 weeks; incidence of

hemosiderosis in the spleen was non-significantly elevated in males at this concentration, but interpretation of results is unclear due to high background rate (Lington et al. 1997). However, other intermediate- and chronic-duration studies in rats did not report organ weight changes or gross or histopathological lesions in the spleen, thymus, or lymph nodes at exposures up to 8,000 ppm (Bevan et al. 1997b; Bird et al. 1997; Greenough et al. 1980). In mice exposed to MTBE for 18 months, absolute spleen weights were decreased in male and female mice at 8,000 ppm, but no treatment-related gross or histopathological lesions accompanied the decreased spleen weights (Bird et al. 1997). Furthermore, no treatment-related lesions were found in the lymph nodes, thymus, or bone marrow.

In 28-day studies in rats and mice, decreased absolute and relative spleen weights were found in both sexes of rats and in female, but not male, mice following exposure to 8,000 ppm; however, no histological examination of the spleen was performed, so adversity could not be determined (Bird et al. 1997).

No animal oral studies evaluating the function of the immune system were identified; several studies evaluated immune organ weight and/or histology. Oral administration of 1,428 mg/kg/day MTBE for 14 days significantly reduced absolute spleen weight and absolute and relative thymus weights in female rats, but not male rats; however, these findings were not associated with histopathological changes in either organ in either sex (Robinson et al. 1990). Similar results were obtained following 90 days of treatment with daily gavage doses of 100–1,200 mg/kg MTBE (Robinson et al. 1990). In a 4-week gavage study, rats given doses up to 1,750 mg/kg/day had no gross pathological changes in the bone marrow, mesenteric lymph nodes, mandibular lymph nodes, spleen, or thymus (Amoco 1992). This treatment did not produce microscopic histopathological changes in all tissues examined (i.e., mesenteric lymph nodes, spleen, or thymus). In intermediate duration drinking water studies, no changes in spleen or thymus weight or histology were reported in rats at doses up to 1,153 mg/kg/day for 13 weeks or 384 mg/kg/day for 6 months (Bermudez et al. 2012).

In a 104-week study, in which male and female rats were given gavage doses of 250 or 1,000 mg/kg/day, 4 days/week, an increased incidence of dysplastic proliferation of lymphoreticular tissues (hyperplastic lymphoid tissues, at various body sites, consisting of atypical lymphoid cells, usually lympho-immunoblasts) was observed in females at both doses (Belpoggi et al. 1995, 1997). The increase was greater at the low dose than at the high dose. Since dose-related increased incidences of lymphomas and leukemia were observed in the female rats (see Section 2.19), more of the dysplastic proliferation lesions might have developed into the lymphomas and leukemias in the high-dose female, suggesting that the dysplastic proliferation represents a preneoplastic lesion. No histopathological lesions were found in the

spleen or thymus. In a 1-year drinking water study, no changes in spleen or thymus weight or histology were reported in male or female rats at doses up to 384 or 1,119 mg/kg/day, respectively (Bermudez et al. 2012). Similarly, no exposure-related changes in spleen weight or spleen, thymus, or lymph node histology were observed in male or female rats at drinking water doses up to 330 or 1,042 mg/kg/day, respectively, for 2 years (Dodd et al. 2013).

In a dermal sensitization test, guinea pigs received an initial intradermal injection of 0.5 mL of a 1% MTBE solution, followed by intradermal injection of 0.1 mL every other day for 3 weeks for a total of 10 injections (ARCO 1980). Two weeks after the 10^{th} injection, a challenge dose of 0.05 mL was injected. The injection sites were evaluated at 24 and 48 hours after treatment and scored for erythema, edema, and color. MTBE produced no significant increase in response to the challenge compared with the initial sensitizing or inducing injection.

2.15 NEUROLOGICAL

Effects consistent with transient CNS depression have been reported in humans exposed to MTBE in fuel or via MTBE therapy for gallstone dissolution, including headache, nausea or vomiting, dizziness, drowsiness, confusion, and a feeling of spaciness or disorientation. No subjective symptoms or alterations in performance on neurobehavioral tests were observed in volunteers following acute exposure to low air levels of MTBE (≤50 ppm). In laboratory animals, MTBE is a CNS depressant following high-concentration inhalation exposure or high-dose gavage. Effects are transient, generally subsiding within hours of exposure, and do not increase in severity with duration of study. Exposure to MTBE via drinking water, as opposed to bolus gavage doses, does not appear to cause CNS depressive effects. There is no evidence of structural damage to the central or peripheral nervous systems via inhalation or oral exposure.

Following several anecdotal reports of neurological symptoms associated with introduction of MTBE into gasoline during the oxyfuel program in the United States during the early 1990s, the CDC conducted several studies evaluating potential associations between MTBE exposure and neurological symptoms (see Table 2-1). Several of these studies report an increase in self-reported neurological symptoms (headache, nausea or vomiting, dizziness, or spaciness) during the oxyfuel program in workers from Alaska with occupational exposure to gasoline containing MTBE (e.g., taxi drivers; policemen, toll booth workers, and parking garage attendants exposed to automobile exhaust; health-care workers who travelled routinely in cars), compared either with individuals with low level exposure (e.g., noncommuter students)

or workers exposed to gasoline that did not contain MTBE (Alaska DHSS 1992a, 1992b; Moolenaar et al. 1994). A similar study in New York reported increased headache and dizziness in one group of individuals occupationally exposed to MTBE (policemen, toll booth workers, parking garage attendants), but not another group with higher exposure levels (automobile repair shop and service station attendants) (CDC 1993a), compared to individuals with low exposure (office workers, college students). However, these studies only provide suggestive evidence due to several limitations, including the lack of a referent group (Alaska DHSS 1992b only), small to modest subject numbers, lack of statistical analysis of incidence data, potential influence of widespread media coverage and public opposition to the oxyfuel program, and/or lack of consideration for other confounding factors (e.g., other exposures, including potential combustion products of MTBE). No evidence of increased neurological symptoms was observed in occupationally exposed workers, compared with unexposed referents, in similar studies during the oxyfuel program conducted in Connecticut (CDC 1993b; White et al. 1995) or New Jersey (Mohr et al. 1994).

Results from population-based studies evaluating the potential association between self-reported neurological symptoms and MTBE exposure due to the oxyfuel program are mixed (see Table 2-1). In a population-based telephone survey, a statistically significant increase in risk of headache, but not nausea, dizziness, or spaciness, was observed in residents of metropolitan Milwaukee, Wisconsin, in which oxyfuel was used, compared to residents of non-metropolitan Wisconsin (MTBE-free gasoline); however, the risk was not increased for any neurological symptom for residents of metropolitan Chicago, Illinois (oxyfuel) compared to non-metropolitan Wisconsin (Wisconsin DHSS 1995). The results in Milwaukee may have been biased by knowledge of the oxyfuel program and potential health effects due to increased media coverage in Milwaukee because, in the telephone survey, familiarity with MTBE as a reformulated gasoline additive was reported by 54% of the Milwaukee residents, 23% of Chicago residents, and 40% of the Wisconsin residents. Additionally, non-metropolitan Wisconsin may not have been an appropriate referent group for the Chicago residents. One ecological study also reported a statistically significant increase in doctor's visits with diagnostic codes pertaining to neurological symptoms (headache, nausea, dizziness) and an increase in visits with diagnostic codes for spaciness in Philadelphia, Pennsylvania in 1997, during the 6th year of the oxyfuel program, compared to 1992, the year that the oxyfuel program was initiated, based on medical record review (Joseph and Weiner 2002). The study authors concluded that "some environmental factor" in the mid-1990s was associated with neurological findings and suggested that this factor is MTBE. However, this study has several major limitations, primarily a study design that does not allow for control for confounders (other chemical exposures, occupation, concomitant diseases, sex, age, race, etc.), that preclude meaningful conclusions. Another ecological

study in Fairbanks and Anchorage, Alaska (Gordian et al. 1995) did not find an increased rate of treatment for headaches (based on medical insurance records) over the winter of 1992–1993 (during the oxyfuel program), compared with the number of claims during the two preceding winters (prior to the oxyfuel program). However, this study would miss mild and/or transient neurological effects associated with MTBE exposure that would not result in seeking medical attention.

In controlled human inhalation experiments, no increases in self-reported neurological symptoms (headache, difficulty in memory or concentration, depressed feelings, unusual tiredness, fatigue, drowsiness, tension, irritability, nervousness, dizziness, lightheadedness, mental fatigue, "fuzziness," or pain, stiffness, or numbness of the back, shoulders, neck, hands, or wrists) were observed in volunteers during or after exposure to MTBE at ≤1.7 ppm for 1 hour (Cain et al. 1996; Prah et al. 1994). Similarly, no increases in headache, fatigue, feeling of sickness, dizziness, or intoxication were observed in volunteers following exposure to ≤50 ppm for 2 hours during light exercise (Johanson et al. 1995; Nihlén et al. 1998a). Additionally, neurobehavioral test evaluating symbol-digit substitution, switching attention, and mood scales did not show any differences in performance when measured 1 hour prior to exposure or during the last 15 minutes of a 1-hour exposure to ≤1.7 ppm (Cain et al. 1996; Prah et al. 1994).

A number of clinical studies of patients receiving MTBE therapy for gallstone dissolution have recorded neurological effects that are typical of transient CNS depression and have been described as drowsiness, mild sedation, somnolence, confusion, coma, vertigo, and dizziness (Allen et al. 1985a; Bonardi et al. 1986; Brandon et al. 1988; Di Padova et al. 1986; Eidsvoll et al. 1993; Kaye et al. 1990; McNulty et al. 1991; Murray et al. 1988; Neoptolemos et al. 1990; Ponchon et al. 1988; Saraya et al. 1990; Thistle et al. 1989; Tobio-Calo et al. 1992; van Sonnenberg et al. 1986; Williams et al. 1990).

Laboratory animal studies conducting neurobehavioral assessments have reported a number of alterations following inhalation exposure. An acute rat study examined neurobehavior using a functional observation battery (FOB) and motor activity evaluation after a 6-hour exposure to MTBE (Daughtrey et al. 1997). Findings included abnormal gait (duck walk progressing to ataxia) in females at ≥4,000 ppm and males at 8,000 ppm. Other effects noted at 8,000 ppm in males included labored respiration pattern, decreased muscle tone, decreased performance on a treadmill, and increased hind limb splay. Other effects noted in females included decreased hind limb grip strength at ≥4,000 ppm and labored respiration and increased latency to rotate on the inclined screen at 8,000 ppm. These effects were seen at 1 hour after exposure, but not at 6 or 24 hours after exposure, consistent with transient CNS depression. The time course of

changes in motor activity corresponded with the functional observation battery findings and supported the exposure-related CNS depression. No neurological effects were observed at 800 ppm for 6 hours.

A detailed neurobehavioral assessment was also conducted in rats in a preliminary 13-day range-finding study (Dodd and Kintigh 1989). Results of the detailed behavioral observations included ataxia, decreased startle and pain reflexes, and/or decreased muscle tone immediately after exposure for all males and most females in the 8,000-ppm group. No treatment-related behavioral alterations were found in any rats at 2,000 or 4,000 ppm when tested immediately following exposure or for the 8,000 ppm groups when retested one hour after the initial testing. However, during the exposure period, clinical signs of CNS depression were observed at ≥2,000 ppm (lowest concentration tested), including hypoactivity at ≥2,000 ppm and ataxia at ≥4,000 ppm. In a 13-week study, ataxia was observed after exposure to 8,000 ppm during the first 4 weeks, but no exposure-related, toxicologically relevant changes were observed in FOB or motor activity testing after 4, 8, or 13 weeks of exposure (Daughtrey et al. 1997).

Another intermediate-duration study evaluated neurobehavioral effects (barbiturate-induced sleeping time, spontaneous motility, motor activity, righting reflex, grasping reflex on horizontal and vertical poles, and inclined screen test) in mice exposed to MTBE at 50,000 ppm for 10 minutes/day or 80,000 ppm for 5 or 10 minutes/day for 30 days (5 days/week). No exposure-related clinical signs or changes in neurobehavior were observed (Snamprogetti 1980).

Numerous other inhalation studies that did not rigorously test neurobehavior also reported clinical signs of CNS depression at high exposure levels; findings apparently did not increase in incidence or severity with duration of study. In acute lethality studies, 4-hour exposures ≥18,892 ppm (lowest concentration tested) result in ataxia, loss of righting reflex, hyperpnea, incoordination, and prostration in rats (ARCO 1980). Repeat-exposure studies across all durations consistently reported transient signs of CNS depression in rats, mice, and rabbits, transient signs of CNS depression were consistently reported during 6-hour exposure periods, including hypoactivity at ≥2,000 ppm, blepharospasm and decreased startle reflex at ≥3,000 ppm, ataxia and drowsiness at ≥4,000 ppm, and prostration and decreased muscle tone at 8,000 ppm (Bevan et al. 1997a, 1997b; Bird et al. 1997; Dodd and Kintigh 1989; Lington et al. 1997; Moser et al. 1996; MTBE Committee 1990a; Vergnes and Chun 1994; Vergnes and Morabit 1989). In a 13-week intermediate-duration study, MTBE induced anesthesia was observed in rats exposed intermittently to 250–1,000 ppm (Greenough et al. 1980), but the lowest concentration resulting in anesthesia was not specified. The incidence and severity of effect did not increase with duration of study. However, one 9-day inhalation study did not report clinical signs of neurotoxicity in rats during or

following 6-hour exposure periods to concentrations up to 3,000 ppm (Texaco Inc. 1981), and no clinical signs were observed in mice exposed to concentrations up to 8,000 ppm for 1 or 2 days (Vergnes and Kintigh 1993).

Consistent with inhalation studies, gavage studies reported clinical signs of CNS depression at high exposure levels. In general, onset of neurological signs was rapid, but they disappeared or were markedly reduced within 24 hours. In acute studies in rats, findings included drowsiness at ≥400 mg/kg/day, lethargy and ataxia at ≥600 mg/kg/day, and transient anesthesia/sedation at ≥1,000 mg/kg/day; no clinical signs of neurotoxicity were observed at 40 mg/kg/day (ARCO 1980; de Peyster et al. 2003, 2014; Dong-mei et al. 2009; MTBE Committee 1990b; Robinson et al. 1990). In mice, acute gavage exposure resulted in ataxia and lethargy at 2,000 mg/kg/day, but not 1,000 mg/kg/day (de Peyster et al. 2008). In intermediate-duration studies, clinical signs of neurotoxicity included transient hypoactivity at ≥440 mg/kg/day and transient ataxia and anesthesia at ≥1,200 mg/kg/day; no clinical signs of neurotoxicity were observed at 90 mg/kg/day (Amoco 1992; Robinson et al. 1990). However, no behavioral changes were reported in rats following exposure to gavage doses up to 1,000 mg/kg/day, 4 days/week, for 104 weeks (Belpoggi et al. 1995, 1997).

In contrast to gavage studies, no clinical signs of neurotoxicity were observed in drinking water studies in male rats at doses up to 972 mg/kg/day for 13 weeks, 384 mg/kg/day for 6 or 12 months, or 330 mg/kg/day for 2 years, or female rats at doses up to 1,153 mg/kg/day for 13 weeks, 1,119 mg/kg/day for 12 months, or 1,042 mg/kg/day for 2 years (Bermudez et al. 2012; Dodd et al. 2013).

There is no evidence of structural damage to the central or peripheral nervous system following inhalation exposure to MTBE. No exposure-related, biologically relevant changes in brain weight were observed at concentrations up to 8,000 ppm for 13 or 28 days in rats or mice (Bird et al. 1997; Dodd and Kintigh 1989), or 13 weeks in rats (Daughtrey et al. 1997; Lington et al. 1997). No gross or histological lesions of the brain were observed in rats intermittently exposed to concentrations up to 3,000 ppm for 9 days (Texaco Inc. 1981). No gross and histological lesions of the brain, spinal cord, and/or sciatic nerve were observed at 8,000 ppm in rats following exposure for 13 weeks or 24 months (Bird et al. 1997; Daughtrey et al. 1997; Greenough et al. 1980; Lington et al. 1997), or in mice following exposure for 18 months (Bird et al. 1997).

There are sporadic findings of alterations in brain weight reported in oral studies. In 2-week gavage studies, inconsistent alterations in brain weight included a significant 7% decrease in absolute (but not

relative) brain weight in male rats at 1,428 mg/kg/day, but not in male rats exposed to doses up to 1,071 mg/kg/day or female rats at doses up to 1,428 mg/kg/day (Robinson et al. 1990); a significant 6–12% increase in relative (but not absolute) brain weight was observed in male rats at ≥600 mg/kg/day (de Peyster et al. 2014); and no exposure-related changes were observed in male or female rats at doses up to 1,600 mg/kg/day (Dong-mei et al. 2009). In intermediate-duration studies, no exposure related changes in brain weight were observed in male or female rats at gavage or drinking water doses up to 1,750 or 1,153 mg/kg/day, respectively (Amoco 1992; Dong-mei et al. 2009; Robinson et al. 1990). In a 1-year drinking water study, relative, but not absolute, brain weights were significantly increased by 11–14% in all male exposure groups (≥29 mg/kg/day), but a dose-related trend was not observed. Additionally, no exposure-related changes in brain weight were observed at drinking water doses up to 1,042 mg/kg/day for 2 years (Dodd et al. 2013). None of these brain weight findings are considered biologically relevant because they are inconsistent, associated with alterations in body weight, and/or are small in magnitude. Additionally, there is no evidence of histopathological changes in studies that evaluated nervous tissue histology. No histopathological lesions were observed in the central or peripheral nervous system of rats exposed to acute gavage doses up to 1,428 mg/kg/day (Robinson et al. 1990), intermediate gavage or drinking water doses up to 1,750 or 1,153 mg/kg/day, respectively (Amoco 1992; Bermudez et al. 2012), or chronic gavage or drinking water doses up to 1,000 or 1,119 mg/kg/day, respectively (Belpoggi et al. 1995, 1997; Bermudez et al. 2012; Dodd et al. 2013).

A number of studies have been conducted in animals by intravenous and intraperitoneal injection, or by infusion into the gallbladder to determine possible side effects of MTBE therapy for gallstone dissolution. Effects noted in animals after administration of MTBE by other routes (Allen et al. 1985b; Dai et al. 1989; McGahan et al. 1988; Snamprogetti 1980; Tritapepe et al. 1989) are similar to those noted for inhalation and oral exposure.

Mechanisms of Neurotoxicity. The presence of MTBE and/or *tert*-butanol in the brain may account for the CNS toxicity of MTBE. A proposed mechanism for CNS depression at high MTBE exposure levels is interaction of MTBE and/or *tert*-butanol with the γ-aminobutyric acid$_A$ ($GABA_A$) receptor, which has been shown to be a target of several classes of well-known volatile anesthetics (e.g., ethers, alcohols) (Martin et al. 2002, 2004). Since potentiation of the $GABA_A$ receptor is correlated with induction of anesthesia for these compounds, the ability of MTBE and its metabolites to bind to the $GABA_A$ receptor was evaluated *in vitro* using a competitive binding assay with *tert*-butylbicycloorthobenzoate (TBOB), a known $GABA_A$ ligand *(*Martin et al. 2002). Both MTBE and *tert*-butanol resulted in concentration-dependent inhibition of TBOB. Further analysis showed that MTBE and *tert*-butanol enhanced $GABA_A$

receptor function in a concentration-related manner, resulting in increased chloride uptake in isolated synaptoneurosomes composed of pre- and postsynaptic membranes from adult rat cerebral cortex (Martin et al. 2004). MTBE was a more potent $GABA_A$ agonist than *tert*-butanol. Together, these studies suggest that MTBE and/or *tert*-butanol can directly interact with the $GABA_A$ receptor, resulting in decreased neuronal excitability via increased chloride conductance. The biological outcome of this interaction would be CNS depression, consistent with observed effects in laboratory animals.

An intracerebral exposure study in rats by Zheng et al. (2009) further supports that MTBE interacts with the $GABA_A$ receptor and associates this interaction with altered neurobehavior. In this study, rats exposed to MTBE via intracerebroventricular injection at doses of 50% MTBE (v/v in saline) or 100% MTBE showed a dose-related impairment in spatial learning and memory (as assessed by the Morris water maze), compared with controls given saline injections only. Study authors attribute impaired learning and memory to observed increases in the $GABA_A$ receptor subunit α1 density in the hippocampus coupled with reduced phosphorylation of extracellular-signal regulated kinase 1/2 (ERK1/2) in the hippocampus, as the cascade initiated by ERK1/2 phosphorylation is considered essential for hippocampus-dependent learning and memory.

Neither rat brain succinate dehydrogenase nor acetylcholinesterase activity was affected by exposure for 15 weeks to 50–300 ppm, indicating these pathways do not contribute to MTBE neurotoxicity (Savolainen et al. 1985).

2.16 REPRODUCTIVE

No studies were located regarding reproductive effects in humans following exposure to MTBE. Based on animal inhalation studies, the male and female reproductive tract do not appear to be primary targets of MTBE toxicity. Based on animal oral studies, there is some evidence of male reproductive toxicity in rats; however, findings are inconsistent across studies and exposure durations. There is no evidence of impaired female fertility or damage to the female reproductive system following oral exposure.

Studies evaluating reproductive function following MTBE exposure include 1- and 2-generation inhalation studies in rats, an oral fertility study in male rats, and an ovarian function and *in vitro* fertilization study following acute oral exposure in female rats. No evidence of reproductive toxicity was observed in 1- and 2-generation inhalation studies in rats (Bevan et al. 1997b; Biles et al. 1987). In the 1-generation study, evaluation of fertility, and reproductive systems, performance of male and female

rats, and the reproductive development of offspring revealed that MTBE had no structural effect on the reproductive system or effect on reproductive performance of male and female rats following exposure to ≤2,500 ppm for 16–28 weeks (pre-mating through gestation of two litters) (Biles et al. 1987). In the 2-generation study, F0 and F1 adult exposure to concentrations up to 8,000 ppm for 14–19 weeks (premating through lactation) had no effect on F0 or F1 reproductive parameters including gestational length and mating, fertility, and gestational indices (Bevan et al. 1997b). No histological lesions were seen in the vagina, uterus, ovaries, testes, epididymides, seminal vesicles, or prostate. However, in the only oral exposure study evaluating male fertility, a 40% decrease in fertility was observed in male rats exposed to 1,600 ppm MTBE for 30 days and mated with unexposed females (Khalili et al. 2015). In a specialized acute female reproductive study in rats, exposure to 520 mg/kg/day via drinking water for 2 weeks did not alter the percentage of female ovulations, number of oocytes per female, fragility of oocytes, *in vitro* fertilization rates of harvested oocytes (incubated with sperm from untreated rats), or number of penetrated sperm/oocyte (Berger and Horner 2003).

Additional inhalation studies evaluating reproductive endpoints, but not reproductive function, are limited to general toxicity studies that included measurement of weight and histopathological examination of male and female reproductive tissues. More data are available from oral studies that evaluated the potential of MBTE to induce alterations in reproductive hormones in male rats and mice, organ weight, and histological alterations of reproductive tissues in male and female rats and mice, and sperm alterations in rats and mice.

In inhalation studies, no changes in testicular weight or histology of male reproductive tissues (testes, epididymides, prostate, and/or seminal vesicles) were observed in rats following exposure to ≤8,000 ppm for acute (Dodd and Kintigh 1989; Texaco Inc. 1981), intermediate (Greenough et al. 1980; Lington et al. 1997), or chronic (Bird et al. 1997) durations. Similar to rats, no changes in testicular weight or histology of male reproductive tissues (testes, epididymides, prostate, and/or seminal vesicles) were observed in mice following chronic inhalation exposure to ≤8,000 ppm (Bird et al. 1997).

In general, oral exposure studies in rats have not reported alterations in testes weights following acute-duration exposure to ≤1,428 mg/kg/day (Bermudez et al. 2012; de Peyster et al. 2014; Robinson et al. 1990), intermediate-duration exposure to ≤1,600 mg/kg/day (Bermudez et al. 2012; de Peyster et al. 2003; Gholami et al. 2015; Li et al. 2008; Robinson et al. 1990), or chronic-duration exposure to ≤1,000 mg/kg/day (Belpoggi et al. 1995, 1997; Dodd et al. 2013). Similarly, no alterations in testes weight were observed in mice exposed to 2,000 mg/kg/day every other day for 1 week (Billitti et al. 2005;

de Peyster et al. 2008), or 1 mg/kg/day for 4 weeks (de Peyster et al. 2008). One study reported a decrease in testicular weight in rats exposed to ≥400 mg/kg/day for 2 weeks (Dong-mei et al. 2009), and one study reported an increase in relative testicular weight in rats exposed to 1,500 mg/kg/day for 28 days, but not 15 days (Williams et al. 2000). Inconsistent results were also found for histological alterations in the testes. In a 2-week study in rats exposed via gavage, histopathological examination of testicular tissues showed a compact and regular arrangement of cells in the seminiferous tubules of control animals; however, rats exposed to 1,600 mg/kg/day showed fewer compact cells in testicular tissue compared to controls (Li et al. 2008). A 4-week study by this group reported abnormally arranged cells and shedding of the seminiferous epithelium in rats exposed to ≥800 mg/kg/day (Li et al. 2008). A third study in rats reported damage to seminiferous tubules, including pyknosis, decreased cell layers, increased cell distance, and vacuoles at doses of ≥400 mg/kg/day; observed lesions increased in severity with increasing dose (Gholami et al. 2015). An increase in the incidence of testicular Leydig cell tumors following chronic exposure to 1,000 mg/kg/day has also been reported (Belpoggi et al. 1995, 1997). Other studies in rats reported no non-neoplastic alterations in the testes following acute exposure to ≤1,428 mg/kg/day (Bermudez et al. 2012; Robinson et al. 1990), intermediate exposure to ≤1,750 mg/kg/day (Amoco 1992; Bermudez et al. 2012; Robinson et al. 1990; Williams et al. 2000), or chronic exposure to ≤1,000 mg/kg/day (Belpoggi et al. 1995, 1997; Bermudez et al. 2012; Dodd et al. 2013). A similar inconsistency was observed in mouse studies. Two studies reported no histological alterations in the testes in mice exposed to 2,000 mg/kg/day for 1 week (de Peyster et al. 2008), or 1 mg/kg/day for 4 weeks (de Peyster et al. 2008). Another 1-week study reported a significant increase in the mean number of seminiferous tubules with gross disruption (compared with controls) in the testes of mice exposed to 2,000 mg/kg/day (Billitti et al. 2005). However, there was no evidence of increased seminiferous epithelial vacuolization, multinucleated giant cells, marginated chromatin, or sloughing, and the study authors did not consider gross disruption alone to be a biologically relevant finding. No alterations in prostate, seminal vesicles, or epididymides weight or histology were observed in rats exposed to ≤1,500 mg/kg/day for intermediate durations (Bermudez et al. 2012; Williams et al. 2000) or ≤1,000 mg/kg/day for chronic durations (Belpoggi et al. 1995, 1997; Bermudez et al. 2012; Dodd et al. 2013).

A small number of studies evaluated potential effects on sperm. Dose-related decreases in the number of spermatocytes and spermatids were observed in rats exposed to ≥800 mg/kg/day for 30 days; no exposure-related changes were observed in Sertoli cells or spermatogonia (Gholami et al. 2015). In a 4-week study in rats, a significant dose-related increase in the percentage of abnormal sperm in the seminiferous tubules was observed in rats at ≥800 mg/kg/day (Li et al. 2008). A third study did not find

any alterations in sperm count in rats exposed to 1 mg/kg/day for 4 weeks (de Peyster et al. 2008). In mice, gavage exposure ≤1,000 mg/kg/day for 3 weeks resulted in no effects on the frequency of germ cells in the testes (Ward et al. 1994).

Male reproductive toxicity associated with MTBE exposure may be attributable to direct toxic effect of MTBE on testicular cells, including Sertoli cells and germ cells. Decreased viability, increased plasma membrane damage, and increased ratio of necrotic cells were observed in cultured spermatogenic cells following *in vitro* exposure to MTBE for ≥12 hours; findings were associated with altered sperm morphology (Li and Han 2006; Li et al. 2007). A direct cytotoxic effect was also noted in Sertoli cells following *in vitro* exposure to MTBE for ≥12 hours (Li et al. 2009). In both cell types, reactive oxygen species production and lipid peroxidation were enhanced with MTBE exposure, suggesting that observed cytotoxicity may be mediated via oxidative stress (Li et al. 2007, 2009).

Several studies have evaluated the effect of MTBE on reproductive hormone levels in male rats following oral exposure. Decreases in serum testosterone levels were observed at ≥800 mg/kg/day in 2-week studies (de Peyster et al. 2003; Li et al. 2008) or ≥800 mg/kg/day in 28–30-day studies (de Peyster et al. 2003; Khalili et al. 2015; Li et al. 2008; Williams et al. 2000); intermediate-duration studies to lower doses did not result in significant alterations (de Peyster et al. 2003). However, one study did not observe exposure-related changes in serum or testicular testosterone levels in rats at gavage doses as high as 1,200 mg/kg/day for 2 weeks (de Peyster et al. 2014). A decrease in dihydrotestosterone levels was also observed in rats exposed to 1,500 mg/kg/day for 28 days (Williams et al. 2000). Inconsistent results have been found in acute- and intermediate-duration studies evaluating serum luteinizing hormone (LH) levels, with one study reporting transient increases at ≥400 mg/kg/day for 2 weeks (Li et al. 2008), some studies reporting decreases at 1,200 mg/kg/day for 2 weeks (de Peyster et al. 2003) or 1,500 mg/kg/day for 28 days (Williams et al. 2000), and others reporting no alterations at doses of 800 or 1,600 mg/kg/day for 4 weeks (de Peyster et al. 2003; Li et al. 2008). Khalili et al. (2015) reported reduced serum LH levels after exposure to 800 mg/kg/day, but not 1,600 mg/kg/day, for 30 days. Most studies examining serum follicle stimulating hormone levels did not find alterations at doses as high as 1,600 mg/kg/day for 2 weeks, 28 days, or 30 days (de Peyster et al. 2003; Khalili et al. 2015; Williams et al. 2000); Li et al. (2008) reported an increase following exposure to ≥800 mg/kg/day for 2 weeks, but not following exposure to ≤1,600 for 4 weeks. For serum estradiol, one 2-week exposure study reported increased levels in rats exposed to 1,200 mg/kg/day (de Peyster et al. 2003), while two other studies reported no exposure-related changes at similar doses for 2 weeks or 28 days (de Peyster et al. 2014; Williams et al. 2000). Two studies evaluated serum prolactin levels; one study found a decrease in rats exposed to

1,500 mg/kg/day for 15 days, but not for 28 days (Williams et al. 2000), and the second study did not find alterations at 800 mg/kg/day for 4 weeks (de Peyster et al. 2008). A small number of studies evaluated reproductive hormone levels in male mice. No alterations in serum testosterone levels were observed in mice exposed to 2,000 mg/kg/day every other day for 1 week (Billitti et al. 2005; de Peyster et al. 2008), or to 1 mg/kg/day for 4 weeks (de Peyster et al. 2008). Collectively, the results of these studies in male rats suggest that oral exposure to high doses of MTBE can decrease serum testosterone levels, but does not appear to affect other reproductive hormone levels.

Additional inhalation studies evaluating female reproductive endpoints, but not reproductive function, are limited to general toxicity studies evaluating female reproductive organs. No histological alterations in female reproductive tissues, including uterus, cervix, vagina, fallopian tubes, and/or mammary glands, were observed in rats following inhalation exposure to ≤8,000 ppm for acute (Texaco Inc. 1981), intermediate (Greenough et al. 1980; Lington et al. 1997), or chronic (Bird et al. 1997) durations. In female mice exposed to 8,000 ppm for 4 or 8 months, a 77–83% decrease in absolute and relative uterus weight; a 46–55% decrease in absolute and relative ovary weight; fewer uterine ducts and glands; reduced convolution of the tubular glands in the uterus, cervix and vagina; reduced epithelial layers in the cervix and vagina; and deceased cell proliferation in the uterus were observed (Moser et al. 1998). No treatment-related gross or histopathological lesions were observed in the reproductive organs of female mice exposed to concentrations up to 8,000 ppm for 18 months (Bird et al. 1997).

Similar to inhalation, additional oral studies evaluating female reproductive endpoints, but not reproductive function, are limited to general toxicity studies evaluating female reproductive organs. No adverse effects on female reproductive organ weights or histology were reported in oral exposure studies. Gavage administration of ≤1,428 mg/kg/day MTBE in rats for 14 days (Robinson et al. 1990), ≤1,750 mg/kg/day in rats for 4 weeks (Amoco 1992), ≤1,200 mg/kg/day for 90 days (Robinson et al. 1990), or ≤1,000 ppm for 2 years (Belpoggi et al. 1995, 1997) did not result in alterations in ovarian weight or histological alterations in female reproductive tissues. In drinking water studies, no biologically significant changes in the weight and/or histopathology of the ovary or uterus were reported in rats at doses up to 1,153 mg/kg/day for 13 weeks (Bermudez et al. 2012), or 1,119 mg/kg/day for 1 year (Bermudez et al. 2012). Similarly, no histopathological changes were observed in the ovary, uterus, vagina, or mammary glands of rats exposed to drinking water doses up to 1,042 mg/kg/day for 2 years (Dodd et al. 2013). In mice, gavage exposure to ≤1,000 mg/kg/day for 3 weeks resulted in no effects on the frequency of germ cells in the ovaries (Ward et al. 1994).

2.17 DEVELOPMENTAL

Human studies were limited to a single cohort study evaluating the potential association between MTBE exposure during birth year and diagnosis of autism spectrum disorder (ASD). No studies were located regarding birth outcomes in humans following exposure to MTBE. In animals, developmental toxicity was only observed following inhalation exposure to high concentrations associated with frank maternal toxicity. Available oral studies in animals are inadequate to comprehensively evaluate potential developmental effects following oral MTBE exposure.

In a case-control study, a significant positive correlation was reported between estimated MTBE exposure during the year of birth and risk of ASD diagnosis (see Table 2-1 for odds ratios) (Kalkbrenner et al. 2018). Further analyses indicated that the MTBE association with ASD diagnosis persisted after adjustment for other traffic pollution toxics, including diesel particulate matter and xylenes. However, no associations were observed between estimated MTBE exposure during the year of birth and continuous measures of autism-related traits from the Social Responsiveness Scale (SRS), or measures of autism severity using the Calibrated Severity Score (see Table 2-1 for odds ratios). The study authors acknowledge that the analysis was not adjusted for all measured air toxics, and that the sample size was inadequate for a comprehensive mixture analysis.

MTBE did not cause adverse developmental effects in rats and rabbits following inhalation exposure during gestation. Exposure of female rats to concentrations up to 2,500 ppm from GD 6 to 15 had no effect on percentage of resorption, percentage of live fetuses, mean fetal weights, crown-rump distances, incidence of external malformations, or incidence of fetal soft-tissue and fetal skeletal malformations (Conaway et al. 1985). Similarly, exposure of rabbits to concentrations up to 8,000 ppm from GD 6 to 18 did not change the number of total nonviable fetuses (such as early or late resorptions or dead fetuses), viable implantations, percentage of pre- or post-implantation loss, fetal body weight, sex ratio, or incidence of fetal malformations (Bevan et al. 1997a).

Long-term exposure of male and female rats to concentrations up to 2,500 ppm during premating, mating, and gestational periods for a total of 16–28 weeks had no effect on pup viability, mean pup body weight, external malformations, gross pathology on GD 1, or gonad histology on GD 1 (Biles et al. 1987). A slight, but not statistically significant, increase in the incidence of dilated renal pelvis was observed at 250 and 1,000 ppm; however, incidence at 2,500 ppm was comparable to controls. Exposure of rats for 10 weeks prior to mating, 3 weeks during gestation, and 3 weeks during the postnatal period resulted in

an approximate 10% reduction in F1 female and F2 male and female body weights at ≥3,000 ppm during lactation (Bevan et al. 1997b). The body weight effects occurred only at exposure levels associated with parental toxicity, including signs of clinical neurotoxicity at ≥3,000 ppm and decreased body weights at 8,000 ppm in both F0 and F1 adults. Parental exposure to MTBE did not affect F1 or F2 pup live birth and survival indices, litter size, or sex ratio. In a study designed to evaluate male fertility in rats, no exposure-related changes were observed in offspring number, sex ratio, or gross anomalies following paternal exposure to gavage doses up to 1,600 mg/kg/day for 30 days prior to mating with unexposed females (Khalili et al. 2015).

MTBE has been found to produce developmental effects in mice at concentrations associated with maternal toxicity. Maternal inhalation exposure to concentrations of 250–2,500 ppm from GDs 6–15 had no effects on percentage of resorption, percentage of live fetuses, mean fetal weights, crown-rump distances, incidence of external malformations, or incidence of fetal soft-tissue malformations (Conaway et al. 1985). A slight, but not statistically significant, increase in fused sternebrae was observed in the offspring at ≥250 ppm, while no fused sternebrae were present in controls. In a similar study that exposed mice to higher concentrations (400–8,000 ppm), adverse developmental effects included a 7–21% decrease in fetal weights at ≥4,000 ppm, with increased post-implantation loss/litter, a 29% reduction in live fetuses, increased incidence of cleft palate, and four completely resorbed litters observed at 8,000 ppm (Bevan et al. 1997a). Decreased skeletal ossification was observed in several areas at ≥4,000 ppm (cervical centra, thoracic centra, caudal centra, skull plates/bones, forepaws, hindpaws, and sternebrae); however, overall litter incidence of skeletal malformations (including reduced ossification) was similar across exposure groups. Maternal toxicity consisted of reduced maternal body weight, reduced maternal weight gain, and reduced food consumption at 8,000 ppm, and increased incidence of treatment-related clinical signs of CNS depression at 4,000 and 8,000 ppm. The study authors speculated that the cleft palate could have resulted from maternal stress, which may be related to elevated endogenous maternal blood levels of corticosterone (see Section 2.13, Endocrine), which may produce cleft palate in susceptible strains of mice.

No evidence of altered male reproductive development was observed in mice exposed to 0.02–2 mg/kg/day via drinking water for 51 days from postnatal day (PND) 25/26 to 76/77 (de Peyster et al. 2008). Reproductive endpoints examined included analysis of serum testosterone and estradiol, reproductive organ weights (testes, epididymides, seminal vesicles), and histopathological examination of testes and associated epididymides. There were no clinical signs of toxicity and no significant changes to body weight or liver, kidney, brain, spleen, heart, or lung weight.

2.18 OTHER NONCANCER

No studies were located regarding other noncancer effects in humans following exposure to MTBE. A few oral studies in animals reported altered glucose homeostasis following exposure to MTBE; no alterations in glucose parameters were noted in available inhalation studies.

No exposure-related changes in serum glucose were observed in rats following intermittent inhalation exposure to concentrations up to 8,000 ppm for 13 weeks (Greenough et al. 1980; Lington et al. 1997). In a gavage study, serum glucose was significantly increased by 17% in female rats exposed to 1,428 mg/kg/day (Robinson et al. 1990). In contrast, serum glucose was significantly decreased by 13–24% in female rats exposed to gavage doses ≥300 mg/kg/day for 90 days (Robinson et al. 1990). No changes in serum glucose were observed in male rats following exposure up to 1,428 mg/kg/day for 14 days, or 1,200 mg/kg/day for 90 days (Robinson et al. 1990).

One study in rats was specifically designed to evaluate zinc and glucose homeostasis in rats following a 3-month exposure to very low doses of MTBE (0.006, 0.03, or 0.15 mg/kg/day) (Saeedi et al. 2017). Endpoints examined included serum analysis of fasting blood glucose, zinc, calcium, and copper and ribonucleic acid (RNA) analysis of genes related to zinc and glucose homeostasis in pancreatic tissues. Fasting blood glucose was significantly increased by 3.3-fold at 0.15 mg/kg/day. A small, but statistically significant, reduction in serum calcium of 5% at 0.15 mg/kg/day was not considered biologically relevant due to its small magnitude. However, a statistically and biologically relevant increase in the copper/zinc ratio was observed at 0.15 mg/kg/day (12-fold increase compared to controls). C-reactive protein was also significantly higher in all MTBE exposed groups by ≥2-fold. Several genes involved in zinc and glucose homeostasis were significantly decreased in exposed groups, including insulin1, insulin2, MT1A, and SLC30A8. Due to the unknown adversity of these findings, limited endpoints evaluated, and lack of consistent findings regarding serum glucose effects following MTBE exposure, a NOAEL/LOAEL determination was not made for this study based on alterations in zinc and glucose homeostasis.

2.19 CANCER

No studies were located regarding cancer in humans following exposure to MTBE. Cancer bioassays in animals are available for rats and mice via inhalation exposure and for rats via oral exposure. Increased renal tubular cell tumors were reported in male rats and hepatocellular adenomas were reported in female

mice following chronic inhalation exposure to MTBE. Increased testicular Leydig cell tumors were reported in male rats and lymphomas and leukemia were reported in female rats following chronic gavage exposure to MTBE.

In a 24-month rat inhalation study, neoplastic lesions were observed in both the kidneys and testes of males (Bird et al. 1997). The incidence of renal tubular cell tumors was increased in male rats at ≥3,000 ppm, with a significant increase in combined incidence of adenomas and carcinomas for the 3,000-ppm group compared to controls. Early mortality may have contributed to the lack of a significant increase at 8,000 ppm; this group was terminated at 82 weeks. No renal tubular cell tumors were found in males at 400 ppm. The incidence of testicular interstitial cell adenomas was also increased significantly at 3,000 and 8,000 ppm, compared to controls. However, observed incidences in the exposure groups were within historical controls and the control incidence was low compared to historical data. Since testicular tumors are the most common tumor in this strain of rat, and findings were within historical controls, these tumors were not considered exposure related. No exposure-related tumors were observed in female rats.

In an 18-month mouse inhalation study, a significantly increased incidence of hepatocellular adenoma was observed in female mice at 8,000 ppm (Bird et al. 1997). This finding was accompanied by hepatocellular hyperplasia. For males, there was a nonsignificant increase in hepatocellular carcinomas in the 8,000-ppm group compared to controls. However, re-evaluation and statistical analysis of the incidence of hepatocellular carcinomas, with exclusion of the animals dying before the first tumor occurred, showed a statistically significant increase in male mice at 8,000 ppm compared to controls (Bogen and Heilman 2015; CalEPA 1998). No hepatocellular hyperplasia was observed in males.

In tumor-promotion studies, there was no evidence of hepatic tumor promotion in mice initiated with the known mutagen, N-nitrosodiethylamine, 6 weeks prior to intermittent inhalation exposure to MTBE at concentrations of 8,000 ppm for 16 or 32 weeks (Moser et al. 1996).

In a 104-week gavage study in rats, a dose-related increase in the incidence of lymphomas and leukemia was observed in female rats at 250 or 1,000 mg/kg/day (Belpoggi et al. 1995, 1997). As noted in Section 2.13, there was also an increased incidence in dysplastic proliferation of lymphoreticular tissues in female rats, which was greater at 250 mg/kg/day than at 1,000 mg/kg/day, suggesting that the dysplastic proliferation was preneoplastic. An increase in uterine sarcomas was found in the females only at 250 mg/kg/day. In male rats, there was a statistically significant increased incidence of testicular Leydig

cell tumors at 1,000 mg/kg/day. In a 2-year drinking water study in rats, no exposure-related increases in tumor incidences were observed in males exposed to doses up to 330 mg/kg/day or females exposed to doses up to 1,042 mg/kg/day (Dodd et al. 2013).

IARC has determined that MTBE was not classifiable as to its carcinogenicity in humans (IARC 1999). EPA (IRIS 1993) and HHS (NTP 2016) have not classified the potential for MTBE to cause cancer in humans.

Mechanisms of Carcinogenicity. As discussed below in Section 2.20, MTBE is not a strong mutagenic or clastogenic agent, and while there is evidence that MTBE (and/or its metabolites) can bind directly to DNA, evidence of DNA damage following exposure is inconsistent. Therefore, several comprehensive reviews have evaluated potential nongenotoxic mechanisms for carcinogenic action of MTBE.

Several reviews have evaluated potential mechanisms for renal tumors in male rats following inhalation exposure (Ahmed 2001; Bogen and Heilman 2015; McGregor 2006; Phillips et al. 2008). Collectively, these reviews propose that development of renal tubular cell tumors in male rats is predominantly, if not exclusively, mediated via the well-established α2u-globulin-mediated carcinogenic mode-of-action (MOA), which is not expected to occur in humans. This MOA is characterized by: (1) chemical binding to α2u-globulin; (2) accumulation of the bound protein in lysosomes, forming hyaline droplets; (3) renal tubule cell death; (4) compensatory cell proliferation; (5) population expansion; and (6) renal tubule cell adenoma and carcinoma formation. As discussed in Section 2.10 (Renal), some repeat-exposure studies indicate accumulation of α2u-globulin in hyaline droplets associated with nephropathy in male rats following MTBE exposure. Metabolism of MTBE to *tert*-butanol (Section 3.1.1) likely underlies or at least contributes to this MOA, as α2u-globulin accumulation, protein droplet accumulation, renal cell proliferation, and kidney tumors have been reported in male rats exposed to *tert*-butanol at roughly the same potency as MTBE. An alternate hypothesis for renal tumors is a genotoxic MOA due to metabolic formation of formaldehyde, which is formed in a 1:1 ratio to *tert*-butanol for each molecule of MTBE metabolized (Bogen and Heilman 2015). However, there are two lines of evidence that do not support this hypothesis: (1) a genotoxic MOA based on formaldehyde production does not explain why renal tumors only occur in male rats, and (2) if formaldehyde production underlies renal tumors following MTBE exposure, carcinogenic potency of MTBE would be expected to be greater than *tert*-butanol instead of similar in potency.

Proposed mechanisms for Leydig testicular cell tumors in male rats following oral exposure to MTBE have also been reviewed (Ahmed 2001; Bogen and Heilman 2015; McGregor 2006; Phillips et al. 2008). Recognized MOAs for Leydig cell tumor formation include: (1) testosterone biosynthesis inhibition; (2) androgen receptor antagonism; (3) aromatase inhibition; (4) 5α-reductase inhibition; (5) dopamine agonism; and (6) peroxisome proliferation. As discussed in Section 2.16 (Reproductive), alterations in male hormonal signaling have been reported in some studies following oral MTBE exposure, namely decreases in testosterone. Decreases in testosterone may result from increased clearance of circulating testosterone due to induction of enzymes involved in testosterone metabolism, such as CYP enzymes, uridine diphosphate, and UDP-glucuronosyltransferase. In support, *in vitro* testosterone production was decreased by up to 50% in Leydig cells exposed to MTBE or its metabolite *tert*-butanol and decreased circulating testosterone levels in rats exposed to MTBE via gavage were associated with increased hepatic CYP enzymes and decreased testicular aromatase activity (de Peyster et al. 2003). However, while Leydig cell tumorigens are generally associated with elevated serum LH levels (Ahmed 2001; Clegg et al. 1997; McGregor 2006), available oral MTBE studies report inconsistent alterations in LH levels following exposure, with results showing transient increases (Li et al. 2008), decreases (de Peyster et al. 2003; Williams et al. 2000), or no alterations following exposure (de Peyster et al. 2003; Li et al. 2008). Additionally, i*n vitro* screening assays did not show competitive binding to androgen receptors, aromatase inhibition, or inhibition of steroidogenesis (de Peyster et al. 2014). There is no evidence supporting the other proposed MOAs (5α-reductase inhibition, dopamine agonism, peroxisome proliferation) following MTBE exposure. An alternate proposed mechanism is a nonspecific effect associated with a hormonally mediated cytotoxic stress response due to increased mortality from high incidence of chronic progressive nephropathy observed at dose levels associated with Leydig cell tumors (Bogen and Heilman 2015).

Several reviews have also evaluated potential mechanisms for hepatocellular adenomas in female mice (Ahmed 2001; Bogen and Heilman 2015; McGregor 2006; Phillips et al. 2008). One proposed mechanism for hepatic tumor formation is a nongenotoxic MOA mediated via hormonal disruption, such as antiestrogen-like effects proposed for gasoline-induced tumors. However, neither MTBE nor its metabolites, *tert*-butanol or formaldehyde, were found to competitively bind to the estrogen receptor *in vitro* (Moser et al. 1998). Additionally, exposure to 8,000 ppm MTBE for 4 or 8 months via inhalation did not alter serum estrogen levels or alter the pattern or intensity of estrogen receptor immunoreactivity in female reproductive organs (Moser et al. 1998). Furthermore, a weight-of-evidence assessment reported that MTBE does not have direct endocrine activity based on studies of mammalian and fish models and *in vitro* screening assays (de Peyster and Mihaich 2014). Alternatively, a cytotoxic MOA has been proposed, in which high exposure levels at or exceeding the maximum tolerated dose (MTD)

overwhelm cellular defenses resulting in cell death followed by increased cell proliferation in target organs. Lastly, as with renal tumors, a genotoxic MOA based on formaldehyde production has also been considered for MTBE hepatic tumors; however, detoxification of formaldehyde occurs more rapidly in isolated hepatocytes than metabolism of MTBE to formaldehyde (CalEPA 1998). Therefore, a genotoxic MOA based on metabolism to formaldehyde is not considered likely following MTBE exposure.

The mechanism by which MTBE produced leukemia in female rats (Belpoggi et al. 1995, 1997) is not known; however, the authors discussed the possibility that formaldehyde, a known metabolite of MTBE (see Section 3.1.3), is involved, since formaldehyde increased the incidence of lymphomas and leukemias in male and female rats in other studies from their laboratories. Evidence of decreased viability associated with oxidative stress, lipid peroxidation, damage to mitochondria and lysosomes, and glutathione depletion was reported in human blood lymphocytes following *in vitro* exposure to MTBE (Salimi et al. 2016).

2.20 GENOTOXICITY

The majority of available evidence indicates that MTBE is not mutagenic or clastogenic. There is evidence that MTBE (and/or its metabolites) can bind directly to DNA both *in vitro* and *in vivo*, but findings from studies evaluating evidence of DNA damage are inconsistent. In addition, MTBE was predicted to be nongenotoxic in an analysis by a structure activity relational expert system using results generated by the National Toxicology Program (NTP) for rodent carcinogenicity, *Salmonella* mutagenicity, induction of sister chromatid exchanges and chromosomal aberrations, and structural alerts for genotoxicity (Rosenkranz and Klopman 1991). Results of *in vitro* and *in vivo* genetic testing of MTBE are presented in Tables 2-5 and 2-6, respectively, and summarized below.

Table 2-5. Genotoxicity of Methyl *tert*-Butyl Ether (MTBE) In *Vitro*

		Results		
		Activation		
Species (test system)	Endpoint	With	Without	Reference
Prokaryotic organisms				
Salmonella typhimurium TA1535, *TA1537*, TA1538, TA98, TA100	Gene mutation	–	–	Cinelli et al. 1992
S. typhimurium TA98, TA100, TA104, TA1535	Gene mutation	–	–	Kado et al. 1998

Table 2-5. Genotoxicity of Methyl *tert*-Butyl Ether (MTBE) In *Vitro*

Species (test system)	Endpoint	Results: Activation With	Results: Activation Without	Reference
S. typhimurium TA102	Gene mutation	–	–	McGregor et al. 2005
S. typhimurium TA98, TA100, YG1041, YG1042	Gene mutation	–	–	Vosahlikova et al. 2006
S. typhimurium TA102	Gene mutation	±	–	Williams-Hill et al. 1999
S. typhimurium TA98, TA100	Gene mutation	–	–	Zhou et al. 2000
Nonmammalian eukaryotic organisms				
Saccharomyces cerevisiae D4	Gene mutation	–	–	ARCO 1980
Mammalian cells				
Mouse lymphoma cells L51785	Gene mutation	+	–	ARCO 1980
Chinese hamster V79 fibroblasts	Gene mutation	–	–	Cinelli et al. 1992
Chinese hamster ovary cells	Sister chromatid exchange	±	–	ARCO 1980
Chinese hamster ovary cells	Chromosomal aberrations	–	–	ARCO 1980
NIH/3T3 murine fibroblast cells	Micronucleus induction	–	NT	Zhou et al. 2000
Human lymphocytes	DNA damage	NT	+	Chen et al. 2008
Rat primary hepatocytes	Unscheduled DNA synthesis	NA	–	Cinelli et al. 1992
Rat primary hepatocytes	Unscheduled DNA synthesis	NA	+	Zhou et al. 2000
Isolated DNA				
Calf thymus DNA (ctDNA)	DNA binding	NT	+	Ghasemi and Ahmadi 2014
Anti-parallel human telomeric G-quadruplex DNA (wtTel22)	DNA binding	NT	+	Ghasemi and Ahmadi 2014

– = negative result; + = positive result; ± = equivocal result; DNA = deoxyribonucleic acid; NA = not applicable; NT = not tested

Table 2-6. Genotoxicity of Methyl *tert*-Butyl Ether (MTBE) *In Vivo*

Species (exposure route)	Endpoint	Results	Reference
Mammals			
Mouse (oral)	*Hrpt* mutant frequency in lymphocytes	–	Ward et al. 1994
Rat (oral)	Chromosomal aberrations	–	ARCO 1980
Rats (inhalation)	Chromosomal aberration	–	McKee et al. 1997
Rat (inhalation)	Chromosomal aberrations	–	Vergnes and Morabit 1989
Mouse (oral)	Chromosomal aberrations	–	Ward et al. 1994
Mouse (oral)	Micronuclei in bone marrow	–	Vergnes and Kintigh 1993
Mouse (inhalation)	Micronuclei in bone marrow	–	McKee et al. 1997
Mouse (intraperitoneal)	Micronuclei in bone marrow	–	Kado et al. 1998

Table 2-6. Genotoxicity of Methyl *tert*-Butyl Ether (MTBE) *In Vivo*

Species (exposure route)	Endpoint	Results	Reference
Mouse (oral)	DNA adducts (lung, liver, kidney)	+	Du et al. 2005
Mouse (oral)	DNA adducts (lung, liver, kidney)	+	Yuan et al. 2007
Mouse (inhalation)	Unscheduled DNA synthesis (hepatocytes)	–	McKee et al. 1997
Mouse (inhalation)	DNA repair (hepatocytes)	–	Vergnes and Chun 1994
Eukaryotic organisms			
Drosophila melanogaster	Sex-linked recessive lethal	–	McKee et al. 1997
D. melanogaster	Sex-linked recessive lethal	–	Sernau 1989

– = negative result, + = positive result; DNA = deoxyribonucleic acid

In vitro assays generally indicate that MTBE is not mutagenic. In bacterial cells, MTBE did not induce reverse mutation in *Salmonella typhimurium* in the majority of tested strains both with and without metabolic activation, including TA1535, TA1537, TA1538, TA98, TA100, TA104, YG1041, and YG1042 (Cinelli et al. 1992; Kado et al. 1998; Vosahlikova et al. 2006; Zhou et al. 2000). Reported findings for *S. typhimurium* strain TA102 were inconsistent, with McGregor et al. (2005) reporting a lack of mutagenic and Williams-Hill et al. (1999) reporting weakly mutagenic effects in the presence of metabolic activation only. However, the number of revertants/place induced by MTBE in the study by Williams-Hill et al. (1999) remained within 2-fold of control values (~1.7-fold induction at the highest tested concentration; estimated from graphically presented data); therefore, findings are considered inconclusive. In nonmammalian eukaryotic cells, MTBE was not mutagenic in *Saccharomyces cerevisiae* D4 with or without metabolic activation (ARCO 1980). In mouse cells, MTBE induced forward mutations in mouse lymphoma L5178Y tk^+/tk^- cells in the presence, but not in the absence, of metabolic activation (ARCO 1980). The observed mutation is not attributable to the metabolite *tert*-butanol, which did not induce forward mutations in the L5178Y tk^+/tk^- mouse lymphoma cell assay with or without metabolic activation (McGregor et al. 1988). In hamster cells, MTBE did not induce gene mutation in Chinese hamster V79 fibroblasts (Cinelli et al. 1992).

Available assays indicate that MTBE is not mutagenic *in vivo*. MTBE did not induce sex-linked recessive mutations in *Drosophila melanogaster* (McKee et al. 1997; Sernau 1989). There was no evidence of a dose-related increase in hypoxanthine-guanine phosphoribosyl transferase (hprt) mutant frequency in spleen lymphocytes in mice treated with gavage doses up to 1,000 mg/kg/day for 3 weeks (Ward et al. 1994).

MTBE produced equivocal results for sister chromatid exchange in Chinese hamster ovary cells in the presence of metabolic activation; sister chromatid exchange was not induced without metabolic activation (ARCO 1980). There was no increase in chromosomal aberrations in Chinese hamster ovary cells with or without metabolic activation (ARCO 1980) or micronuclei in NIH/3T3 murine fibroblast cells without metabolic activation (Zhou et al. 2000). Available data indicate that MTBE is not clastogenic *in vivo.* Chromosomal aberrations were not induced in male or female rats following inhalation exposure to MTBE at concentrations up to 8,000 ppm for 6 hours/day for 5 days, compared with unexposed controls (McKee et al. 1997; Vergnes and Morabit 1989). MTBE did not cause chromosomal aberrations in the bone marrow of rats following gavage exposure to 0.04, 0.13, or 0.4 mL/kg/day (30, 96, or 296 mg/kg/day) for 5 days (ARCO 1980). Similarly, no significant induction of chromosome aberrations was observed in spleen lymphocytes in mice following gavage exposure to MTBE doses up to 1,000 mg/kg/day for 3 weeks (Ward et al. 1994). No statistically significant increases in the incidence of micronucleated polychromatic erythrocytes were found in CD-1 mice bone marrow after oral, inhalation, or intraperitoneal exposure (Kado et al. 1998; McKee et al. 1997; Vergnes and Kintigh 1993).

In isolated human lymphocytes, MTBE induced single and double strand breaks and oxidative-based modifications (Chen et al. 2008). Unscheduled DNA synthesis was induced in primary rat hepatocytes following *in vitro* exposure to MTBE in one study (Zhou et al. 2000), but not in another (Cinelli et al. 1992).

In vivo, DNA repair and unscheduled DNA synthesis were not induced in hepatocytes of male or female CD-1 mice exposed to MTBE vapor at concentrations up to 8,000 ppm 6 hours/day for 1 or 2 days (McKee et al. 1997). However, in the Vergnes and Chun (1994) study, the MTBE exposed mice were sacrificed 18 hours after the second exposure, which may have been too late to detect DNA repair. The positive control mice, which were treated intraperitoneally with N-nitrosodemethylamine at 10 mg/kg, were sacrificed 2 hours after the dose and showed increased DNA repair (Vergnes and Chun 1994).

MTBE was shown to directly interact (bind) with isolated human telomeric G-quadruplex DNA and calf thymus DNA (Ghasemi and Ahmadi 2014). Similarly, MTBE forms DNA adducts *in vivo.* Du et al. (2005) administered 0.95, 5.71, and 75.59 µg/kg via gavage to male Kunming mice and found DNA adducts in the lungs, livers, and kidneys, with levels peaking at 12 hours post-exposure. A follow-up study by Yuan et al. (2007), exposed male Kunming mice to 1.86, 13.9, 133, 990, and 11,190 µg/kg via gavage and found similar results. Yuan et al. (2007) also demonstrated a positive dose-response relationship between levels of DNA adducts and MTBE oral exposure.

CHAPTER 3. TOXICOKINETICS, SUSCEPTIBLE POPULATIONS, BIOMARKERS, CHEMICAL INTERACTIONS

3.1 TOXICOKINETICS

- MTBE is readily absorbed following inhalation or oral exposure, and to a lesser extent following dermal exposure.
- Absorbed MTBE is initially widely distributed; the liver contains a large percentage of the initial body burden; smaller amounts are found in lungs, kidney, and testes.
- Most absorbed MTBE is rapidly metabolized; hepatic first-pass metabolism of MTBE is likely following oral exposure.
- Biotransformation of MTBE is generally similar between rats and humans and between sexes.
- MTBE metabolites are rapidly excreted, predominantly in the urine.

3.1.1 Absorption

Results from human studies that employed single inhalation exposures to MTBE at concentrations in the range of 0.5–75 ppm for time periods ranging from 30 minutes to 8 hours indicate that inhaled MTBE is rapidly absorbed from the respiratory tract (e.g., Amberg et al. 1999; Cain et al. 1996; EPA 2003a; Johanson et al. 1995; Lee et al. 2001; Nihlén et al. 1998b; Prah et al. 2004; Vainiotalo et al. 2007). For example, in a study of volunteers exposed at rest to airborne MTBE for 4 hours at 4 or 40 ppm, mean blood MTBE concentrations measured 1.9 and 6.7 µM, respectively, immediately following cessation of exposure (Amberg et al. 1999). Collectively, these studies demonstrate that MTBE plasma levels reach steady state as early as 30 minutes to 2 hours following initiation of exposure and that plasma levels rapidly decrease upon cessation of exposure. Pulmonary retention of inhaled MTBE has been estimated to range from 32 to 66% in humans (Lee et al. 2001; Nihlén et al. 1998b; Vainiotalo et al. 2007). Another study showed that following a 30-minute exposure to 0.5 ppm, the mean fraction of absorbed MTBE dose was 0.73, with blood levels of 0.9–2.5 µg/L at the end of exposure (EPA 2003a). The mean uptake residence time was 5.7 minutes.

The toxicokinetics of inhaled MTBE have been studied in rats (e.g., Amberg et al. 1999; Benson et al. 2001; Miller et al. 1997). Amberg et al. (1999) demonstrated similarities between humans and rats regarding absorption of inhaled MTBE. Following 4-hour exposures to MTBE at 4 ppm, blood MTBE levels measured 1.9 and 2.3 µM among humans and rats, respectively. Similar exposure at 40 ppm resulted in blood MTBE levels of 6.7 and 5.9 µM in humans and rats, respectively.

Benson et al. (2003) exposed male rats to ^{14}C-MTBE by 4-hour inhalation (nose-only) at 4, 40, or 400 ppm. MTBE equivalents were rapidly absorbed into the blood; peak blood concentrations were achieved prior to the end of the 4-hour exposure period and increased with increasing MTBE exposure level. In a rat study involving exposure to high levels of MTBE (400 or 8,000 ppm) for 6 hours, plasma concentrations of MTBE increased rapidly to apparent steady state within 2 hours following the end of a single exposure; peak plasma concentrations reached 14 and 493 µg/mL, respectively (Miller et al. 1997).

Blood MTBE levels were generally related to inhaled dose in rats repeatedly exposed to MTBE at 50, 100, or 300 ppm for 2–5 weeks (Savolainen et al. 1985). At the lower exposure concentrations, peak blood MTBE levels of 11 and 24 nmol/g, respectively (about 1.3 and 2.9 µg/mL, respectively) were reached at 6 weeks. At the highest exposure concentration, the peak blood level of 72 nmol/g (about 8.6 µg/mL) was reached at 15 weeks after decreasing from 66 nmol/g at week 6 to 55 nmol/g at week 10. Thus, MTBE blood levels continue to rise for a substantial amount of time during prolonged exposure, indicating a relatively long time for steady state to be reached following repeated exposures.

MTBE is readily absorbed from the gastrointestinal tract of humans. Among three male and three female volunteers administered ^{13}C-MTBE orally (in water) at 5 or 15 mg, MTBE blood concentrations averaged 0.10 and 0.69 µM, respectively, at 1-hour posttreatment and declined rapidly thereafter (Amberg et al. 2001). In another study of 14 volunteers administered 2.8 mg of MTBE in 250 mL of Gatorade®, a mean peak blood MTBE level of 0.17 µmol/L was reached at 15 minutes posttreatment and declined rapidly thereafter (Prah et al. 2004).

MTBE is also readily absorbed from the gastrointestinal tract of rats. Peak MTBE blood concentrations (average of nearly 20 µg/mL) were reached within 15 minutes posttreatment at 40 mg MTBE/kg (Miller et al. 1997). Blood MTBE levels declined rapidly thereafter. A peak blood concentration of 5.9 µg/mL MTBE was reached in 0.9 hours in rats given a single oral dose of MTBE at 0.379 mg/kg (Li et al. 1991).

Limited information regarding absorption of dermally applied MTBE indicates that absorption occurs to a lesser extent than absorption from the respiratory or gastrointestinal tract. Prah et al. (2004) immersed the hand and forearm of 14 male volunteers in a sealed container (mean concentration of 50 µg MTBE/mL) for 1 hour and took periodic blood samples during and following exposure period. Dermal absorption peaked at 0.05 µmol/L at 65 minutes following the initiation of exposure. An estimated permeability coefficient (K_p) was 0.028 cm/hour. Another study evaluated dermal uptake in volunteers showering or

bathing with water containing 150 µg/L MTBE for 30 minutes using continuous breath analysis (EPA 2003b). Small increases in breath concentrations of MTBE indicated dermal absorption from bath water, with the mean uptake residence time of 21.2 minutes. No measurable increase in exhaled MTBE was observed following a 30-minute shower (EPA 2003b).

In rats exposed to MTBE via 6-hour dermal application at 40 or 400 mg/kg in isotonic saline under occlusive conditions, MTBE was detected in plasma within 10 minutes following the initiation of treatment and peak plasma MTBE concentration was achieved within 2–4 hours after dosing (Miller et al. 1997). Based on mass balance studies, MTBE absorption was estimated to have been approximately 16 and 34% of the administered radioactivity at the low and high dose, respectively. Schenk et al. (2018) reported an *in vitro* steady-state flux of 0.00194 g/cm^2/hour (19.4 g/m^2/hour) and a permeability coefficient of 0.000585 cm/hour for MTBE across pig skin.

3.1.2 Distribution

As MTBE is a small molecular weight, volatile, lipophilic compound, it is expected to readily cross biological membranes during its transport via the blood. Although no studies were located regarding distribution of MTBE in humans after inhalation, oral, or dermal exposure, there is no reason to expect that the tissues to which MTBE distributes would differ from those of animals (fatty tissue, brain, liver kidney). Furthermore, MTBE has been detected in fatty tissue and breast milk of patients who received MTBE via intracystic infusion for dissolution of gallstones (Leuschner et al. 1991).

Benson et al. (2003) evaluated the disposition of ^{14}C-MTBE equivalents in rats following 4-hour inhalation exposures at 4, 40, or 400 ppm. Immediately following cessation of exposure, MTBE equivalents were highest in the liver and accounted for approximately 10, 8, and 3% of the initial body burden for the 4, 40, and 400 ppm exposure groups, respectively. At 72 hours postexposure, MTBE equivalents in the liver were only 1, 0.8, and 0.4% of the initial body burden. At all exposure levels, other tissues (lung, kidney, heart, brain, and testes) each accounted for ≤ 2% of the initial body burden immediately following cessation of exposure and <0.2% of the initial body burden at 72 hours postexposure.

Levels of MTBE in samples of blood, cerebral hemispheres, and perirenal fat were monitored in Wistar rats sacrificed at selected times following repeated inhalation exposure to MTBE for up to 15 weeks at 50, 100, or 300 ppm (Savolainen et al. 1985). Blood MTBE levels were generally related to exposure

concentration. At the two lower exposure concentrations, peak blood MTBE levels of 11 and 24 nmol/g, respectively (about 1.3 and 2.9 µg/mL, respectively) were reached at 6 weeks. At the highest exposure concentration, the peak blood level of 72 nmol/g (about 8.6 µg/mL) were reached at 15 weeks. Brain MTBE levels peaked at 2–6 weeks at all exposure levels, with brain levels of 11, 28, and 87 nmol/g at 10, 100, and 300 ppm, respectively (about 1.3, 3.4, and 10 µg/mL, respectively). MTBE levels were considerably higher in perirenal fat than in blood and brain tissues at all exposure concentrations. At 2 weeks, the perirenal fat concentrations of MTBE were 184, 245, and 642 nmol/g at 50, 100, and 300 ppm, respectively. The perirenal concentration of MTBE declined to 81–92 nmol/g at 6–15 weeks in the 50-ppm exposed group but remained relatively unchanged at the higher exposure concentrations.

The disposition of radioactivity was evaluated in rats exposed to ^{14}C-MTBE by nose-only inhalation (400 or 8,000 ppm once for 6 hours or 400 ppm repeatedly for 15 days), dermal application (40 or 400 mg/kg for 6 hours), or intravenous injection (40 mg/kg) (Miller et al. 1997). Radioactivity from expired air, urine, and feces was determined for 48 hours following inhalation exposures and for 7 days following dermal and intravenous injection exposures. Determination of total radioactivity in tissues/carcass was performed at sacrifice.

Radioactivity recovered from tissue/carcass following single inhalation exposure was approximately 13% in the 400-ppm exposure group and 4% in the 8,000-ppm exposure group (Miller et al. 1997). The higher percentage of radioactivity in the tissues after the low dose may be due to shifts in metabolic and elimination pathways as enzyme systems become saturated at high doses (e.g., increased exhalation of unchanged MTBE at 8,000 ppm; see Section 3.1.4 for more details). In the rats repeatedly exposed at 400 ppm for 15 days, the percentage of total radioactivity recovered from tissues/carcass was approximately 11%. Percentages of radioactivity in tissues/carcass following dermal exposure at 40 or 400 mg/kg were 0.12 and 0.07%, respectively. Only 0.42% of the administered radioactivity was recovered in the tissues/carcass of rats administered ^{14}C-MTBE intravenously at 40 mg/kg. In both single and repeated exposure studies, mean radioactivity in various tissues (e.g., liver, kidneys, lungs, heart, brain, gonads, femur, perirenal fat, muscle) was very low (<1% of the total dose), indicating that MTBE or its metabolites do not accumulate in tissues after short-term exposure (MTBE Committee 1990a, 1990b).

In rats that received a single intraperitoneal dose of 232 mg/kg ^{14}C-MTBE, the total accumulation of radioactivity in tissues averaged 3.39, 1.94, and 1.14% of the administered dose at 15 minutes, 6 hours, and 24 hours after dosing, respectively (API 1984). At 15 minutes, radioactivity was found primarily in

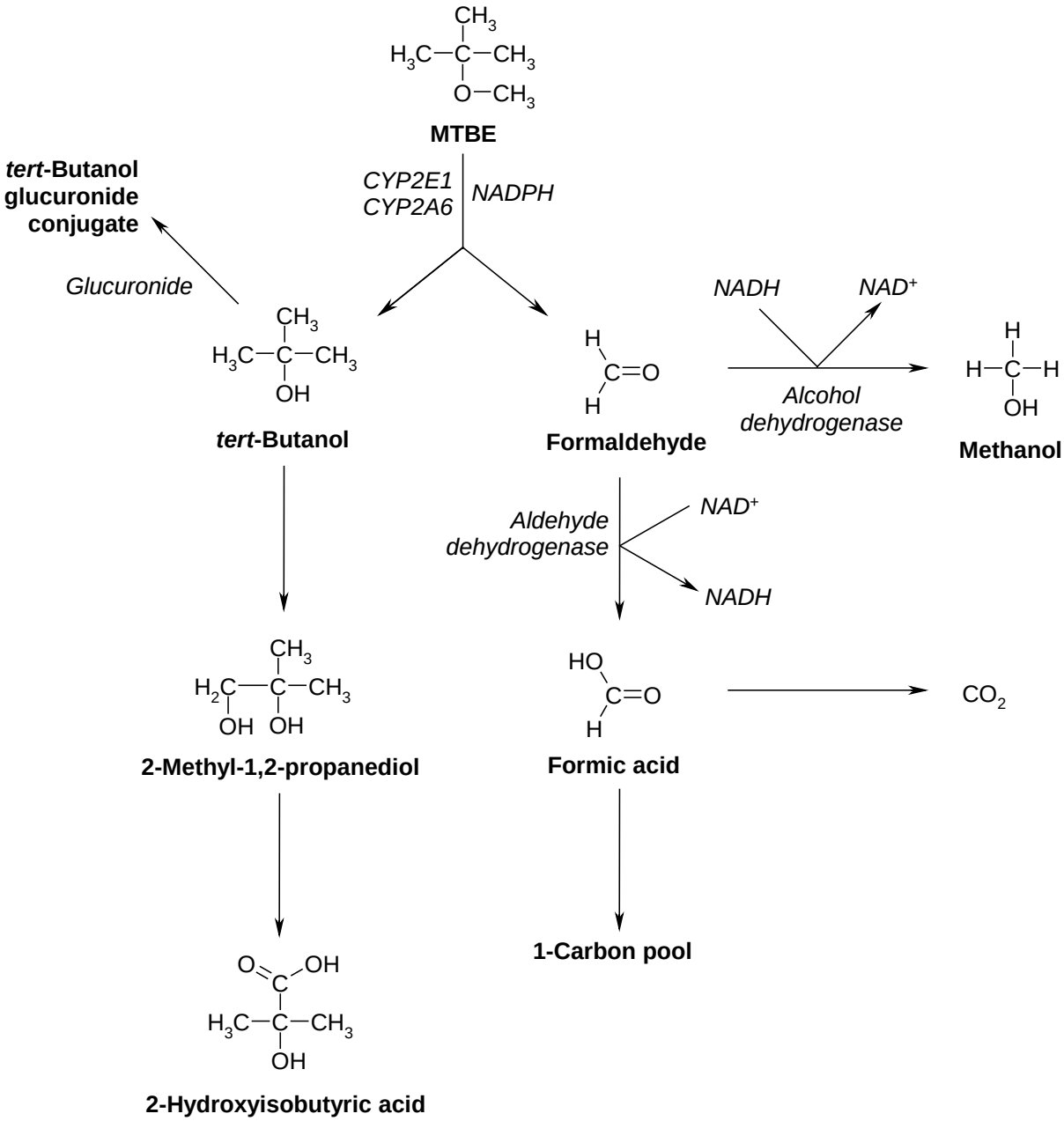
mesenteric fat (325 ppm in males, 138.5 ppm in females), liver (93.7 ppm in males, 68.7 ppm in females), and kidney (49.8 ppm in males, 19.4 ppm in females). At 6 hours, mesenteric fat radioactivity levels were more comparable to liver and kidney levels, and radioactivity levels declined in all three tissues at 24 hours. Radioactivity levels in liver were 65.5 ppm at 6 hours and 37.7 ppm at 24 hours. Levels in the kidney were 40 ppm at 6 hours and 28.5 ppm at 24 hours. Qualitative data indicated that radiolabeled formic acid and methanol were present in the liver and kidney, but quantification of the metabolites was not possible.

3.1.3 Metabolism

The proposed metabolic scheme for MTBE biotransformation presented in Figure 3-1 is based on available information from toxicokinetic studies of rats and humans and *in vitro* assays using selected rodent and human tissues. According to the scheme, MTBE rapidly undergoes CYP-dependent demethylation in the liver to form equimolar amounts of *tert*-butanol and formaldehyde. Additional rapid biotransformation in the liver includes the oxidation of *tert*-butanol to 2-methyl-1,2-propanediol and its subsequent oxidation to α-hydroxyisobutyric acid. Both 2-methyl-1,2-propanediol and α-hydroxy-isobutyric acid are urinary metabolites. *tert*-Butanol may undergo glucuronide conjugation and subsequent excretion in the urine. Formaldehyde is reduced to methanol or oxidized to formic acid and CO_2; the carbon atom may enter the physiological 1-carbon pool. The biotransformation of MTBE is generally similar among rats and humans and between sexes (Amberg et al. 1999).

Prah et al. (2004) indicated that the degree of metabolism in humans differs based on exposure route, with increased metabolism to *tert*-butanol following oral ingestion (compared to inhalation or dermal exposure) due to first-pass metabolism. However, Amberg et al. (2001) indicated that MTBE biotransformation observed following oral exposure in humans is similar to what they observed for inhalation exposure (Amberg et al. 1999), with no evidence of significant first-pass metabolism. Higher exposure levels in the studies by Amberg et al. (1999, 2001), compared to the study by Prah et al. (2004), may contribute to this discrepancy (15 versus 2.8 mg in oral studies, 40 versus 3.1 ppm in inhalation studies).

Figure 3-1. Proposed Metabolic Pathway for Methyl *tert*-Butyl Ether (MTBE) in Rats



Sources: API 1984; Brady et al. 1990; Dekant et al. 2001; MTBE Committee 1990a, 1990b, 1990d, 1991; Phillips et al. 2008; Snyder 1979

3.1.4 Excretion

Excretion of MTBE metabolites occurs primarily via the urine. Urinary metabolites of MTBE common to humans and rats are *tert*-butanol, 2-methyl-1,2-propanediol, and 2-hydroxyisobutyric acid. Very little unchanged MTBE is excreted in the urine.

Amberg et al. (1999) designed studies to evaluate the biotransformation and excretory kinetics of inhaled MTBE in humans and rats. Six human subjects (three men and three women) were exposed to MTBE by 4-hour inhalation at 4 or 40 ppm (the two exposure levels were separated by a 4-week rest period). Urine was collected prior to MTBE exposure and for 72 hours postexposure. Urine samples taken prior to MTBE exposure at 4 ppm contained small amounts of *tert*-butanol (0.6 µmol) and 2-methyl-1,2-propanediol (0.2 µmol), and a relatively larger amount of 2-hydroxyisobutyric acid (42.7 µmol); MTBE was not detected. Following MTBE exposure, total urinary excretion was 0.3 µmol for MTBE, 3.4 µmol for *tert*-butanol, 16.5 µmol for 2-methyl-1,2-propanediol, and 78.9 µmol for 2-hydroxy-isobutyric acid. Markedly greater increases in the urinary concentrations of MTBE and its metabolites were observed following MTBE exposure at 40 ppm. Pre-exposure urine samples from similarly exposed rats assigned to the 4 ppm MTBE exposure level contained 0.2 µmol *tert*-butanol, 0.1 µmol 2-methyl-1,2-propanediol, and 0.8 µmol 2-hydroxyisobutyric acid; MTBE was not detected. Following MTBE exposure, total urinary excretion was 0.3 µmol for *tert*-butanol, 0.7 µmol for 2-methyl-1,2-propanediol, and 1.7 µmol for 2-hydroxyisobutyric acid; MTBE was not detected. Markedly greater increases in the urinary concentrations of MTBE metabolites were observed following MTBE exposure at 40 ppm; urinary MTBE was not detected in the urine from rats of the 40-ppm exposure level.

The human and rat studies identified 2-hydroxyisobutyric acid as the major urinary metabolite of MTBE. All identified MTBE metabolites excreted in the urine were rapidly eliminated in both species. Approximately 35–69% of the MTBE retained at the end of the inhalation exposure period was eliminated in the urine of both species.

Several other human studies evaluated the toxicokinetics of MTBE following inhalation exposure (Johanson et al. 1995; Lee et al. 2001; Nihlén et al. 1998b; Vainiotalo et al. 2007). Urinary excretion of MTBE and *tert*-butanol represented only a very small portion of absorbed MTBE. These studies did not monitor the urinary metabolites, 2-methyl-1,2-propanediol and 2-hydroxyisobutyric acid. Vainiotalo et al. (2007) estimated that approximately 2.5% of absorbed MTBE was excreted in exhaled breath as *tert*-butanol during 48 hours postexposure.

Two studies evaluated exhalation of isotopically labeled MTBE in volunteers during and after 30-minute inhalation exposure to 0.5 ppm or dermal exposure to 150 µg/L (EPA 2003a, 2003b). In the inhalation study, the fraction of exhaled MTBEd12, compared to air concentrations, was 0.29 (EPA 2003a). The breath decay phase data, which fit a two-compartment model, estimated decay residence times of 3.8 and 61 minutes for the first and second compartments, respectively. In the dermal study, the fraction of exhaled MTBEd12, compared to water concentrations, was 0.00011 (EPA 2003b). The mean residence time for decay (assumed one-compartment model) was 41.5 minutes. However, Prah et al. (2004) indicated that excretion via all routes in humans follows a three-compartment model. Half-lives for the first, second, and third compartment for blood were calculated to be 14.9, 102.0, and 417.3 minutes, respectively, for oral exposure to 2.8 mg; 1.9, 59.0, and 313.7 minutes, respectively, for inhalation exposure to 3.1 ppm for 1 hour; and 5.5, 126.6, and 403.1 minutes, respectively, for dermal exposure to 51.3 µg/mL for 1 hour. For breath, first-, second-, and third-compartment half-lives following oral exposure were 13.0, 63.1, and 254.0 minutes, respectively. Half-lives in breath following inhalation and dermal exposure were only reported for the first and second compartment and were 30.2 and 265.7 minutes and 58.4 and 256.0 minutes, respectively.

Limited information regarding excretion of MTBE and its metabolites was provided in a study of 27 patients who received MTBE via intracystic infusion for dissolution of gallstones (Leuschner et al. 1991). Urine samples were collected before treatment, immediately after treatment, and for up to 18 hours after treatment; levels of MTBE, methanol, *tert*-butanol, formic acid, and formaldehyde were determined. Mean urinary levels of MTBE were about 0.018 mg/mL at 5 hours after treatment and <0.005 mg/mL at 12–18 hours. Mean urinary levels of *tert*-butanol were higher than levels of MTBE, and were approximately 0.036 mg/mL at 5 hours and 0.03 mg/mL at 12–18 hours after treatment. Trace levels of methanol were detected in the urine from three patients; no formaldehyde or formic acid were detected in the urine.

Miller et al. (1997) evaluated the disposition of radioactivity in rats exposed to ^{14}C-MTBE by nose-only inhalation (40 or 400 ppm once for 6 hours or repeatedly for 15 days), dermal application (40 or 400 mg/kg for 6 hours), or intravenous injection (40 mg/kg). Radioactivity from expired air, urine, and feces was determined for 48 hours following inhalation exposures and for 7 days following dermal and intravenous injection exposures. For inhalation studies, recoveries of radioactivity were based on the total amount measured in the excreta, expired air, and tissues (48 hours postexposure) because the total radioactivity inhaled by the rats could not be determined. Following single inhalation exposure at

40 ppm, radioactivity in expired air, urine, and feces accounted for 21.2, 64.7, and 0.76%, respectively, of the total radioactivity recovered (Miller et al. 1997). The disposition of excreted radioactivity was similar for both single and repeated inhalation exposures at 40 ppm. A larger fraction of radioactivity was eliminated in exhaled breath of the 400-ppm exposure group. For all inhalation exposure scenarios, >90% of the exhaled radioactivity occurred during the first 6 hours postexposure. Following exposure at 40 ppm, MTBE accounted for 66–69% and *tert*-butanol accounted for 31–34% of the exhaled radioactivity. A higher proportion of MTBE was exhaled following exposure at 400 ppm. Initial urinary excretion was more rapid in the rats exposed at 40 ppm (27–38% at 6 hours versus 10% in the 400-ppm group).

For single dermal exposure at 40 mg/kg, radioactivity in expired air, urine, and feces accounted for 7.58, 6.33, and 0.25%, respectively, of the total dose during the 7-day post-exposure evaluation period; MTBE and *tert*-butanol were not detected (lower limit of quantitation: 0.1 µg/mL), indicating that the radioactivity in expired air was largely in the form of $^{14}CO_2$ (Miller et al. 1997). At the 400 mg/kg dose level, radioactivity in expired air, urine, and feces accounted for 18.9, 16.2, and 0.39%, respectively, of the total dose. MTBE and *tert*-butanol accounted for 96.7 and 3.3% of the radioactivity in expired air monitored for 9 hours posttreatment at 400 mg/kg.

Following intravenous injection at 40 mg/kg, radioactivity in expired air, urine, and feces accounted for 59.9, 34.9, and 2.2%, respectively, of the total dose over a 7-day post-exposure period (Miller et al. 1997). Approximately 91% of the radioactivity in exhaled air was recovered during the first 3 hours posttreatment and was identified as MTBE (97.4%), *tert*-butanol (1.0%), and $^{14}CO_2$ (1.6%).

Urinary metabolic profiles were assessed in the rats exposed to MTBE by inhalation (Miller et al. 1997). The urinary metabolites, 2-hydroxyisobutyric acid and 2-methyl-1,2-propanediol, accounted for 70 and 14% of the total urinary radioactivity. Two additional unidentified metabolites accounted for 15% of the radioactivity in the urine. MTBE and *tert*-butanol were not detected the urine of rats treated by inhalation, dermal, or intravenous exposure.

The biotransformation of absorbed MTBE to *tert*-butanol occurs rapidly, as demonstrated by rapid elimination of MTBE from blood and increasing blood levels of *tert*-butanol. Elimination half-lives of 36–156 minutes for MTBE have been reported in studies of volunteers exposed to MTBE by inhalation (Amberg et al. 1999; Cain et al. 1996; Nihlén et al. 1998b; Prah et al. 2004). Amberg et al. (2001) reported that elimination of MTBE from blood of volunteers administered MTBE orally occurred in three

phases. The average half-lives were 0.8, 1.8, and 8.1 hours following dosing with 5 mg MTBE and 0.7, 1.2, and 3.7 hours following dosing at 15 mg MTBE.

MTBE was rapidly eliminated from the blood of male rats following inhalation, oral, or dermal exposure (Miller et al. 1997). Calculated half-lives of elimination were 0.51–0.57 hours following single inhalation exposure at 400 or 8,000 ppm or repeated exposures at 400 ppm, 0.52 and 0.79 hours following oral dosing at 40 or 400 mg/kg, respectively, 2.3 and 1.8 hours following dermal exposure at 40 or 400 mg/kg, respectively, and 0.45 hours following intravenous injection at 40 mg/kg.

Benson et al. (2003) determined blood MTBE equivalent elimination half-times among male rats exposed to ^{14}C-MTBE for 4 hours at 4, 40, and 400 ppm, respectively. The half-time for the exposure at 400 ppm (30.1 hours) was significantly longer than half-times at 4 and 40 ppm (14.7 and 16.5 hours, respectively).

Only small amounts of unchanged MTBE are excreted in the urine. Most of the *tert*-butanol formed from MTBE metabolism is further oxidized to 2-methyl-1,2-propanediol and α-hydroxyisobutyric acid; only small amounts of *tert*-butanol are excreted. *In vitro* assays using human microsomes have identified CYP2A6 as the major liver enzyme responsible for MTBE metabolism (Hong et al. 1997, 1999; Le Gal et al. 2001; Shamsipur et al. 2012). Results from rats exposed to MTBE by inhalation at 400 or 8,000 ppm or oral administration at 40 or 400 mg/kg indicate that MTBE metabolic pathways are saturated at the high-dose level, as evidenced by increased proportions of excreted MTBE and/or *tert*-butanol via the pulmonary route compared to the renal excretion route (Miller et al. 1997).

3.1.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

PBPK models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic endpoints.

A PBPK model for MTBE and *tert*-butanol in male Fischer 344 rats was developed (Borghoff et al. 1996). The model is based on chemical-specific parameters of solubility of MTBE and *tert*-butanol in blood and selected tissues (lung, liver, rapidly perfused tissue, slowly perfused tissue, fat, and kidney) and metabolic rate constants using vial equilibration and gas uptake techniques performed by Borghoff et al. (1996) and the pharmacokinetic data for male Fischer 344 rats obtained in the studies by the MTBE Committee (1990c, I990b, 1990d, 1990a) and for humans in the study by Cain et al. (1996). The model describes MTBE metabolism as occurring via two saturable pathways and predicts gas uptake data up to 2,000 ppm initial concentrations. The model predicted faster blood clearance of MTBE post exposure, thereby underpredicting blood MTBE levels after exposure in humans administered 1.7 ppm of MTBE for 1 hour (Cain et al. 1996). The model accurately predicts blood MTBE levels in rats when exposed via inhalation administration at 400 ppm MTBE for 6 hours, but underpredicts blood MTBE levels after 8,000 ppm exposure (MTBE Committee 1990a, 1990d). The model accurately predicted MTBE blood levels after oral (40 or 400 mg/kg) or intravenous exposure (40 mg/kg) (MTBE Committee 1990c, 1990b). The stomach was included as a compartment for oral exposure scenarios. Since the pharmacokinetics of *tert*-butanol appeared to be more complex than those of MTBE, Borghoff et al. (1996) indicated that additional experimental data on the distribution and elimination of *tert*-butanol were needed to refine the model.

Rao and Ginsberg (1997) expanded the model of Borghoff et al. (1996) to include compartments for the brain, since it is a known target of MTBE toxicity, and skin (to address dermal exposure). The model was validated using published rat and human data. Analysis of the model using animal data indicated that MTBE-induced CNS toxicity was principally attributable to the parent compound rather than the metabolite, *tert*-butanol. Rao and Ginsberg (1997) combined this model with an exposure model for inhalation and dermal exposure to evaluate pharmacokinetics associated with bathing and showering. The combined model results indicated that exposure to MTBE at 1 mg/L during showering or bathing would result in brain concentrations approximately 1,000-fold below levels resulting in CNS effects in animals.

Kim et al. (2007) developed a human PBPK model to predict the metabolism of MTBE and its metabolite, *tert*-butanol, following aggregate inhalation, oral, or dermal exposures. The model is an expansion of the six-compartment model of Borghoff et al. (1996) to include compartments for skin, stomach, and intestine. The model is based on measured blood MTBE and *tert*-butanol levels following controlled human exposures. Inhalation data were derived from 1-hour exposures of human subjects to MTBE at 3.1 ppm. Oral data were derived from the ingestion of 2.8 mg of MTBE (in Gatorade®).

Dermal data were collected following dermal application of 51.3 mg/L MTBE in tap water. The model underpredicted blood MTBE levels in females and underpredicted MTBE blood levels in males. The study authors noted a need for additional information to evaluate human variability such as age, sex, body mass index, and ethnicity.

Blancato et al. (2007) updated the models of Borghoff et al. (1996) and Rao and Ginsberg (1997). The updated model includes inputs for bolus dosing and rate ingestions, intraperitoneal injection, intramuscular injection, dermal exposure, and intravenous bolus and infusion dosing. The model includes compartments for gastrointestinal tract, spleen, liver, carcass, kidney, fat, slowly perfused tissue, rapidly perfused tissue, dermis, brain, and lung. The updated model was configured for humans and assigned values for MTBE metabolism using scaled metabolic parameters from rodents and extrapolated human microsomal values. Model predictions were compared to experimentally derived values. The model underpredicted MTBE blood levels in rats at a modeled lower dose (4.5 ppm) and overpredicted MTBE blood lead levels in rats at a higher dose (38.7 ppm). In humans, the predicted MTBE blood levels were within 3-fold of the reported mean MTBE blood levels. Blancato et al. (2007) performed an impact analysis of variability in metabolism for dose metrics considered of potential usefulness in evaluation of noncancer health risks in humans. For the impact analysis, dose metrics from inhalation exposures included peak MTBE in venous blood, area-under-the-curve (AUC) in venous blood at 24 hours, amount of MTBE metabolized in the liver at 24 hours, and peak *tert*-butanol concentration in venous blood. Modeling of selected scenarios allows for different dose-metric estimates at environmentally relevant exposure levels; results indicated that *tert*-butanol concentration in the blood varied to a much greater extent than MTBE when PBPK metabolic parameters were varied.

Licata et al. (2001) used a flow-limited human model similar in structure to that of Borghoff et al. (1996) in that it included compartments for lung, liver, rapidly perfused tissue, slowly perfused tissue, fat, and kidney. In the model, metabolic rate constants were measured *in vitro* using human liver microsomes and extrapolated to *in vivo* whole-body metabolism. Maximum metabolic rate was assumed to be proportional to body weight raised to the 0.75 power; the affinity constant was assumed to be equal to the *in* vitro value. Data on MTBE blood levels during and after 1-hour inhalation exposure to MTBE at 1.7 ppm and 4-hour exposures at 4 or 40 ppm were used to compare model predictions with measured results. The study authors stated that the model accurately predicted MTBE pharmacokinetics at the 40 and 1.7 ppm exposure levels, but underpredicted early time points at the 4-ppm exposure level. Variability analysis indicated that measured blood MTBE levels varied more than PBPK model-predicted blood levels based on metabolic parameters from *in vitro* human liver samples.

Leavens and Borghoff (2009) designed a PBPK model of MTBE and *tert*-butanol dosimetry in male rats based on binding to α2u-globulin, a mechanism postulated to be responsible for renal effects in rats exposed to MTBE. Borghoff et al. (2010) applied this model to evaluate MTBE and *tert*-butanol dosimetry in rats following a variety of exposure scenarios. The model applies only to the male rat and is not applicable to human risk assessment.

3.1.6 Animal-to-Human Extrapolations

The limited data in humans suggest some similarities in metabolism between rats and humans, that is, *tert*-butanol as a common metabolite. However, finding the rat urinary metabolites, 2-methyl-1,2-propanediol and α-hydroxyisobutyric acid, in the urine of patients who receive MTBE therapy would provide a better basis for considering the rat a good model to predict the behavior of MTBE in the human body. The data on distribution and excretion are too limited to be compared. Data are not available in other laboratory animal species, which would allow for a determination of whether the disposition of MTBE is similar across species.

The available epidemiological data and laboratory animal data suggest that the toxicity of MTBE may be similar across species, with the possible exception of renal effects observed in male rats. Studies in rats suggest that α2u-globulin may play a role in the observed renal effects. α2u-Globulin-induced renal effects are not relevant to humans (Ahmed 2001; Bogen and Heilman 2015; McGregor 2006; Phillips et al. 2008).

3.2 CHILDREN AND OTHER POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Children may be more or less susceptible than adults to health effects from exposure to hazardous substances and the relationship may change with developmental age.

This section also discusses unusually susceptible populations. A susceptible population may exhibit different or enhanced responses to certain chemicals than most persons exposed to the same level of these chemicals in the environment. Factors involved with increased susceptibility may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters can reduce detoxification or excretion or compromise organ function.

Populations at greater exposure risk to unusually high exposure levels to MTBE are discussed in Section 5.7, Populations with Potentially High Exposures.

A susceptible population will exhibit a different or enhanced response to MTBE than will most persons exposed to the same level of MTBE in the environment. Reasons include genetic make-up, developmental stage, age, health and nutritional status (including dietary habits that may increase susceptibility, such as inconsistent diets or nutritional deficiencies), and substance exposure history (including smoking). These parameters result in decreased function of the detoxification and excretory processes (mainly hepatic, renal, and respiratory) or the pre-existing compromised function of target organs (including effects or clearance rates and any resulting end-product metabolites). For these reasons, it is expected that the elderly with declining organ function and the youngest of the population with immature and developing organs will generally be more vulnerable to toxic substances than healthy adults.

No specific human populations that are unusually susceptible to the toxic effects of MTBE have been identified. EPA (1995a) and Fiedler et al. (2000) conducted studies to determine whether symptoms associated with MTBE were reported at an increased rate among subjects with known multiple chemical sensitivities (MCS) or chronic fatigue syndrome (CFS) compared to normal control individuals. No significant differences in self-reported respiratory or neurological symptoms were reported in MCS or CFS subjects, compared to healthy referents, while in situations in which gasoline containing MTBE was used (driving a car, gasoline stations) and not used (shopping malls, grocery stores, office buildings, parks) (EPA 1995a). Similarly, no significant differences were found between subjects with self-reported sensitivity (SRS) to MTBE and “non-sensitive” controls for self-reported respiratory or neurological symptoms, psychophysiological measures, or neurobehavioral tests of cognitive performance during 15-minute controlled exposures to clean air, gasoline, gasoline with 11% MTBE, or gasoline with 15% MTBE (Fiedler et al. 2000). Subjects with MCS reported a greater number of symptoms compared to controls when in circumstances more likely to be exposed to MTBE (riding in a car or at a gas station) (EPA 1995a) and subjects with SRS also reported a greater number of symptoms compared to controls when exposed to 15% MTBE (Fiedler et al. 2000). The authors concluded that these studies did not provide clear evidence to support an increase of symptoms occurred uniquely with MTBE exposure in sensitive subjects. It is also possible that some persons are or can become more chronically sensitive to MTBE as a result of prolonged low-level exposure, but no studies were located that specifically addressed this possibility.

Studies in rats (Brady et al. 1990; Snyder 1979) indicate that exposure to microsomal inducers of CYP2B1 and CYP2E1 enhances metabolism of MTBE, suggesting that people who are exposed to inducers of CYP2B1 (e.g., phenobarbital) or CYP2E1 (e.g., acetone, alcohol) may be more susceptible to toxic effects mediated via MTBE metabolites. However, because the toxicity of MTBE relative to the toxicities of its metabolites is unknown, the relative susceptibility cannot be determined.

Pharmacokinetic studies in rats indicated some differences between males and females in absorption and elimination kinetics (MTBE Committee 1990c, 1990b, 1990d, 1990a, 1991). In general, these studies indicated that female rats absorbed more MTBE than males after inhalation, oral, or dermal exposure, and eliminated it more quickly. Whether or not these relations would operate in humans is not known.

Studies in rats and mice indicate that developmental toxicity was only observed following inhalation exposure to high concentrations associated with frank maternal toxicity (Bevan et al. 1997a, 1997b; Conaway et al. 1985), suggesting that the developing animal is not uniquely susceptible to MTBE. No developmental effects were noted in rabbits, even at maternally toxic concentrations (Bevan et al. 1997a). Available oral studies in animals are inadequate to comprehensively evaluate potential developmental effects following oral MTBE exposure.

Both male and female rats show increased incidence and severity of age-related chronic progressive nephropathy following chronic exposure to MTBE. Since humans often develop age-related nephropathy, elderly people or people with pre-existing nephropathy may be more susceptible to the nephrotoxicity of MTBE.

3.3 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as biomarkers of exposure, biomarkers of effect, and biomarkers of susceptibility (NAS/NRC 1989).

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. Biomarkers of

exposure to MTBE are discussed in Section 3.3.1. The National Report on Human Exposure to Environmental Chemicals provides an ongoing assessment of the exposure of a generalizable sample of the U.S. population to environmental chemicals using biomonitoring (see http://www.cdc.gov/exposurereport/). If available, biomonitoring data for MTBE from this report are discussed in Section 5.6, General Population Exposure.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that (depending on magnitude) can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effect caused by MTBE are discussed in Section 3.3.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.2, Children and Other Populations that are Unusually Susceptible.

3.3.1 Biomarkers of Exposure

Much of absorbed MTBE is excreted unchanged in the expired air. Lower levels of its metabolite, *tert*-butanol, are found in expired air. MTBE and *tert*-butanol can be measured in the blood. A strong correlation was found between workroom air levels of MTBE in service stations and dealership garages and the difference in blood concentrations of MTBE between measurements preshift and postshift during an oxygenated fuel program in which MTBE (about 15% by volume) was added to gasoline to reduce emission levels of carbon monoxide (Moolenaar et al. 1994). In a similar study conducted in Stamford, Connecticut, personal breathing zone levels of MTBE were strongly correlated with blood levels of both MTBE and *tert*-butanol, although the breathing zone levels varied widely among the different garage locations, as well as within garages (White et al. 1995). For mechanics, TWA concentrations of personal breathing zone levels ranged from <0.03 to 12.04 ppm. Vainiotalo et al. (1998) reported a strong correlation between MTBE in the breathing zone of fuel tanker drivers during loading procedures and

blood MTBE levels approximately 20 minutes later; there was no significant correlation between MTBE in the breathing zone and urinary *tert*-butanol. MTBE and *tert*-butanol blood levels were generally related to inhalation exposure concentrations in rats (Savolainen et al. 1985).

Pleil et al. (2007) performed a series of controlled human MTBE exposure tests and applied first-order kinetic calculations to estimate the ability of spot measurements of MTBE and *tert*-butanol to predict various exposure scenarios of previous exposures to MTBE. They determined that these biomarkers in both spot blood and breath samples could reliably reconstruct recent inhalation exposure. They also determined that the urinary metabolite, 2-hydroxyisobutyric acid, could serve as a biomarker of very recent exposure to MTBE.

Urinary metabolites found in rats exposed by the inhalation, oral, or dermal routes were identified as *tert*-butanol, 2-methyl-1,2-propanediol, and 2-hydroxyisobutyric acid (Amberg et al. 1999; MTBE Committee 1990a, 1990b, 1991). Urinary metabolites found in humans following 4-hour inhalation exposures to MTBE included *tert*-butanol, 2-methyl-1,2-propanediol, and 2-hydroxyisobutyric acid (Amberg et al. 1999. The major urinary metabolite in both rats and humans was 2-hydroxyisobutyric acid, although this compound was detected in high amounts in rats and humans prior to MTBE exposure (Amberg et al. 1999).

In rats exposed to ^{14}C-MTBE by inhalation for 6 hours (MTBE Committee 1990a), the rate of excretion of radioactivity via the lungs was rapid, with a total of 82% of the recovered radioactivity in expired air excreted by 3 hours and 91–92% excreted by 6 hours (MTBE Committee 1990a). Urinary excretion of radioactivity was 96–98% complete by 36 hours after exposure. Similar rates of excretion of radioactivity were found in rats exposed by the oral route (MTBE Committee 1990b). Excretion was considerably slower in rats exposed dermally to MTBE. Half-lives for MTBE and *tert*-butanol for plasma clearance in rats exposed by the inhalation and oral routes were generally <1 or 2 hours (MTBE Committee 1990c, 1990d).

Based on available rat and human data, monitoring of expired air, blood, or urine for MTBE, *tert*-butanol, and/or 2-hydroxyisobutyric acid in humans could be used for determining very recent exposure to MTBE, but after exposure ceases, MTBE is rapidly eliminated from the body (Buckley et al. 1997). Additionally, MTBE metabolites are not unique to MTBE.

3.3.2 Biomarkers of Effect

MTBE exposure can lead to CNS depression characterized by ataxia, hypoactivity, drowsiness, anesthesia, duck-walk gait, decreased muscle tone, prostration, lack of startle response, and lack of righting reflex (see Section 2.15). MTBE exposure can induce hepatic microsomal enzymes (Brady et al. 1990; de Peyster et al. 2003; Moser et al. 1996), or lead to elevated levels of ALT, AST, or serum lactic dehydrogenase (de Peyster et al. 2003; Robinson et al. 1990), and may increase (Greenough et al. 1980) or decrease BUN levels (Robinson et al. 1990). However, many ethers, alcohols, and other chemicals can lead to these effects or combination of effects; therefore, no known effect or combination of effects can be used as a biomarker to identify or quantify effects from exposure to MTBE specifically.

For more information on biomarkers for renal and hepatic effects of chemicals see ATSDR/CDC Subcommittee Report on Biological Indicators of Organ Damage (ATSDR 1990) and for information on biomarkers for neurological effects see OTA (1990).

3.4 INTERACTIONS WITH OTHER CHEMICALS

Benson et al. (2003) exposed rats (nose-only) for 4 hours to MTBE vapor or unleaded gas containing MTBE vapor. Co-exposure to unleaded gas and MTBE resulted in lower tissue burdens of MTBE equivalents and enhanced the elimination of MTBE and its metabolites compared to MTBE exposure alone. The study authors suggested that the toxicity of MTBE alone could potentially be reduced by co-exposure to unleaded gas containing MTBE. However, in a subsequent 2-year rat study designed to evaluate the carcinogenicity of unleaded gas alone or in combination with MTBE, both exposure scenarios resulted in similar production of renal adenomas and carcinomas (Benson et al. 2011).

Pretreatment of rats with phenobarbital or acetone enhanced the metabolism of MTBE to *tert*-butanol and formaldehyde in liver microsomes, by inducing CYP2B1 and CYP2E1, respectively (Brady et al. 1990; Snyder 1979). *In vitro* assays using human microsomes have identified CYP2A6 as the major liver enzyme responsible for MTBE metabolism (Hong et al. 1997, 1999; Le Gal et al. 2001; Shamsipur et al. 2012). Thus, acetone and phenobarbital, as well as other inducers of these enzymes, would be expected to enhance the metabolism of MTBE. Conversely, competitive metabolic inhibitors may slow the metabolism of MTBE. Whether alterations in metabolism of MTBE would lead to greater or lesser toxicity is not clear, because the toxicity of MTBE relative to the toxicities of its metabolites is not known. Pretreatment of rats with MTBE resulted in a 47-fold induction of liver microsomal

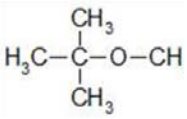
pentoxyresorufin O-dealkylase, an activity associated with CYP2B1 (Brady et al. 1990). Thus, MTBE itself is an inducer of CYP2B1, which can lead to the enhanced metabolism and toxicity of other chemicals. Elovaara et al. (2007) designed a rat study to evaluate the effects of MTBE on liver toxicity and induction of CYP2E1 and CYP2B1 by known liver toxicants (ethanol, 13-*cis*-retinoic acid, acetaminophen, phenobarbital, pyrazole). MTBE did not appear to enhance the toxicity of these liver toxicants.

CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

MTBE is a VOC that was added to gasoline to reduce air pollution. MTBE and other components, commonly known as "oxygenates," were added to gasoline to increase the octane number and reduce carbon monoxide emissions. Information regarding the chemical identity of MTBE is located in Table 4-1.

Table 4-1. Chemical Identity of Methyl *tert*-Butyl Ether (MTBE)

Characteristic	Information	Reference
Chemical name	Methyl *tert*-butyl ether	Budavari 1989
Synonym(s) and registered trade name(s)	*tert*-Butyl methyl ether; 2-methoxy-2-methylpropane; MTBE; methyl *t*-butyl ether	Budavari 1989
Chemical formula	$C_5H_{12}O$	Budavari 1989
Chemical structure		
CAS Registry Number	1634-04-4	Budavari 1989

CAS = Chemical Abstracts Service

4.2 PHYSICAL AND CHEMICAL PROPERTIES

MTBE is a relatively volatile chemical and is moderately soluble in water. It is very soluble in some organic solvents such as alcohol and ether. MTBE is flammable and is a moderate fire risk (Lewis 1987). Information regarding the physical and chemical properties of MTBE is located in Table 4-2.

Table 4-2. Physical and Chemical Properties of Methyl *tert*-Butyl Ether (MTBE)

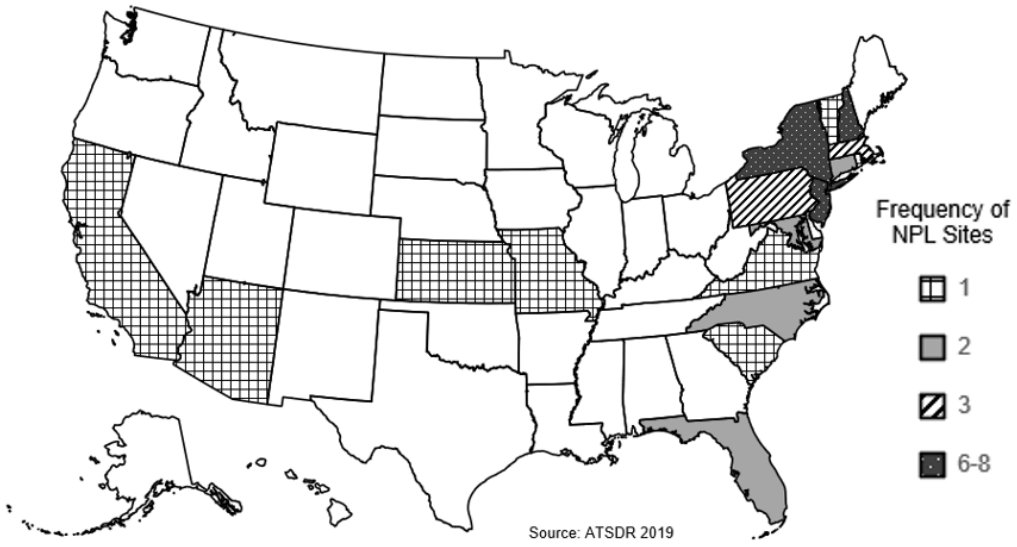
Property	Information	Reference
Molecular weight	88.15	Lide 1994
Color	Colorless	Winterberg et al. 2012
Physical state	Liquid	Budavari 1989
Melting point	-109°C	Lide 1994
Boiling point	55.2°C	Lide 1994
Density at 20°C	0.7405 g/cc	Lide 1994
Odor	Terpene-like	Gilbert and Calabrese 1992
Odor threshold:		
Water	15–680 ppb	Angle 1991; EPA 1997; Gilbert and Calabrese 1992
Air	180 ppb	Prah et al. 1994
Solubility:		
Water at 20°C	4–5%	Gilbert and Calabrese 1992
Organic solvents	Soluble in alcohol, ether	Lide 1994
Partition coefficients:		
Log K_{ow}	0.94	NLM 2020
Log K_{oc}	1.05 (estimated) 2.13±0.060 (measured)	Gilbert and Calabrese 1992 Greenwood et al. 2007
Vapor pressure at 20°C	245 mm Hg at 25°C	Budavari 1989
Henry's law constant at 25°C	5.87×10^{-4} atm-m^3/mol	Hine and Mookerjee 1975
Autoignition temperature	224°C	Budavari 1989
Flashpoint	-28°C	Budavari 1989
	28°C (closed cup)	Gilbert and Calabrese 1992
Flammability limits	No data	
Conversion factors		
ppm (v/v) to mg/m^3 in air at 25°C	1 ppm=3.61 mg/m^3	
mg/m^3 to ppm (v/v) in air at 25°C	1 mg/m^3=0.28 ppm	
Explosive limits	1.65–8.4% in air	Gilbert and Calabrese 1992

CHAPTER 5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Methyl *tert*-butyl ether has been identified in at least 44 of the 1,867 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (ATSDR 2019). However, the number of sites in which methyl *tert*-butyl ether has been evaluated is not known. The number of sites in each state is shown in Figure 5-1. Of these sites, 43 are located within the United States, and 1 is located in the Virgin Islands (not shown).

Figure 5-1. Number of NPL Sites with Methyl *tert*-Butyl Ether Contamination



- Since MTBE is no longer used as an oxygenate in gasoline in the United States, exposure is significantly lower today as compared to previous decades.
- MTBE is still manufactured within the United States, primarily for export; inhalation and dermal exposure may occur in occupational settings.
- The general population may be exposed to MTBE via inhalation of ambient air, ingestion of drinking water, and dermal exposure from contaminated water.
- Exposure to MTBE from indoor air by vapor intrusion can occur if the residence is near a contaminated aquifer.
- MTBE possesses high mobility in soil and leaches into groundwater.
- MTBE volatilizes from surface water and surface soils.
- MTBE is slow to degrade in the environment.
- MTBE does not bioconcentrate in aquatic or terrestrial organisms.

During the 1970s, EPA moved to phase out leaded gasolines and to reduce the levels of air pollution from pre- or post-combustion vehicular emissions. This conversion to unleaded fuels tended to reduce the

octane ratings. Additives such as benzene or toluene increase octane levels, but these aromatic VOCs can lead to serious air pollution problems due to their known toxic properties. Various highly oxygenated blending agents, including several ethers and alcohols, can boost the octane of unleaded gasoline and, since they are less toxic, can mitigate many of the air pollution concerns. MTBE is one such product that was used in Reformulated Gasoline (RFG). Some states started requiring the seasonal use of RFGs in the 1970s, and this became a requirement for many parts of the country under provisions of the 1990 Clean Air Act. This requirement led to a rapid expansion in the production and use of MTBE starting in the late 1980s as part of the oxyfuel program. As MTBE possesses high mobility in soil and was being detected in groundwater, concern grew over the continued use of it as an additive to gasoline and many states began restricting or banning its use entirely. In 2005, Congress passed the Energy Policy Act that removed the oxygenate requirement for RFG and added a requirement for renewable blends of RFG (USC 2005). Consequently, ethanol replaced MTBE in gasoline and MTBE use as a gasoline additive in the United States has essentially been eliminated. In 1980, commercial production in the United States was only 19,000 barrels (around 5 million pounds or 2.2 million kg) per day; its domestic use peaked in 1999 at 260,000 barrels per day (EIA 2018). MTBE is still used as an oxygenate in fuels in other countries and the United States still exports substantial quantities of MTBE or gasoline blends containing MTBE to other nations, especially Mexico (EIA 2018).

5.2 PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.2.1 Production

Typical production processes use feedstocks like isobutylene, often in combination with methanol, in adiabatic fixed reactors (Winterberg et al. 2012). The isobutylene and methanol react in the presence of ion-exchange resin catalysts at medium pressures and temperatures. Highly volatile byproducts are removed through distillation, and methanol is reclaimed using water washing or molecular sieves. In a variant of this basic technology called reaction distillation, the catalysis and distillation steps take place simultaneously (Shanley 1990). There are numerous variants in these manufacturing processes, the details of which are protected under patents or license agreements (Lorenzetti 1994; Rhodes et al. 1991).

Until the late 1980s, isobutylene and other feedstocks could be readily obtained from existing refinery operations. With minor investments, these refineries could add MTBE production with yields in the range of 8,000–20,000 barrels per day. As demand for MTBE increased, large specialized production

facilities were built. These larger specialized plants accounted for the vast majority of domestic production (Lorenzetti 1994).

Nearly all the MTBE produced in the United States was used as octane boosters and oxygenating agents in reformulated gasoline, and these uses are the only ones for which reliable production figures are readily available. Starting in the late 1980s, MTBE production increased rapidly. According to data submitted to the Chemical Data Reporting (CDR) database, U.S. production of MTBE was 4,774,345,888 pounds ($2.16x10^6$ metric tons) in 2011 (EPA 2019b). In 2012, 2014, and 2015, the national aggregated production volume was estimated to be 1,000,000,000–5,000,000,000 pounds ($4.53x10^5$–$2.27x10^6$ metric tons). In 2013, the estimated production volume range was 5,000,000,000–10,000,000,000 pounds ($2.27x10^6$–$4.53x10^7$ metric tons) (EPA 2019b). There were 18 companies that reported manufacturing or importing MTBE in the United States in 2016 (EPA 2019b).

Table 5-1 lists the facilities in each state that manufactured or processed MTBE in 2018, the intended use, and the range of maximum amounts of MTBE that are stored on site. The data from the Toxics Release Inventory (TRI) listed in Table 5-1 should be used with caution, however, since only certain types of facilities were required to report (EPA 1995b). This is not an exhaustive list.

Table 5-1. Facilities that Produce, Process, or Use Methyl *tert*-Butyl Ether (MTBE)

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AL	2	1,000	99,999	6, 10
AR	2	100	999,999	12
CA	4	1,000	99,999	9, 10, 12
CO	2	100,000	999,999	10
GA	2	10,000	99,999	6, 9
HI	1	1,000	9,999	9
IA	3	1,000	999,999	8, 10, 12
IL	3	1,000	99,999	1, 5, 7, 10, 12, 13
IN	3	1,000	999,999	9, 10, 12
KS	2	100	99,999	6, 12
KY	3	1,000	9,999	9
LA	6	0	9,999,999	1, 3, 4, 5, 6, 9, 12, 13, 14
MA	2	10,000	99,999	10
MD	4	0	0	0
MI	4	10,000	999,999	1, 5, 7, 8, 10, 12
MN	2	10,000	99,999	2, 3, 6, 7, 12

Table 5-1. Facilities that Produce, Process, or Use Methyl *tert*-Butyl Ether (MTBE)

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
MO	5	10,000	99,999	9, 10, 12
MP	1	1,000,000	9,999,999	1, 5, 9
MS	6	100,000	999,999	9
NC	5	10,000	99,999	9, 10, 12
NE	1	1,000,000	9,999,999	9, 12
NJ	4	1,000	999,999	2, 3, 4, 9, 10, 12
NV	2	0	99	1, 9, 12, 13, 14
NY	9	1,000	99,999	10, 12
OH	4	10,000	999,999	7, 8, 9, 12
OR	2	10,000	99,999	10, 12
PA	3	10,000	99,999	10
PR	1	1,000	9,999	9
SC	7	100	99,999	6, 9, 10, 12
TN	4	10,000	999,999	7, 9, 10, 11, 12
TX	17	0	99,999,999	1, 3, 4, 6, 7, 8, 9, 12, 14
UT	1	100,000	999,999	12
VA	2	1,000	999,999	9
VI	2	10,000	9,999,999	7, 9, 14
WA	1	1,000	9,999	14
WI	9	1,000	99,999	7, 9, 10, 12
WV	1	10,000	99,999	10

[a]Post office state abbreviations used.
[b]Amounts on site reported by facilities in each state.
[c]Activities/Uses:

1. Produce
2. Import
3. Used Processing
4. Sale/Distribution
5. Byproduct
6. Reactant
7. Formulation Component
8. Article Component
9. Repackaging
10. Chemical Processing Aid
11. Manufacture Aid
12. Ancillary
13. Manufacture Impurity
14. Process Impurity

Source: TRI18 2019 (Data are from 2018)

5.2.2 Import/Export

Virtually all of the MTBE produced domestically in the United States is now exported to other nations, primarily Mexico, Chile, and Venezuela (EIA 2019). The monthly U.S. exports of MTBE from 2004 to 2019 are illustrated in Table 5-2.

Table 5-2. U.S. Exports of Methyl *tert*-Butyl Ether (MTBE) (Thousands of Barrels)

Year	January	February	March	April	May	June	July	August	Septem-ber	October	Novem-ber	Decem-ber
2004	482	617	680	556	783	513	831	757	605	404	481	734
2005	1,000	417	549	898	984	1,312	906	1,424	1,079	888	969	1,007
2006	1,080	716	1,049	2,779	2,035	2,599	2,690	3,253	1,883	1,822	1,104	1,303
2007	1,021	1,713	2,346	1,310	2,833	1,216	1,569	1,842	1,696	1,682	1,550	1,685
2008	1,087	1,471	1,553	1,351	1,528	1,573	1,524	1,981	882	1,794	1,509	964
2009	1,184	1,293	2,067	1,298	1,773	1,860	1,639	2,096	1,789	1,209	498	647
2010	935	421	897	999	856	876	1,277	1,718	1,317	1,196	1,060	1,482
2011	1,026	638	1,537	1,089	1,218	862	1,111	1,811	820	1,333	1,087	1,453
2012	1,514	1,279	790	1,319	1,757	1,682	1,300	1,608	1,649	1,235	1,254	1,080
2013	624	1,770	1,403	1,233	1,371	1,443	1,878	1,528	1,499	1,368	1,285	1,770
2014	985	789	1,159	1,106	1,391	1,411	1,284	1,237	1,129	1,253	1,136	1,179
2015	962	548	436	1,160	1,180	1,496	1,444	1,539	1,181	1,212	1,205	1,028
2016	1,362	895	1,308	1,773	1,694	1,277	1,382	1,223	1,246	1,379	1,245	817
2017	1,376	1,130	1,124	915	679	1,485	1,072	1,130	1,500	1,124	1,276	1,362
2018	1,501	810	1,116	1,136	917	958	1,184	1,193	1,491	1,324	1,294	1,206
2019	874	699	1,420	906	1,218	1,377	1,618	1,361	1,353			

Source: EIA 2019

5.2.3 Use

Nearly all of the MTBE produced in the United States was produced for use in reformulated gasolines as part of the oxyfuel program. MTBE has been used as a non-surgical pharmaceutical treatment to dissolve gallstones in cases in which surgical treatments are considered too risky (e.g., elderly patients) (Angle 1991; Bergman et al. 1994; Edison et al. 1993; Gilbert and Calabrese 1992; Kim et al. 2015). This treatment was first used in 1986, declined in usage with development of minimally invasive laparoscopic procedures, and (as of 2015) is no longer approved in the United States due to concerns over MTBE toxicity (Aetna 2020; Kim et al. 2015). In countries that still utilize MTBE dissolution (e.g., South Korea), safer alternative dissolution agents are being developed (You et al. 2019). MTBE can also be used in other petroleum related applications. It can be cracked (broken down) to produce isobutene and methanol, resulting in high purity (>99.8%) isobutene (Winterberg et al. 2012). It can also be used in chemical reactions such as the production of methacrolein and methacrylic acid (Winterberg et al. 2012).

5.2.4 Disposal

Since most MTBE is used as a component in reformulated gasoline, provisions for its disposal are generally subsidiary to regulations for disposing of gasolines or similar volatile or semi-volatile organic compounds such as benzene or toluene. MTBE is likely to be encountered in waste sites or NPL sites where blended gasoline has been disposed of, or at NPL sites around pipelines, large tank batteries, or refineries and other facilities involved in the manufacture of reformulated fuels. Once dissolved in water, MTBE can readily leach into groundwater supplies. MTBE from past disposal in dumps and waste sites or from spills, leakage from underground storage tanks (USTs), or other releases to the environment are recognized as a pollutant to groundwater supplies (NJDEP 1994; USGS 1995). Chapter 7 contains an overview of regulations and guidelines regarding disposal practices for MTBE. No information was located on the quantities of MTBE disposed of by each disposal method, or on trends in disposal amounts or practices. Enhanced biodegradation of MTBE can be accomplished using degrading bacterial consortiums, which can then be used to clean up contaminated soils or water (Li et al. 2014). Bioremediation methods have been used to remove MTBE from aqueous solution such as gasoline-contaminated waters using continuous up-flow packed-bed biofilm reactors (Alfonso-Gordillo et al. 2016; Bianchi et al. 2009).

5.3 RELEASES TO THE ENVIRONMENT

The Toxics Release Inventory (TRI) data should be used with caution because only certain types of facilities are required to report (EPA 2005a). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ ≥10 full-time employees; if their facility is included in Standard Industrial Classification (SIC) Codes 10 (except 1011, 1081, and 1094), 12 (except 1241), 20–39, 4911 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4931 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4939 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4953 (limited to facilities regulated under RCRA Subtitle C, 42 U.S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited to facilities primarily engaged in solvents recovery services on a contract or fee basis); and if their facility produces, imports, or processes ≥25,000 pounds of any TRI chemical or otherwise uses >10,000 pounds of a TRI chemical in a calendar year (EPA 2005a).

5.3.1 Air

Estimated releases of 182,127 pounds (~82.6 metric tons) of MTBE to the atmosphere from 132 domestic manufacturing and processing facilities in 2018, accounted for about 76% of the estimated total environmental releases from facilities required to report to the TRI (TRI18 2019). These releases are summarized in Table 5-3.

Table 5-3. Releases to the Environment from Facilities that Produce, Process, or Use Methyl *tert*-Butyl Ether (MTBE)[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
AL	2	2,284	0	0	0	0	2,284	0	2,284
AR	2	98	0	0	0	1,142	98	1,142	1,240
CA	4	466	0	0	37,757	0	38,223	0	38,223
CO	2	1,850	0	0	0	0	1,850	0	1,850
GA	2	379	0	0	0	0	379	0	379
HI	1	402	0	0	0	0	402	0	402
IA	3	2,716	1	0	0	0	2,717	0	2,717

Table 5-3. Releases to the Environment from Facilities that Produce, Process, or Use Methyl *tert*-Butyl Ether (MTBE)[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
IL	3	32	0	0	26	0	32	26	58
IN	3	3,112	0	0	3,249	0	3,112	3,249	6,361
KS	2	4,508	5	0	0	0	4,513	0	4,513
KY	3	1	0	0	0	0	1	0	1
LA	6	7,611	121	0	0	90	7,732	90	7,822
MA	2	1,258	1	0	0	0	1,258	1	1,259
MD	4	0	0	0	0	0	0	0	0
MI	4	333	0	0	0	0	333	0	333
MN	2	257	5	0	0	0	262	0	262
MO	5	4,188	0	0	0	1,604	4,188	1,604	5,792
MP	1	1,054	0	0	0	0	1,054	0	1,054
MS	6	1,966	0	0	0	0	1,966	0	1,966
NB	1	234	0	0	3,100	0	234	3,100	3,334
NC	5	3,250	0	0	0	0	3,250	0	3,250
NJ	4	1,473	0	0	0	0	1,473	0	1,473
NV	2	92	0	0	0	0	92	0	92
NY	9	142	250	0	0	0	142	250	392
OH	4	133	0	0	0	0	133	0	133
OR	2	3,968	0	0	0	0	3,968	0	3,968
PA	3	97	0	0	0	0	97	0	97
PR	1	567	0	0	0	0	567	0	567
SC	7	3,651	0	12	0	0	3,651	12	3,663
TN	4	6,852	0	0	0	95	6,852	95	6,946
TX	17	100,214	75	2,764	3,021	5,694	103,053	8,715	111,768
UT	1	46	0	0	0	0	46	0	46
VA	2	1,048	0	0	0	0	1,048	0	1,048
VI	1	21,471	0	0	1	0	21,472	0	21,472
WA	1	138	0	0	0	0	138	0	138

Table 5-3. Releases to the Environment from Facilities that Produce, Process, or Use Methyl *tert*-Butyl Ether (MTBE)[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
WI	9	6,232	1	0	0	0	6,232	1	6,233
WV	1	7	0	0	0	0	7	0	7
Total	132	182,127	459	2,776	47,154	8,625	222,856	18,285	241,141

[a]The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, wastewater treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II-V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other onsite landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI18 2019 (Data are from 2018)

Although MTBE was listed as a hazardous air pollutant under the 1990 Clean Air Act Amendments, it was also an EPA-approved alternative for use in reformulated gasoline (EPA 1994). When it was being used as a gasoline additive in the United States, the most common types of releases to the air would involve refueling operations at fuel terminals or service stations and emissions from automobile exhaust or background levels in the ambient air encountered during commuting (Lioy et al. 1994). A risk assessment conducted by the European Union Chemicals Bureau estimated that emissions from the exhaust of various types of automobiles commonly used in Europe ranged from approximately 7 to 250 kg of MTBE emitted per metric ton of gasoline used (ECB 2002). According to the National Emissions Inventory (NEI) database, which includes air emissions sources of both criteria and hazardous air pollutants, 1,644,282 pounds of MTBE were emitted to the atmosphere from point and non-point sources in 2014 (EPA 2014). The largest amount (58% of the total) was attributed to consumer and commercial solvent use.

5.3.2 Water

Estimated releases of 459 pounds (~0.21 metric tons) of MTBE to surface water from 132 domestic manufacturing and processing facilities in 2018, accounted for <1% of the estimated total environmental releases from facilities required to report to the TRI (TRI18 2019). This estimate includes releases to wastewater treatment and publicly owned treatment works (POTWs) (TRI18 2019). These releases are summarized in Table 5-3.

Most releases of MTBE to surface water would likely result from leaks or spills. On March 9, 2015, a collision between a bulk carrier and a tanker named the Carla Maersk occurred in the Houston Ship Channel near Morgan Point, Texas, resulting in the estimated release of 2,100 barrels of MTBE into the Galveston Bay (NTSB 2016).

Since MTBE has a fairly high degree of solubility in water, precipitation could also transfer MTBE from the atmosphere to surface waters (USGS 1995). Wet weather runoff will often wind up being diverted into storm drains or wastewater treatment facilities in urban areas or industrial facilities, where the MTBE may then be introduced to receiving waters. Given its high vapor pressure of 245 mmHg and Henry's Law constant of around 5.87×10^{-4} atm-m^3/mole, however, MTBE would be expected to volatilize rapidly from surface water or soil surfaces (EPA 1994).

A source of groundwater contamination is from leaking USTs. There are around 1.4 million small underground storage facilities regulated under the EPA Underground Storage Tank program. Up to 20% of these facilities may either be leaking now or can be expected to start leaking in the future (Mihelcic 1990).

5.3.3 Soil

Estimated releases of 47,154 pounds (~21.3 metric tons) of MTBE to soil from 132 domestic manufacturing and processing facilities in 2018, accounted for about 20% of the estimated total environmental releases from facilities required to report to the TRI (TRI18 2019). An additional 2,776 pounds (~1.2 metric tons) accounted for about 1% of the total environmental emissions, were released via underground injection (TRI18 2019). These releases are summarized in Table 5-3.

Emissions to surface soils can occur following an accidental spill of MTBE or MTBE-containing gasoline as well as atmospheric deposition. Leaks from storage tanks would frequently release MTBE to subsurface soils when it was being used as a gasoline additive; however, amounts released from these sources have not been quantified.

5.4 ENVIRONMENTAL FATE

5.4.1 Transport and Partitioning

If released to the atmosphere, MTBE is expected to exist entirely in the vapor phase where it can be transported to the earth by wet and dry deposition. Based upon a vapor pressure of 245 mm Hg at 25°C (Budavari 1989) and Henry's Law constant of $5.87x10^{-4}$ atm-m^3/mol (Hine and Mookerjee 1975), MTBE is expected to volatilize rapidly if released to soil or water surfaces. However, the soil-adsorption coefficient (K_{oc}) of MTBE indicates that it possesses high mobility in soil, and MTBE that is not volatilized is likely to leach into lower soil horizons and contaminate groundwater. MTBE released from USTs has been shown to move rapidly in the soil column and contaminate groundwater; this has been verified in large monitoring studies (USGS 2006). The actual rate of volatilization of MTBE from surface water is dependent upon the environmental conditions of the surrounding air and water body such as the flow rate, wind velocity, temperature, and depth of the water body. Pankow et al. (1996) estimated the rate of volatilization of MTBE under various environmental conditions by varying these factors and using a two-layer model to calculate the mass transport parameters that were used to estimate the half-life. Volatilization half-lives ranged from several minutes at very shallow depths, ambient temperature, and high wind speeds to >80 days at a water depth of 32 feet, temperature of 5°C, and low flow velocities and wind speed. The study authors noted that MTBE and benzene, toluene, ethylbenzene, and xylene (BTEX) have similar estimated volatilization rates in deep slow-moving water bodies (e.g., lakes for example), but compounds such as benzene volatilize significantly faster in shallow, fast-moving water bodies due to its greater Henry's Law constant.

Few experimental measurements of the bioconcentration factor (BCF) in aquatic organisms (e.g., fish) are available for MTBE. In one study that used a flow-through water system with exposures carried out over a 4-week period, the highest measured BCF value measured in carp was 1.5 (Fujiwara et al. 1984). Using the EPA's EPI Suite™ software (EPA 2012), an estimated BCF value of 3 was derived using its log K_{ow} and a regression derived equation (Meylan et al. 1999). These data indicate that MTBE is unlikely to

bioconcentrate in aquatic organisms. It is also true that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable.

5.4.2 Transformation and Degradation

Air. If released to the atmosphere, MTBE is expected to undergo degradation thorough reaction with photochemically generated hydroxyl radicals. Based on available laboratory studies, a total atmospheric lifetime for MTBE of approximately 4 days has been estimated (Cox and Goldstone 1982; Smith et al. 1991; Wallington et al. 1988). In other studies, atmospheric half-lives of approximately 3 days are reported in polluted urban air and around 6.1 days in nonpolluted rural air (EPA 1994). An estimated hydroxyl radical rate constant of $2.2x10^{-12}$ cm^3/molecule-second was calculated using a structure-based estimation method (Meylan and Howard 1993). This corresponds to an atmospheric half-life of about 2.4 days assuming a hydroxyl radical concentration of $1.5x10^6$ hydroxyl radicals per cm^3 of air. MTBE does not absorb light in the environmental ultraviolet (UV) spectrum (λ >290 nm); therefore, direct photolysis is not expected to be an important environmental fate process.

There are two main decomposition pathways depending on whether the methyl group or the *tert*-butyl group is attacked by hydroxyl radicals. The pathway involving OH radical decomposition on the methyl group results in such final products as acetone and *tert*-butyl formate. While acetone would be relatively resistant to further OH radical degradation, there is very little research on the reactivity of the *tert*-butyl formate degradation products, with available research suggesting atmospheric residence times of up to 15 days (Cox and Goldstone 1982). This would make the *tert*-butyl formate much more persistent in the atmosphere than the original MTBE. There is very limited information available on the toxicology and human health impacts of *tert*-butyl formate. The pathway involving decomposition of the *tert*-butyl group can become extremely complex, with the final products being dependent on the levels of other free radicals and such pollutants as NOx. Under conditions typical of polluted urban air (Japar et al. 1990), decomposition products were shown to include 2-methoxyl-2-methyl propanol, acetone, acetaldehyde, and peroxyacetyl nitrate (PAN). Other laboratory studies also indicate that decomposition products include formaldehyde (Tuazon et al. 1991) and methyl acetate (Smith et al. 1991; Tuazon et al. 1991). Studies in highly polluted urban airsheds such as Mexico City have documented statistically significant increases in the ambient levels of formaldehyde following efforts to encourage greater use of reformulated gasolines such as MTBE (Bravo et al. 1991).

Several of the decomposition products stemming from the *tert*-butyl group breakdown pathway are products that can be produced from non-oxygenated unleaded gasolines or from reformulated products using such alternative oxygenating agents as ethanol (Shanley 1990). This can make it difficult to relate laboratory studies or modeling predictions to actual monitoring observations.

Water. In surface waters, MTBE shows little tendency to degrade due to hydrolysis or other abiotic processes. Due to its high volatility, it will usually be removed from surface waters very rapidly. It is also resistant to biodegradation (EPA 1994) and not readily biodegradable in screening-level tests. MTBE present at 100 mg/L achieved 0% of its theoretical oxygen demand over the course of a 4-week incubation period using an activated sludge inoculum in a Japanese Ministry of International Trade and Industry (MITI) test (Organisation for Economic Cooperation and Development [OECD] 301C) (CITI 2019). These results were consistent with two closed bottle studies (OECD 301D) in which MTBE achieved 0–1.8 % of its theoretical oxygen demand after 28 days using 2 mg/L of test substance exposed to a sewage inoculum (ECB 2002).

In groundwater, the persistence of MTBE would be more prominent since volatilization to the air is reduced or eliminated and this ether is resistant to most types of bacterial biodegradation (Yeh and Novak 1991). Finneran and Lovley (2001) investigated the biodegradation of MTBE in petroleum contaminated aquifer sediments maintained under anaerobic conditions. It was shown that MTBE degradation was enhanced by the addition of humic material in sediments containing Fe(III), which acts as an electron acceptor in iron-reducing microorganisms; however, little degradation was observed in sediments lacking humic substances and Fe(III).

The behavior of a plume of MTBE mixed with gasoline and other organic hydrocarbons such as the BTEX series in contact with water in an aquifer can become very complicated. A key factor is the percentage of MTBE in the original fuel mixture. Over time, higher percentages of MTBE in reformulated gasoline were used in the United States, with the percentage being at 7% in 1979 and increasing to 11% and 15%, respectively in 1981 and 1988 (Lorenzetti 1994). Below levels of about 5%, the pollution chemistry of a reformulated gasoline plume mixing with fresh groundwater will be driven mostly by the effects from the BTEX components. At higher MTBE levels, however, studies based on theoretical considerations and modeling exercises suggest that MTBE may increase the partitioning of the BTEX toxics into groundwater by increasing BTEX water solubilities (Mihelcic 1990; Poulsen et al. 1992). These impacts will be minor when the levels of MTBE in a reformulated gasoline mixture are <10% by volume but become greater as the levels of MTBE increase. For instance, a reformulated

gasoline mixture containing 0.1% MTBE by volume could increase BTEX water solubilities by only around 1%; a 10% MTBE mixture could result in a 100% increase in BTEX water solubilities (Mihelcic 1990). The MTBE co-solvent can also change the sorption/desorption characteristics of other hydrocarbons, thus increasing their mobility.

Sediment and Soil. There is limited information available on degradation processes in soils or sediments. Results from field or laboratory microcosm studies suggest considerable persistence in deeper soil layers or in sediments since this ether appears to be highly refractory to microbial decomposition (Jensen and Arvin 1990; Yeh and Novak 1991). For instance, microcosm studies using several soil types and bacterial flora showed no significant biodegradation in experiments carried out over a 250-day period, with most losses due to sorption to organic matter or volatilization (Yeh and Novak 1991). Soils in these microcosm studies were taken from agricultural sites showing moderate acidity (pH 5–6) and a wide range in organic matter content. Li et al. (2014) used mixed microbial cultures to identify and isolate various strains of bacterium that could use MTBE as a sole carbon source. Other investigators studied the aerobic biodegradation of MTBE in a microbial consortium using a continuous up-flow packed-bed biofilm reactor (Alfonso-Gordillo et al. 2016). While MTBE was shown to be toxic to the microbes at high loading rates, lower levels of MTBE could be degraded in the bioreactor with a theoretical chemical oxygen demand of up to 90%.

Kuder et al. (2005) utilized a novel approach using compound-specific stable isotope analysis (CSIA) to study the anaerobic biodegradation mechanisms of MTBE in enrichment cultures and field studies. Following the isotopic fractionation allows for a better understanding of the degradation of MTBE in gasoline plumes since following the concentration of MTBE's main metabolite, *tert*-butyl alcohol, is confounded in plumes since it is often a constituent in gasoline anyway. Martienssen et al (2006) studied the degradation of MTBE in a contaminated groundwater plume located in Leuna (eastern Germany). They determined that degradation occurred primarily under microaerobic conditions with little or no degradation under anoxic conditions.

5.5 LEVELS IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to MTBE depends, in part, on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of MTBE in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical methods. In reviewing data on MTBE levels monitored or estimated in the

environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable.

Table 5-4 shows the lowest limit of detections that are achieved by analytical analysis in environmental media. An overview summary of the range of concentrations detected in environmental media is presented in Table 5-5.

Table 5-4. Lowest Limit of Detection Based on Standards[a]

Media	Detection limit	Reference
Air[b]	0.009 ppbv	EPA 2018a
Drinking water	0.006 ppb	USGS 2016
Surface water and groundwater	0.006 ppb	USGS 2016
Soil[c]	1.7–2.6 µg/kg	USGS 2019
Sediment[c]	1.7–2.6 µg/kg	USGS 2019
Whole blood	0.232 ng/mL	CDC 2019

[a]Detection limits based on using appropriate preparation and analytics. These limits may not be possible in all situations.
[b]Detection limit depends on sampling time and volume.
[c]Reporting limit of the method.

Table 5-5. Summary of Environmental Levels of Methyl *tert*-Butyl Ether (MTBE)

Media	Low	High[a]	For more information and references
Outdoor air (ppbv)	<LOD	131.6	Section 5.5.1
Indoor air (ppbv)	No data	No data	
Surface water (ppb)	<LOD	0.226	Section 5.5.2
Ground water (ppb)	<LOD	23,000	Section 5.5.2
Drinking water (ppb)	<LOD	40,000	Section 5.5.2
Food (ppb)	No data	No data	
Soil (ppb)	<LOD	2–3	Section 5.5.3

[a]Highest mean daily value obtained when MTBE was still being used as a gasoline additive.

LOD = limit of detection

Detections of MTBE in air, water, and soil at NPL sites are summarized in Table 5-6.

Table 5-6. Methyl *tert*-Butyl Ether (MTBE) Levels in Water, Soil, and Air of National Priorities List (NPL) Sites

Medium	Median[a]	Geometric mean[a]	Geometric standard deviation[a]	Number of quantitative measurements	NPL sites
Water (ppb)	38.0	26.5	11.1	31	23
Soil (ppb)	No data	No data	No data	No data	No data
Air (ppbv)	1.4	1.9	6.0	7	4

[a]Concentrations found in ATSDR site documents from 1981 to 2019 for 1,867 NPL sites (ATSDR 2019). Maximum concentrations were abstracted for types of environmental media for which exposure is likely. Pathways do not necessarily involve exposure or levels of concern.

5.5.1 Air

MTBE is a pollutant monitored in the national Air Quality System (AQS) database, which contains ambient air pollution data collected by EPA, state, local, and tribal air pollution control agencies from monitors throughout the country. To illustrate the differences in ambient levels in the atmosphere of the United States over time, daily monitoring data from 2000, 2005, 2010, and 2018 were downloaded from the AQS website. Table 5-7 shows the daily mean 24-hour percentile distributions of MTBE measured during these years at all of the sites nationwide that tested for MTBE. As expected, the trend shows a rapid decrease in atmospheric levels following the phase-out of MTBE usage in gasoline after the 2005 Energy Policy Act.

Table 5-7. Percentile Distribution of Daily Mean Methyl *tert*-Butyl Ether (MTBE) Concentrations (ppbv) Measured in Ambient Air at Locations Across the United States[a]

Year	Number of samples	25th	50th	75th	95th	Maximum
2000	5,873	0.000	0.202	0.800	2.700	18.6
2005	8,490	0.000	0.006	0.095	0.640	131.6
2010	7,026	0.000	0.000	0.000	0.060	0.890
2018	3,146	0.000	0.000	0.000	0.004	0.700

[a]Values were originally reported in parts per billion carbon (ppbC) and converted to ppbv.

Source: U.S. Environmental Protection Agency (EPA) Air Quality System (AQS) annual summaries (EPA 2019a)

In 2018, EPA released its report for air monitoring conducted as part of the 2015 and 2016 National Monitoring Programs (National Air Toxics Trends Stations, Urban Air Toxics Monitoring Program, and Community-Scale Air Toxics Ambient Monitoring) (EPA 2018a). These are three individual programs

with different goals, but all analyze atmospheric data on pollutants that can affect air quality. The 2015–2016 National Monitoring Program focused on data from samples collected at 53 monitoring locations in the AQS database. The 53 monitoring sites were located in or close to 30 urban or rural locations in 18 states and the District of Columbia, including 28 metropolitan or micropolitan statistical areas. MTBE was detected in 270 out of 2,934 samples collected at these 53 locations at concentrations ranging from 0.003 to 0.174 ppbv.

A regional ambient air monitoring study from the Houston Regional Monitoring Network (LaGrone 1991) included MTBE in a suite of VOC target analytes to be monitored. This part of Texas contains the Houston Ship Channel and includes some of the nation's largest MTBE manufacturing facilities, many in close proximity to residential neighborhoods. Data collections on every 6th day were obtained over a period from September 8, 1987, through September 18, 1988, following the EPA National Sampling Day protocols. Monitoring results for the Harris and Chambers county area showed total yearly MTBE emissions of 285 tons, with a mean ambient air concentration for MTBE less than the detection limit of 0.2 ppbv (0.0007 mg/m^3). The Michigan Department of Environmental Quality monitored air samples at nine locations around the city of Detroit to gather air quality data in 2001–2002 (Michigan DEQ 2005). MTBE was detected in 72 out of 480 samples with a maximum concentration of 2.11 µg/m^3 (0.584 ppbv). Outdoor MTBE levels were measured in New York City, New York and Los Angeles, California (Sax et al. 2004). Median levels in the winter and summer months in New York were 10.0 and 10.9 µg/m^3 (2.77 and 3.02 ppbv), respectively. In Los Angeles, the median levels were 16.0 and 13.0 µg/m^3 (4.43 and 3.60 ppbv) in the winter and fall, respectively.

No current information was identified on typical levels for indoor residential air spaces. There are a number of older studies where data were collected around automobile service or filling stations that would bear on exposures in special locations for the general population as well as for occupational groups that work at these automobile service facilities; however, these data are not currently relevant since MTBE is no longer used in gasoline in the United States. Levels from several urban locations suggested that MTBE levels around such automobile service facilities would be <1 ppmv (Hartle 1993). A research initiative by the Health Effects Institute (HEI) measured indoor, outdoor, and personal exposure concentrations of pollutants between the summer of 1999 and the spring of 2001 that included measurements obtained from 100 homes in Los Angeles, California; Houston, Texas; and Elizabeth, New Jersey (HEI 2005). The mean concentration of MTBE in indoor air samples was 11.8 µg/m^3 (3.27 ppbv) with 93% of all samples (N=553) at or above the detection limits. Hun et al. (2011) also analyzed indoor air data collected from the HEI and determined that homes with attached garages had higher indoor air

levels as compared with homes that did not have attached garages, presumably due to automobile exhaust that infiltrated the residences. The mean MTBE level in garages of residences located in Boston, Massachusetts was reported as 131 µg/m^3 (36.3 ppbv), whereas the mean MTBE ambient outdoor level was 1.2 µg/m^3 (0.33 ppbv) (Dodson et al. 2008). Indoor air levels in randomly sampled homes located in Ottawa, Canada during the winter of 2002–2003 ranged from 0.025 to 3.32 µg/m^3 (0.0069–0.920 ppbv) and the detection frequency was 9% (Zhu et al. 2005). MTBE was detected in indoor air of homes that heat with fuel oil at a mean concentration of 11.8 µg/m^3 (3.27 ppbv) in air sampling conducted by the New York State Department of Health (NYSDOH) from 1997 to 2003 (NYSDOH 2006). Jo et al. (2003) analyzed outdoor and indoor air MTBE levels as a function of height in 56 high-rise apartment buildings located in South Korea and found levels were significantly greater for lower floor apartments than for the higher floor apartments, most likely due to closer proximity to mobile sources. These indoor air levels are not likely to be relevant to exposure levels currently in the United States since MTBE is no longer used as a gasoline additive.

MTBE in water is expected to rapidly volatilize; thus, there is potential for inhalation exposure during showering and bathing. ATSDR's three-compartment Shower and Household-Use Exposure (SHOWER) model predicts air concentrations in the shower stall, bathroom, and main house throughout the day by estimating the contribution from showering or bathing and the contribution from other water sources in the house, such as the dishwasher, clothes washer, and faucets. This information, along with human activity patterns, is used to calculate a daily TWA exposure concentration via inhalation exposure and from dermal uptake from skin contact. ATSDR's SHOWER model is available by sending a request to showermodel@cdc.gov.

Vapor intrusion may be a potential source of MTBE exposure, though indoor and ambient sources may also contribute to indoor air levels. EPA's compilation of four studies of background indoor air concentrations found a 9–70% detection rate for MTBE in 502 U.S. resident samples between 1990 and 2005 (EPA 2011). The background medians ranged from 0.025 to 3.5 µg/m^3, 95th percentiles ranged from 71 to 72 µg/m^3, and maximum values ranged from 3.3 to 470 µg/m^3. ATSDR compared detected MTBE concentrations from 20 vapor intrusion sites to ATSDR vapor intrusion comparison values from air, soil gas, or groundwater in a review of 148 public health assessments published between 1994 and 2010 (Burk and Zarus 2013). The AM/PM Gas Station site in Belmont California was the only site to exceed an ATSDR vapor intrusion comparison value for MTBE with groundwater concentrations up to 190,000 ppb (ATSDR 2005). The soil gas concentrations were all less than the comparison value at the site. Remedial actions that occurred at the site could decrease the potential for exposures in the future.

The site was not considered a public health hazard. Ma et al. (2017) developed a numerical model that used groundwater monitoring data from the EPA Underground Storage Tank program to estimate the potential vapor intrusion into buildings depending upon the characteristics of the buildings, soils, and MTBE level in groundwater. Their findings indicated that indoor air concentrations can exceed the EPA indoor air screening level for MTBE for highly contaminated groundwater plumes. Sanders and Hers (2006) analyzed indoor air in buildings potentially affected by contaminated groundwater due to a leaking underground gasoline storage tank in Stafford Township, New Jersey. Groundwater levels of MTBE ranged from 0.370 to 590 mg/L at five sampling locations. Indoor air was sampled on the main floor, in the basement, and under the foundation slab. In the location with the highest groundwater MTBE level, the indoor air concentrations were reported as 130 and 52.0 µg/m^3 (36.0 and 14.4 ppbv) in the basement and main floor, respectively. The vapor concentration of MTBE 2 m below the slab was 18,000 µg/m^3 (~5,000 ppbv).

5.5.2 Water

During the mid-1980s, New Jersey conducted some screening analysis for public drinking water supplies that included MTBE tests, as well as analyses from public and private wells as part of spill investigations or testing related to leaking USTs (NJDEP 1994). During this period, at least 30 wells serving six different community drinking water systems and at least 150 private wells had documented detectable amounts of MTBE. In cases involving a petroleum product spill or leakage, MTBE levels tended to be very high; in one case, it was as high as 40,000 ppb. When MTBE levels of ≥100 ppb were detected, there were also detections of such gasoline constituents such as benzene, toluene, xylene, or other hydrocarbons. The highest incidence of MTBE detections involved non-public wells, where 10% of the wells sampled showed MTBE levels of ≥70 ppb. Extrapolating the available samples to all private wells and public wellheads in New Jersey led to the estimate that 0.5–1% of the state's drinking water wells might show MTBE levels >70 ppb (NJDEP 1994). MTBE was monitored as part of the Unregulated Contaminant Monitoring Rule (UCMR-1) program to collect data for contaminants suspected to be present in drinking water, but that do not have health-based standards set under the Safe Drinking Water Act (SDWA). Between 2001 and 2005, MTBE was detected above its minimum reporting level (5 ppb) in 26 out of 34,131 samples of drinking water obtained from public water systems (PWSs) (EPA 2005b). It was detected above its minimum reporting level in 19 out of 3,877 PWSs that reported results. The maximum observed level was reported as 49 ppb and the mean of all positive detects was 15.2 ppb. Flanagan et al. (2017) monitored MTBE concentrations in private wells located in the state of New Hampshire from 2005 to 2015. Of 195 wells sampled in 2015, 10.3% had levels greater than the

reporting level of 0.2 µg/L (ppb) as compared to 26.7% of the wells in 2005. Maximum concentrations in the wells sampled ranged from 4.47 to 151 µg/L (ppb) in 2005 and declined over the next decade. The maximum concentration range in 2015 was reported as 0.2–4.55 µg/L (ppb). There appeared to be a correlation with frequency of detection and population density. For example, in 2015, wells in areas of higher population densities had a 15.5% detection frequency, whereas wells in areas of low population density the detection frequency was about a third of that value (5.1%). MTBE may also contaminate drinking water by leaching out of cross-linked polyethylene (PEX) constructed water pipes (some PEX products may utilize the catalyst *tert*-butyl peroxide, and MTBE is a breakdown product of this). Rajasarkka et al. (2016) detected levels of MTBE ranging from 1.45 to 11.7 µg/L (ppb) in water samples obtained from six apartment houses with epoxy-lined drinking water pipes in Helsinki, Finland.

The United States Geological Survey (USGS 1995) summarized VOC data on MTBE derived from a series of studies in its National Water-Quality Assessment (NAWQA) Program. Many of the NAWQA studies include a groundwater component. NAWQA data are available from 211 shallow wells in 8 urban areas and 524 shallow wells in 20 agricultural areas. MTBE was detected in 27% of the urban wells, but in only 1.3% of the rural wells. Only 3% of the urban wells showed MTBE concentrations that exceeded 20 ppb. The highest concentration of MTBE detected in a groundwater sample was around 23,000 ppb. Certain parts of the country with longer histories in the use of reformulated gasolines showed a higher incidence of MTBE detections. For instance, 79% of the test wells in the Denver, Colorado, area showed detectable traces of MTBE, and 37% of wells in New England showed detectable levels (detection limit, 0.2 ppb). While the shallow wells targeted for analysis in the NAWQA studies would seldom be part of the aquifers used in public drinking water systems, the USGS suggests that urban areas with a long history of reformulated gasoline usage may face increased risks of groundwater contamination from MTBE (USGS 1995).

A groundwater assessment conducted by the USGS from 1985 to 2001 analyzed 55 VOCs, including MTBE, from approximately 2,400 domestic and 1,100 public wells (USGS 2006). MTBE was the third most frequently detected VOC in the assessment. The median concentration of MTBE was reported as 0.20 µg/L (ppb) (n= 2,422). In a subset of samples from 1,687 wells that were analyzed using a lower assessment level (0.02 µg/L [ppb]), MTBE was detected in 7.1% of the wells. USGS (2016) analyzed 262 groundwater samples and 14 surface water samples in 2013 collected from 25 USGS projects nationwide and determined that MTBE was detected in 7% of the samples, with a concentration range of 0.016–0.226 µg/L (ppb).

In groundwater, studies of NPL and UST program remediation sites can provide highly site-specific indications of MTBE levels in groundwater. UST sites with MTBE groundwater contamination may potentially affect a larger total population since older gasoline stations are ubiquitous. Detections of MTBE triggered by reports of offensive odors in groundwater are common. Reported odor thresholds for MTBE in water range from 15 to 680 µg/L (ppb) (Angle 1991; EPA 1997; Gilbert and Calabrese 1992). Since the odor thresholds of much more dangerous chemicals like benzene are considerably higher (4,700 µg/L [ppb] for benzene), odor detections of MTBE are viewed as a type of early warning indicator of potentially more serious groundwater problems (Angle 1991).

5.5.3 Sediment and Soil

The USGS conducted an environmental monitoring study at a U.S. Army ammonium perchlorate destruction facility located in Chambersburg, Pennsylvania in 2016 (USGS 2019). MTBE was identified at levels above the detection limit of 1.7–2.6 µg/kg in 50% of samples; however, exact quantitative levels were not identified. MTBE was detected at a concentration of 18,000 µg/kg in soil (depth of 3 m) contaminated by a leaking underground gasoline storage tank in Stafford Township, New Jersey (Sanders and Hers 2006).

Studies in England's Southampton Harbor, with conditions that may find parallels in other countries in temperate climates where there is extensive use of reformulated gasoline (Bianchi et al. 1991), found that MTBE could accumulate in sediments in the pollutant sink environment of the harbor area. The sediment was then a major source of MTBE re-introduction to the surface waters. For an 18-month period of record, concentrations from sediment interstitial water samples were reported with a range of 14–20,645 ng/kg (ppt) (Bianchi et al. 1991).

5.5.4 Other Media

A laboratory study conducted on fish (Fujiwara et al. 1984) does not suggest any tendencies for bioconcentration, biomagnification, or bioaccumulation of MTBE that would present human health threats.

Where chemicals have a tendency to bioconcentrate, biomagnify, or bioaccumulate, they may show up in fish consumption advisories issued by the states. Examination of EPA's Fish Consumption Advisory Database (EPA 1995c) showed that no advisories had been issued for MTBE through September 1994.

MTBE has been detected in milk samples purchased in Las Vegas, Nevada in January and February 2002 (Hiatt and Pia 2004). Maximum concentrations in whole milk, 2% milk, and 1% milk were 0.03, 0.02, and 0.03 ng/mL, respectively, with a minimum detection limit of 0.01 ng/mL.

5.6 GENERAL POPULATION EXPOSURE

MTBE can be emitted to any or all environmental media (air, surface water, groundwater, and soil) depending on the source of the release, formulation mixture, and prevailing environmental conditions. The Fourth National Report on Human Exposures to Environmental Chemicals (CDC 2019) summarizes blood levels of MTBE for the U.S. population categorized by age, sex, and race. Table 5-8 shows these levels for survey years 2001–2008 and Table 5-9 provides these data for survey years 2011–2016 (MTBE levels were not measured in survey years 2009–2010). MTBE was still being used in gasoline for many of the years depicted in Table 5-8, but this use was generally discontinued after 2005. The decrease in blood MTBE levels after 2005 indicate that the general population was largely exposed to this substance due to its use as a fuel additive; current exposure levels are much lower than in previous decades. Silva et al. (2019) analyzed NHANES data prior to the discontinued use of MTBE and afterwards. They determined that the unweighted proportion of the individuals with MTBE blood levels above the limit of detection (LOD) for years 2001–2002 was 93%; this dropped to 25.4% of the population for the period 2011–2012. Prior to discontinuation of MTBE as a fuel additive, the general population was exposed via inhalation and dermal exposure during fueling operations, inhalation of ambient air including automobile exhaust, and oral exposure from drinking water. Current routes of exposure may arise from oral ingestion of drinking water, inhalation of ambient air, and possible dermal and inhalation exposure during showering activities of water containing MTBE. Vapor intrusion of MTBE into buildings and residences from contaminated groundwater may result in indoor air inhalation exposure. Since MTBE has been detected at NPL sites (see Section 5.1), populations living near hazardous waste sites may be exposed. MTBE is readily absorbed by oral and inhalation routes; however, it is reported to have low absorption dermally (EPA 2003b; Prah et al. 2004).

Table 5-8. Geometric Mean and Selected Percentiles of Methyl-*tert*-Butyl Ether (MTBE) Whole Blood Concentrations (in pg/mL) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) (2001–2008)

	Survey years[a]	Geometric mean (95% CI)	Selected percentiles (95% CI) 50th	75th	90th	95th	Sample size
Total	2001–2002	16.4 (4.77–56.7)	27.7 (7.29–64.9)	73.8 (35.5–127)	132 (64.0–278)	188 (109–339)	672
	2003–2004	11.0 (5.98–20.1)	10.0 (4.60–25.1)	45.0 (16.0–98.0)	110 (70.0–180)	170 (110–340)	1,307
	2005–2006	6.16 (2.94–12.9)	4.60 (1.80–15.0)	20.0 (5.20–73.0)	75.0 (22.0–140)	110 (49.0–250)	3,080
	2007–2008	*[b]	<LOD	<LOD	3.50 (2.00–7.83)	7.27 (3.40–22.3)	2,964
Age group							
12–19 years	2005–2006	5.85 (2.61–13.1)	4.20 (1.40–18.0)	18.0 (4.60–75.0)	70.0 (18.0–140)	110 (62.0–180)	911
	2007–2008	*	<LOD	<LOD	3.74 (1.90–8.47)	8.43 (3.10–19.0)	476
20–59 years	2001–2002	16.4 (4.77–56.7)	27.7 (7.29–64.9)	73.8 (35.5–127)	132 (64.0–278)	188 (109–339)	672
	2003–2004	11.0 (5.98–20.1)	10.0 (4.60–25.1)	45.0 (16.0–98.0)	110 (70.0–180)	170 (110–340)	1,307
	2005–2006	6.26 (3.05–12.9)	4.80 (2.00–14.0)	20.0 (5.50–70.0)	71.0 (21.0–150)	110 (46.0–250)	1,512
	2007–2008	*	<LOD	<LOD	3.16 (1.90–5.10)	5.10 (2.87–19.0)	1,597
≥60 years	2005–2006	6.00 (2.67–13.5)	3.80 (1.60–14.0)	22.0 (4.00–94.0)	22.0 (4.00–94.0)	120 (55.0–290)	657
	2007–2008	*	<LOD	1.80 (<LOD–3.10)	1.80 (<LOD–3.10)	14.0 (5.25–28.0)	891
Sex							
Males	2001–2002	16.9 (4.96–57.7)	27.9 (6.82–64.6)	75.0 (35.5–131)	132 (54.9–307)	167 (109–417)	334
	2003–2004	12.2 (6.29–23.6)	11.0 (4.80–29.0)	55.0 (18.0–110)	130 (79.0–200)	200 (110–470)	641
	2005–2006	6.24 (3.07–12.7)	4.60 (1.90–15.0)	20.0 (5.90–69.0)	73.0 (25.0–120)	110 (52.0–230)	1,462
	2007–2008	*	<LOD	1.40 (<LOD–2.21)	3.40 (1.93–8.40)	7.27 (3.00–26.0)	1,481
Females	2001–2002	16.0 (4.12–61.8)	26.6 (5.93–74.6)	72.7 (32.6–132)	142 (73.5–255)	194 (92.3–336)	338
	2003–2004	9.88 (5.62–17.4)	8.90 (4.30–23.0)	38.0 (14.0–85.0)	94.0 (58.0–160)	140 (90.0–250)	666
	2005–2006	6.08 (2.81–13.1)	4.50 (1.70–14.0)	19.0 (4.90–79.0)	76.0 (20.0–160)	110 (48.0–250)	1,618
	2007–2008	*	<LOD	<LOD	3.50 (1.90–8.40)	7.30 (3.60–16.5)	1,483
Race/ethnicity							
Mexican Americans	2001–2002	23.3 (4.96–110)	33.4 (2.92–187)	91.3 (26.1–255)	225 (80.6–339)	273 (182–358)	166
	2003–2004	11.6 (5.35–25.3)	12.0 (3.80–29.0)	32.0 (14.0–80.0)	80.0 (38.0–190)	160 (74.0–220)	245
	2005–2006	7.61 (2.99–19.3)	5.40 (2.00–33.0)	30.0 (4.60–90.0)	67.0 (26.0–190)	100 (45.0–330)	735
	2007–2008	*	<LOD	1.71 (<LOD–2.90)	4.10 (2.19–9.60)	8.80 (5.20–11.5)	559

Table 5-8. Geometric Mean and Selected Percentiles of Methyl-*tert*-Butyl Ether (MTBE) Whole Blood Concentrations (in pg/mL) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) (2001–2008)

	Survey years[a]	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Non-Hispanic blacks	2001–2002	14.9 (6.11–36.4)	26.4 (3.11–55.6)	52.6 (30.0–86.8)	87.4 (38.6–155)	120 (70.0–155)	119
	2003–2004	9.63 (4.83–19.2)	10.0 (3.50–28.0)	32.8 (11.0–85.0)	77.0 (36.0–160)	140 (61.0–210)	285
	2005–2006	9.14 (3.16–26.5)	5.70 (1.80–50.0)	48.0 (5.00–150)	120 (46.0–280)	180 (88.0–460)	820
	2007–2008	*	<LOD	1.90 (<LOD–3.80)	3.50 (2.40–7.27)	5.80 (3.50–15.3)	587
Non-Hispanic whites	2001–2002	16.0 (4.13–62.4)	27.9 (4.71–74.6)	72.7 (33.3–132)	132 (59.6–249)	165 (92.8–366)	333
	2003–2004	11.5 (5.51–23.8)	11.0 (4.00–33.5)	59.0 (14.0–120)	120 (73.0–230)	180 (110–430)	673
	2005–2006	5.55 (2.47–12.5)	4.00 (<LOD–15.0)	16.0 (4.30–75.0)	70.0 (15.0–150)	110 (40.0–250)	1,291
	2007–2008	*	<LOD	<LOD	3.30 (1.42–12.0)	7.10 (2.59–31.0)	1,349

[a]The limit of detection for survey years 2001–2002, 2003–2004, 2005–2006, and 2007–2008 were 0.232, 2.0, 1.4, and 1.4 pg/mL, respectively.
[b]Not calculated: proportion of results below limit of detection was too high to provide a valid result.

CI = confidence interval; LOD = limit of detection

Source: CDC 2019

Table 5-9. Geometric Mean and Selected Percentiles of Methyl-*tert*-Butyl Ether (MTBE) Whole Blood Concentrations (in pg/mL) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) (2011–2016)

	Survey years[a]	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Total	2011–2012	*[b]	<LOD	1.62 (<LOD–2.11)	3.50 (2.98–4.12)	4.63 (4.05–5.63)	2,509
	2013–2014	*	<LOD	<LOD	< LOD	<LOD	3,027
	2015–2016	*	<LOD	<LOD	< LOD	<LOD	2,858
Age group							
12–19 years	2011–2012	*	<LOD	<LOD	3.21 (2.53–3.49)	3.83 (3.38–4.43)	455
	2013–2014	*	<LOD	<LOD	<LOD	<LOD	555
	2015–2016	*	<LOD	<LOD	<LOD	<LOD	502
≥20 years	2011–2012	*	<LOD	1.70 (<LOD–2.14)	3.60 (3.07–4.15)	4.77 (4.12–5.96)	2,054
	2013–2014	*	<LOD	<LOD	<LOD	<LOD	2,472
	2015–2016	*	<LOD	<LOD	<LOD	<LOD	2,356
Sex							
Males	2011–2012	*	<LOD	1.77 (<LOD–2.18)	3.62 (3.15–4.28)	4.85 (4.15–5.96)	1,286
	2013–2014	*	<LOD	<LOD	<LOD	<LOD	1,458
	2015–2016	*	<LOD	<LOD	<LOD	<LOD	1,407
Females	2011–2012	*	<LOD	1.49 (<LOD–2.11)	4.49 (3.72–5.55)	4.49 (3.72–5.55)	1,286
	2013–2014	*	<LOD	<LOD	<LOD	<LOD	1,458
	2015–2016	*	<LOD	<LOD	<LOD	10.0 (<LOD–12.0)	1,407
Race/ethnicity							
Mexican Americans	2011–2012	*	<LOD	1.94 (<LOD–2.50)	3.66 (2.70–4.33)	4.66 (3.05–17.6)	271
	2013–2014	*	<LOD	<LOD	<LOD	<LOD	494
	2015–2016	*	<LOD	<LOD	<LOD	10.0 (<LOD–18.0)	499
Non-Hispanic blacks	2011–2012	*	<LOD	<LOD	2.42 (1.90–2.96)	3.55 (2.89–4.31)	639
	2013–2014	*	<LOD	<LOD	<LOD	<LOD	571
	2015–2016	*	<LOD	<LOD	<LOD	10.0 (<LOD–13.0)	574

Table 5-9. Geometric Mean and Selected Percentiles of Methyl-*tert*-Butyl Ether (MTBE) Whole Blood Concentrations (in pg/mL) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) (2011–2016)

			Selected percentiles (95% CI)				
	Survey years[a]	Geometric mean (95% CI)	50th	75th	90th	95th	Sample size
Non-Hispanic whites	2011–2012	*	<LOD	1.77 (<LOD–2.37)	3.71 (3.15–4.41)	4.80 (4.10–5.96)	891
	2013–2014	*	<LOD	<LOD	<LOD	<LOD	1,208
	2015–2016	*	<LOD	<LOD	<LOD	<LOD	941
All Hispanics	2011–2012	*	<LOD	1.80 (<LOD–2.23)	3.24 (2.51–4.01)	4.21 (3.25–6.09)	548
	2013–2014	*	<LOD	<LOD	<LOD	<LOD	792
	2015–2016	*	<LOD	<LOD	<LOD	10.0 (<LOD–14.0)	885
Asians	2011–2012	*	<LOD	<LOD	2.33 (1.41–3.89)	3.89 (2.01–6.85)	356
	2013–2014	*	<LOD	<LOD	<LOD	<LOD	353
	2015–2016	*	<LOD	<LOD	<LOD	<LOD	339

[a]The limit of detection for survey years 2011–2012, 2013–2014, and 2015–2016 were 1.40, 10.0, and 10.0 pg/mL, respectively.
[b]Not calculated: proportion of results below limit of detection was too high to provide a valid result.

CI = confidence interval; LOD = limit of detection

Source: CDC 2019

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Although it is no longer used as a gasoline additive in the United States, MTBE is still manufactured and exported to other nations that still use it as an oxygenate in fuels. Workers employed in industries that manufacture, formulate, store, or transport MTBE, and workers involved in the disposal of MTBE-containing wastes, are expected to have greater exposures than the general population. In occupational settings, inhalation and dermal exposure with subsequent absorption through intact skin are the most important routes of exposure. Persons residing near facilities that manufacture or blend MTBE into fuels for export will likely have greater exposure than the general population. Andreoli et al. (2015) studied a population of children in Sicily residing near a gasoline refinery and an additional group residing approximately 70 km away from the refinery to assess exposure to BTEX and MTBE. Levels of urinary MTBE and other compounds consistent with gasoline exposure were significantly higher at two sampling times (morning and evening) for the group residing near the refinery as compared to the group 70 km away. The geometric mean urinary MTBE levels for the children living close to the refinery were 0.79 µg/L (evening) and 0.82 µg/L (morning). The geometric mean urinary MTBE levels for the population living far-removed from the refinery were 0.56 µg/L (evening) and 0.59 µg/L (morning). It is possible that similar trends will exist in the United States for populations in close proximity to MTBE manufacturing facilities.

Two studies carried out by the National Institute for Occupational Safety and Health (NIOSH) at the request of the National Center for Environmental Health, Centers for Disease Control and Prevention, gathered case study measures of levels of MTBE in the air at a variety of workplaces in Stamford, Connecticut (NIOSH 1993a), and in Fairbanks, Alaska (NIOSH 1993b). Both studies focused on automobile repair centers where workers might be exposed to emissions or combustion byproducts. The Alaskan study was conducted after January 1993, at which time the use of MTBE as an anti-pollutant oxygenating agent had been suspended regionally. MTBE was still in use as an octane booster in high-octane (premium) grades of gasoline, but this would have been at levels (≤1% by weight) well below the levels associated with the use of MTBE as an anti-pollutant additive. The highest workplace concentrations found during the Alaskan studies were <1 ppmv. In Stamford, Connecticut, where MTBE was still being used as an anti-pollutant additive, the mean workplace concentration at automotive repair centers was 0.4 mg/m^3 (0.11 ppmv), with a range of 0.11–43.41 mg/m^3 (0.03–12.04 ppmv).

CHAPTER 6. ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of MTBE is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the adverse health effects (and techniques for developing methods to determine such health effects) of MTBE.

Data needs are defined as substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.1 INFORMATION ON HEALTH EFFECTS

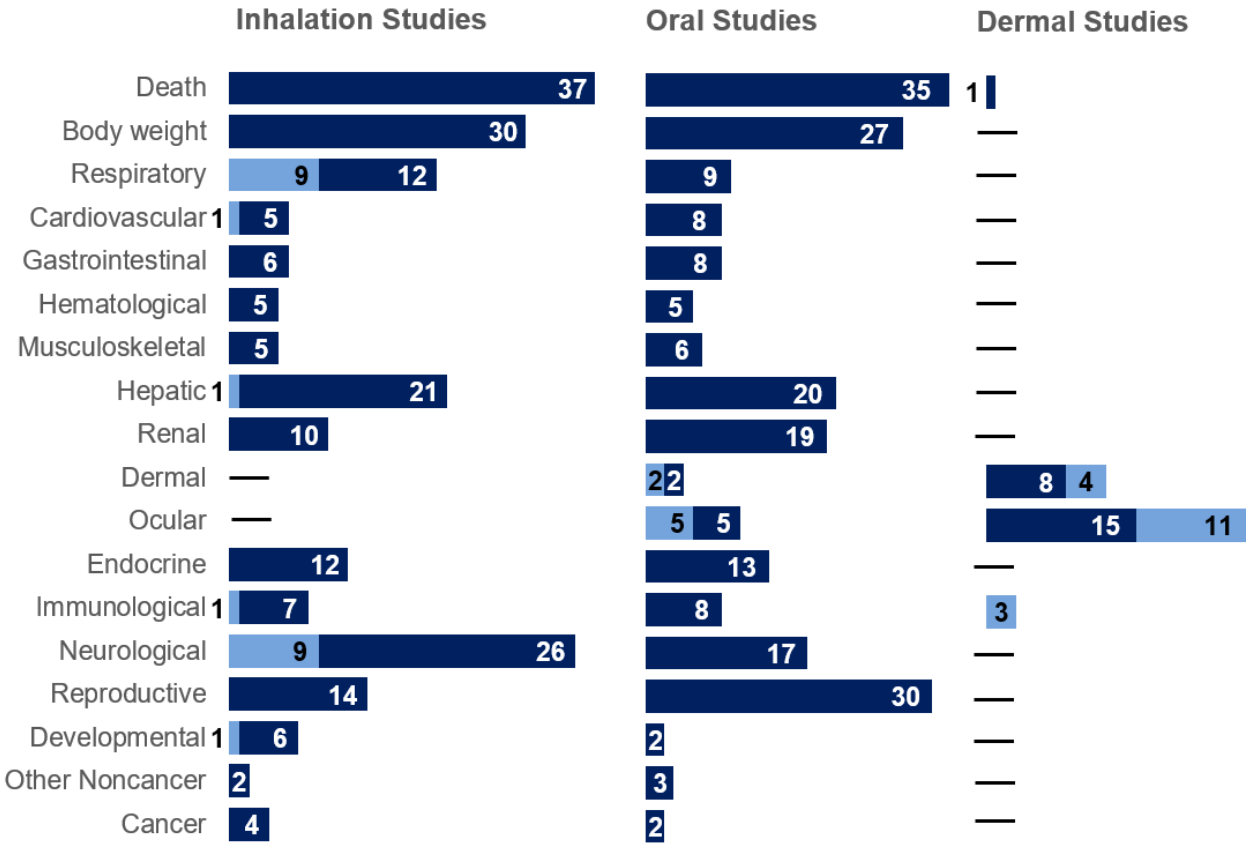
Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to MTBE that are discussed in Chapter 2 are summarized in Figure 6-1. The purpose of this figure is to illustrate the information concerning the health effects of MTBE. The number of human and animal studies examining each endpoint is indicated regardless of whether an effect was found and the quality of the study or studies.

Most data on the toxicity of MTBE come from inhalation and oral studies in laboratory animals, as shown in Figure 6-1. The number of oral and inhalation studies in animals is approximately equal. The most examined endpoints in animal studies were body weight, neurological, reproductive, and hepatic effects. Available human studies were limited to inhalation studies; however, ocular effects in these studies were considered attributable to direct eye contact with MTBE vapor in the air. Therefore, ocular effects were categorized as dermal exposure. Most human studies were occupational and population-based surveys that primarily evaluated potential associations between MTBE in the air with respiratory, ocular, and neurological endpoints.

Figure 6-1. Summary of Existing Health Effects Studies on MTBE By Route and Endpoint*

Potential body weight, neurological, reproductive, and hepatic effects were the most studied endpoints

The majority of the studies examined inhalation exposure in **animals** (versus **humans**)



*Includes studies discussed in Chapter 2; the number of studies include those finding no effect. Most studies examined multiple endpoints.

6.2 IDENTIFICATION OF DATA NEEDS

Missing information in Figure 6-1 should not be interpreted as a "data need." A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Acute-Duration MRLs. The inhalation database is adequate to derive a provisional acute-duration inhalation MRL. The oral database is not considered adequate for derivation of an acute-duration oral MRL. While neurological and male reproductive effects were identified as candidate critical effects following acute oral exposure, available studies evaluating neurological endpoints were inadequate in design and/or reporting and male reproductive findings were inconsistent between studies and exposure durations following oral exposure. Additional acute oral studies examining a wide range of potential effects including observations for neurological and male reproductive effects, are needed to identify the most sensitive targets of toxicity and establish dose-response relationships.

Intermediate-Duration MRLs. The inhalation database is adequate to derive a provisional intermediate-duration inhalation MRL. Additional inhalation studies with adequate data to further refine the NOAEL for the critical effect (neurological) and/or provide data adequate for benchmark dose (BMD) modeling could decrease uncertainty in the provisional intermediate-duration inhalation MRL. The oral database is considered adequate to derive a provisional intermediate-duration oral MRL; however, the critical effect (CNS depression) is reported inconsistently following oral exposure. Additional studies evaluating comprehensive neurological endpoints following oral exposure may reduce uncertainty in the provisional intermediate-duration oral MRL.

Chronic-Duration MRLs. The inhalation database is adequate to derive a provisional chronic-duration inhalation MRL. Additional inhalation studies with adequate data to further refine the NOAEL for the critical effect (renal effects in female rats) and/or provide data adequate for BMD modeling could decrease uncertainty in the chronic-duration inhalation MRL. The oral database is inadequate to derive a provisional chronic-duration oral MRL because no adverse nonneoplastic effects relevant to human health were reported at doses below the dose associated with serious effects (death and cancer). Well-designed, chronic-duration oral studies designed to evaluate a wide array of endpoints at low exposure levels,

particularly neurological, female renal, or male reproductive endpoints, could potentially identify an appropriate point of departure (POD) to use as the basis for a chronic-duration MRL.

Health Effects.

Gastrointestinal. Oral exposure studies in laboratory animals have reported diarrhea following gavage administration of MTBE. Gastrointestinal effects have not been reported in drinking water studies and have not been reported in inhalation studies. The difference in the results from the gavage and drinking water studies may be due to the administration route; daily intake administered as a single bolus dose versus being spread out throughout the day. In order to assess whether diarrhea is a relevant endpoint for humans typically exposed to MTBE via drinking water, additional studies are needed to evaluate whether the administration route influences gastrointestinal toxicity.

Renal Effects. Sex-related differences in the renal toxicity of MTBE have been observed in rat studies, with males being more sensitive than females. Renal effects observed in male rats following inhalation or oral exposure may be due, in part, to α2u-globulin accumulation, which is not relevant to human health (Ahmed 2001; Bogen and Heilman 2015; McGregor 2006; Phillips et al. 2008). However, some studies have not reported increases in α2u-globulin accumulation in male rats. Another study did not find the classical lesions of other α2u-globulin inducing agents. The available data suggest that other mechanisms (potentially another protein specific to male rats) may also play a role. Additional studies are needed to elucidate the mechanisms of renal toxicity in male rats and to assess whether these mechanisms are relevant to humans.

Endocrine. Several laboratory animal studies have reported adrenal gland effects, including increases in organ weight, histopathological alterations, and alterations in serum corticosterone level. However, these findings have not been consistently found across studies. Additional studies are needed to evaluate whether the adrenal gland is a target of MTBE toxicity.

Neurological. The inhalation database evaluating neurological effects is adequate; however, evidence for neurological effects following oral exposure is less robust. Acute- and intermediate-duration gavage studies indicate that bolus MTBE exposure results in transient CNS depression consistent with findings in inhalation studies. However, drinking water studies do not report CNS depression. In order to assess whether CNS depression following oral exposure is a relevant

endpoint for humans typically exposed to MTBE via drinking water, additional studies are needed to evaluate whether the oral administration route influences neurotoxicity.

Reproductive. Additional low-exposure oral studies in several species may better define potential male reproductive effects and inform the dose-response relationships. No human data are available regarding reproductive effects. However, there are some data from oral studies suggesting that the male rat reproductive system may be a potential target of MTBE toxicity. In contrast, there is no evidence from the inhalation database that exposure to MTBE alters reproductive function or organs. Mechanistic studies may help explain observed differences in male reproductive findings following oral versus inhalation exposure.

Developmental. There are limited epidemiological data evaluating the potential developmental toxicity of MTBE and no studies evaluated birth outcomes. Laboratory animal studies evaluated developmental endpoints following inhalation exposure and reported adverse effects (decreased offspring weight, delayed ossification, cleft palate) at concentrations associated with frank maternal effects. Oral exposure studies are limited to a study involving paternal exposure and a study evaluating male reproductive development following early postnatal exposure. Additional studies are needed to assess whether exposure to MTBE would result in developmental effects at dose levels not associated with maternal toxicity. Developmental toxicity studies in animals following oral exposure would address this data gap and may identify toxicity targets and/or inform dose-response relationships.

Other Noncancer Effects. Additional low-exposure animal studies in several species (inhalation and oral exposure) may better define potential alterations in glucose homeostasis following exposure to MTBE. One oral exposure study with extremely low doses reports alterations in glucose and zinc homeostasis in rats (Saeedi et al. 2017); however, limited evidence from other studies does not provide consistent evidence of alterations in serum glucose.

Epidemiology and Human Dosimetry Studies. Experimental studies of volunteers exposed to realistic exposure levels for longer durations are needed to establish the threshold for irritation and mild CNS effects (available controlled exposure studies are of brief duration [≤2 hours] and do not identify a threshold). Since MTBE is used as a gasoline additive in some countries, more studies of workers involved in the gasoline industry, and of people who work at or live near gasoline filling stations, could provide more reliable information on atmospheric levels that produce effects, especially signs of irritation

and CNS depression, and to eliminate biases in subjective symptom reporting. Epidemiological data from people who live in areas where the air, groundwater, or soil is contaminated from major production sites, large tank batteries, transfer terminals, active or abandoned waste sites, and gasoline leaks may also provide information regarding potential adverse health effects. Additionally, these data may address the possibility that some persons are or can become more chronically sensitive to MTBE, that a combustion product of MTBE may be playing a role in causing symptoms, and that such factors as cloud cover may contribute to reported adverse effects of exposed humans.

Biomarkers of Exposure and Effect.

Exposure. The amount of MTBE in blood or expired air appears to be the most useful biomarker of exposure because much of the absorbed MTBE is excreted unchanged in expired air (MTBE Committee 1990a, 1990b). In addition, expired air or blood levels of its metabolite, *tert*-butanol, can be useful indicators of MTBE exposure. Based on limited information in humans and based on clearance data in rats, monitoring of expired air, blood, or urine for MTBE or *tert*-butanol in humans could be used for determining very recent exposure to MTBE. However, after exposure ceases for a few days, MTBE and its metabolites would be cleared. The development of an alternative biomarker does not seem necessary or possible, because MTBE and its metabolites are cleared rapidly and no evidence of interactions with biological macromolecules was located.

Effect. MTBE exposure can lead to CNS depression characterized by ataxia, hypoactivity, drowsiness, anesthesia, duck-walk gait, decreased muscle tone, prostration, lack of startle response, and lack of righting reflex (see section 2.15). Exposure can induce hepatic microsomal enzymes (Brady et al. 1990; Savolainen et al. 1985), or lead to elevated levels of ALT, AST, or serum lactic dehydrogenase (Robinson et al. 1990), and may increase (Greenough et al. 1980) or decrease BUN (Robinson et al. 1990) levels. However, many ethers, alcohols, and other chemicals can lead to these effects or combination of effects; therefore, no known effect or combination of effects can be used as a biomarker to identify or quantify effects from exposure to MTBE specifically.

Absorption, Distribution, Metabolism, and Excretion. The absorption, distribution, metabolism, and excretion of MTBE has been well studied in rats after inhalation, oral, dermal, and intravenous exposure. Available studies provided information on rates and extent of absorption, retention in tissues, metabolism, and rates and extent of excretion of relatively low and high doses of MTBE. Based on shifts in elimination pathways following exposure to high doses compared to low doses, saturation of

metabolizing enzymes appears to occur, but does not appear to influence the overall elimination of MTBE from the body. Information on respiratory and urinary metabolites and results of *in vitro* studies with rat liver microsomes have provided sufficient information to propose a plausible metabolic pathway. Metabolism does not appear to be route specific. One area of research that is lacking is evaluation of the potential for direct olfactory transport of MTBE (or its metabolites) to the brain following inhalation exposure.

Comparative Toxicokinetics. Comprehensive information on toxicokinetics of MTBE is available only for rats. The only toxicokinetic information for MTBE in mice involves pulmonary excretion after intraperitoneal dosing (Yoshikawa et al. 1994). Studies in motorists and workers occupationally exposed to MTBE (Moolenaar et al. 1994; White et al. 1995) and an experimental inhalation study in humans (Cain et al. 1996) indicated that MTBE is well absorbed from lungs and metabolized to *tert*-butanol. Limited information regarding distribution, metabolism, and excretion of MTBE was available for humans who received MTBE via percutaneous intracystic infusion for dissolution of gallstones (Leuschner et al. 1991). The limited data in humans suggest some similarities in metabolism between rats and humans (i.e., *tert*-butanol as a common metabolite). However, finding the rat urinary metabolites, 2-methyl-1,2-propanediol and α-hydroxyisobutyric acid, in the urine of patients who receive MTBE therapy would provide a better basis for considering the rat a good model to predict the behavior of MTBE in the human body. The data on distribution and excretion are too limited to be compared. Toxicokinetic studies in other species are needed to determine if the disposition of MTBE is similar across species. The studies in rats provide some pharmacokinetic parameters and have allowed for the development and refinement of some PBPK models. However, actual data vary much more than model predictions, especially considering the potential for human variability in metabolism (e.g., Blancato et al. 2007; see Section 3.1.5 for more details). Therefore, further refinement of the models is needed for extrapolating pharmacokinetic, toxicity, and dose-response data to humans.

Children's Susceptibility. Developmental effects have not been evaluated in animals following dermal exposure, and developmental effects in animals following oral exposure have only been evaluated in studies with limited scope (e.g., male reproductive development; paternal exposure only). Studies in young animals and/or epidemiological data for children would be useful to address these data gaps. Available data from inhalation developmental studies in animals do not indicate that developing animals are uniquely susceptible to toxicity following exposure to MTBE.

Physical and Chemical Properties. The chemical and physical information available for MTBE is generally adequate (EPA 1994; Mackay et al. 1993). No major data needs have been identified in this area.

Physical and Chemical Properties. The chemical and physical information available for MTBE is generally adequate (EPA 1994; Mackay et al. 1993). No major data needs have been identified in this area.

Production, Import/Export, Use, Release, and Disposal. While the United States no longer uses MTBE in gasoline, there were 18 companies that reported manufacturing or importing MTBE in the United States in 2016 (EPA 2019b). Although exact numbers are often cited as confidential business information (CBI), it was estimated that between 1,000,000,000 and 5,000,000,000 pounds ($4.53x10^5$–$2.27×10^6$ metric tons) of MTBE were produced or imported in the United States in 2015. Data from the U.S. Energy Information Administration (EIA 2019) showed that manufacturers in the United States exported $1.4x10^7$ barrels of MTBE in 2018. TRI estimated that 241,141 pounds of MTBE were released from 132 facilities processing MTBE in 2018 (TRI18 2019). Continued production volume data along with release and import/export data are needed to evaluate potential human exposure.

Environmental Fate. The fate and transport of MTBE is well understood, and no major data needs are identified. MTBE released to soil or water will volatilize due to its high vapor pressure and Henry's Law constant. The rate at which MTBE volatilizes in water as a function of environmental conditions (e.g., water body depth, flow rate, temperature, and wind velocity) has been studied **(**Pankow et al. 1996). MTBE is broken down in the atmosphere by reacting with hydroxyl radicals (Cox and Goldstone 1982; Smith et al. 1991; Wallington et al. 1988). Limited data indicate that MTBE does not bioconcentrate in aquatic organisms (Fujiwara et al. 1984) and is slow to biodegrade (Finneran and Lovley 2001). MTBE possesses high mobility in soil, which causes it to leach into groundwater (USGS 2006).

Bioavailability from Environmental Media. Based on its physical properties and results from species tested so far, it is unlikely that MTBE will bioconcentrate to any degree (Fujiwara et al. 1984; Mackay et al. 1993). There is no indication that MTBE is a concern in any raw or processed food items. MTBE is highly volatile and shows little tendency to sorb to soil particles; therefore, even if it is in bioavailable form, it is not likely to be found in soils except under conditions of large contamination (e.g., leaking underground storage tanks). The main concerns involve inhalation of fumes in the air or

volatilized from water or surface soils. Additional information on bioavailability is not viewed as a significant data need.

Food Chain Bioaccumulation. While there is limited information on food chain bioaccumulation of MTBE, data for other similar nonchlorinated chemical solvents indicate no potential for bioaccumulation (Fujiwara et al. 1984; Gilbert and Calabrese 1992; Mackay et al. 1993). Toxicokinetics, metabolism, and excretion data similarly suggest no potential for bioaccumulation (Brady et al. 1990; Gilbert and Calabrese 1992; MTBE Committee 1990a, 1990b, 1990c, 1990d). Therefore, information in this area is not considered a major data need.

Exposure Levels in Environmental Media. Data needs exist to continue to conduct monitoring studies or update older studies for MTBE in air, water, and soil. Data exist for MTBE levels in air from 1980 through 2019 in the Air Quality System database from EPA (2019a). Groundwater assessments in major U.S. aquifers are available from USGS (2006), but sampling occurred from 1985 to 2001 and newer results would be useful, especially to determine its persistence in U.S. groundwater. MTBE was monitored as part of the UCMR-1 program to collect data for contaminants suspected to be present in drinking water, but that do not have health-based standards set under the SDWA. This monitoring occurred in 2001–2005 (EPA 2005b). Newer studies showing the levels of MTBE nationwide in drinking water are needed. There is a data gap in knowledge of potential ongoing population exposure via increases in indoor air from vapor intrusion into homes or buildings that are near contaminated groundwater (e.g., NPL sites, leaking underground storage tanks).

Additional reliable monitoring data for the levels of MTBE in contaminated media at hazardous waste sites are needed so that the information obtained on levels of MTBE in the environment can be used in combination with the known body burden of MTBE to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Exposure Levels in Humans. The Fourth National Report on Human Exposures to Environmental Chemicals summarized blood levels of MTBE for the U.S. population in 2001–2008 and 2011–2016 (CDC 2019). These data show a sharp decline in MTBE blood levels in the United States since its use as a gasoline additive was discontinued. Continued biological monitoring programs are needed to assess overall exposure to MTBE and possibly identify populations with high MTBE blood levels and trace the source of exposure. MTBE continues to be manufactured in large quantities in the United States and

exported. A data need exists to conduct biological monitoring studies for workers employed in industries that produce, transport, or store this product.

Exposures of Children. Biological monitoring for children aged 12–19 years are available in the most recent NHANES survey. Exposure pathways for children will be similar to those for adults. A data need exists to conduct biological monitoring studies for children of workers employed in industries that produce, transport, or store this product, or for children who reside in close proximity to MTBE-producing facilities.

6.3 ONGOING STUDIES

No ongoing studies were identified (RePORTER 2019).

CHAPTER 7. REGULATIONS AND GUIDELINES

Pertinent international and national regulations, advisories, and guidelines regarding MTBE in air, water, and other media are summarized in Table 7-1. This table is not an exhaustive list, and current regulations should be verified by the appropriate regulatory agency.

ATSDR develops MRLs, which are substance-specific guidelines intended to serve as screening levels by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites. See Section 1.3 and Appendix A for detailed information on the MRLs for MTBE.

Table 7-1. Regulations and Guidelines Applicable to Methyl *tert*-Butyl Ether (MTBE)

Agency	Description	Information	Reference
	Air		
EPA	RfC	3 mg/m^3 (0.83 ppm)	IRIS 1993
WHO	Air quality guidelines	Not listed	WHO 2010
	Water & Food		
EPA	Drinking water standards and health advisories	Health-based values not provided[a]	EPA 2018b, EPA 1997
	National primary drinking water regulations	Not listed	EPA 2009
	RfD	Not evaluated	IRIS 1993
WHO	Drinking water quality guidelines	Not derived[b]	WHO 2017
FDA	Substances Added to Food	Not listed[c]	FDA 2019
	Cancer		
HHS	Carcinogenicity classification	No data	NTP 2016
EPA	Carcinogenicity classification	No data	IRIS 1993
IARC	Carcinogenicity classification	Group 3[d]	IARC 1999
	Occupational		
ACGIH	TLV (TWA)	50 ppm	ACGIH 2002
OSHA	PEL (8-hour TWA) for general industry, shipyards, and construction	No data	OSHA 2019a, 2019b, 2019c
NIOSH	REL (up to 10-hour TWA)	No data	NIOSH 2018

Table 7-1. Regulations and Guidelines Applicable to Methyl *tert*-Butyl Ether (MTBE)

Agency	Description	Information	Reference
	Emergency Criteria		
EPA	AEGLs-air		EPA 2018c
	AEGL 1[e]		
	10-minute, 30-minute, 60-minute, 4-hour, 8-hour	50 ppm	
	AEGL 2[e]		
	10-minute	1,400 ppm	
	30-minute	800 ppm	
	60-minute	570 ppm	
	4-hour, 8-hour	400 ppm	
	AEGL 3[e]		
	10-minute	13,000 ppm[f]	
	30-minute	7,500 ppm[g]	
	60-minute	5,300 ppm[g]	
	4-hour	2,700 ppm[g]	
	8-hour	1,900 ppm[g]	
DOE	PACs-air		DOE 2018a
	PAC-1[h]	50 ppm	
	PAC-2[h]	570 ppm	
	PAC-3[h]	5,300 ppm	

[a]Advisory recommends that keeping contamination levels in the range of 20–40 µg/L or below (odor/taste thresholds) to protect consumer acceptance of the water would also provide a margin of safety from toxic effects.
[b]Reason for not establishing guideline value: guideline would be significantly higher than concentrations at which MTBE would be detected by odor.
[c]The Substances Added to Food inventory replaces EAFUS and contains the following types of ingredients: food and color additives listed in FDA regulations, flavoring substances evaluated by FEMA or JECFA, GRAS substances listed in FDA regulations, substances approved for specific uses in food prior to September 6, 1958, substances that are listed in FDA regulations as prohibited in food, delisted color additives, and some substances "no longer FEMA GRAS."
[d]Group 3: not classifiable as to its carcinogenicity to humans.
[e]Definitions of AEGL terminology are available from EPA (2018d).
[f]Value is higher than 50% of the LEL of MTBE in air (16,000 ppm); therefore, extreme safety considerations on the hazard of explosion must be taken into account.
[g]Value is higher than 10% of the LEL of MTBE in air (16,000 ppm); therefore, safety considerations on the hazard of explosion must be taken into account.
[h]Definitions of PAC terminology are available from U.S. DOE (2018b).

ACGIH = American Conference of Governmental Industrial Hygienists; AEGL = acute exposure guideline levels; DOE = Department of Energy; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; FEMA = Flavor and Extract Manufacturers Association of the United States; GRAS = generally recognized as safe; HHS = Department of Health and Human Services; IARC = International Agency for Research on Cancer; IRIS = Integrated Risk Information System; JECFA = Joint FAO/WHO Expert Committee on Food Additives; LEL = lower explosive limit; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PAC = protective action criteria; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TLV = threshold limit value; TWA = time-weighted average; WHO = World Health Organization

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APPENDIX A. ATSDR MINIMAL RISK LEVEL WORKSHEETS

MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified route and duration of exposure. MRLs are based on noncancer health effects only; cancer effects are not considered. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the NOAEL/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (≥365 days) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive substance-induced endpoint considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

APPENDIX A

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Office of Innovation and Analytics, Toxicology Section, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published MRLs. For additional information regarding MRLs, please contact the Office of Innovation and Analytics, Toxicology Section, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop S102-1, Atlanta, Georgia 30329-4027.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Methyl *tert*-Butyl Ether (MTBE)
CAS Numbers: 1634-04-4
Date: January 2022
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Acute
MRL: 2 ppm (provisional)
Critical Effect: Neurobehavior (altered gait)
Reference: Daughtrey et al. 1997; Gil 1989
Point of Departure: $BMCL_{10}$ of 454 ppm ($BMCL_{HEC}$ of 70.1 ppm)
Uncertainty Factor: 30
LSE Graph Key: 8
Species: Rat

MRL Summary: A provisional acute-duration inhalation MRL of 2 ppm was derived for MTBE based on neurological effects in female rats exposed to concentrations ≥4,000 ppm for 6 hours/day; a NOAEL of 800 ppm was identified (Daughtrey et al. 1997; Gil 1989). The MRL is based on a $BMCL_{10}$ of 454 ppm for increased incidence of altered gait in female rats. The $BMCL_{10}$ was adjusted to continuous duration exposure and converted to a human equivalent concentration ($BMCL_{HEC}$) of 70.1 ppm and divided by a total uncertainty factor of 30 (3 for extrapolation from animals to humans after dosimetric adjustment and 10 for human variability).

Selection of the Critical Effect: Available acute inhalation studies report numerous MTBE-related effects at lowest-observed-adverse-effect levels (LOAELs) in the range of 1,000–4,000 ppm, including neurological effects in rats and mice, hepatic effects in female mice, and decreased fetal weights in mouse offspring (see Table A-1). Renal effects in male rats were also observed at exposure levels ≥1,500 ppm; however, these effects were not considered an appropriate basis for the MRL because available toxicity and mechanistic studies indicate that renal effects in males are partially attributable to α2u-globulin, which is not relevant for human health (Ahmed 2001; Bogen and Heilman 2015; McGregor 2006; Phillips et al. 2008). Therefore, only neurological, respiratory, hepatic, and developmental effects were considered for MRL derivation.

Table A-1. Summary of Relevant NOAEL and LOAEL Values Following Acute Inhalation MRL to Methyl *tert*-Butyl Ether (MTBE)

Species	Duration	NOAEL (ppm)	LOAEL (ppm)	Effect	Reference
Neurological effects					
Fischer-344 rat	13 days 6 hours/day	ND	2,000	Hypoactivity	Dodd and Kintigh 1989
CD-1 mouse	13 days 6 hours/day	ND	2,000	Hypoactivity	Dodd and Kintigh 1989
CD-1 mouse	2 days 6 hours/day	400	3,000	Hypoactivity, decreased startle effect	Vergnes and Chun 1994
Fischer-344 rat	6 hours	800	4,000	Altered gait and decreased limb strength in females	Daughtrey et al. 1997; Gil 1989

Table A-1. Summary of Relevant NOAEL and LOAEL Values Following Acute Inhalation MRL to Methyl *tert*-Butyl Ether (MTBE)

Species	Duration	NOAEL (ppm)	LOAEL (ppm)	Effect	Reference
Respiratory effects					
Sprague-Dawley rat	9 days 5 days/week 6 hours/day	ND	1,000	Inflammation of nasal mucosa and trachea	Texaco Inc. 1981
Hepatic effects					
CD-1 mouse	13 days 6 hours/day	ND	2,000	Increased relative liver weight in females	Dodd and Kintigh 1989
Developmental effects					
CD-1 mouse	10 days (GDs 6–15) 6 hours/day	1,000	4,000	Decreased fetal weights	Bevan et al. 1997a

LOAEL = lowest observed adverse effect level; MRL = Minimal Risk Level; ND = not determined; NOAEL = no-observed-adverse-effect level

In order to identify the most sensitive point of departure (POD), benchmark dose (BMD) modeling was attempted for critical neurological, respiratory, hepatic, and developmental endpoints in Table A-1 when data were amenable to modeling. The data were fit to all available dichotomous or continuous models in EPA's Benchmark Dose Software (BMDS; version 3.1.2) using a benchmark response (BMR) of 1 standard deviation (grip strength, liver weight), 10% extra risk (altered gait incidence), or 5% relative deviation (developmental body weight). Adequate model fit was judged by three criteria: goodness-of-fit statistics (p-value >0.1), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined BMR. Among all of the models providing adequate fit to the data, the lowest BMCL (95% lower confidence limit on the BMC) was selected as the POD when the difference between the BMCLs estimated from these models was >3-fold; otherwise, the BMCL from the model with the lowest Akaike information criterion (AIC) was chosen.

Suitable models were identified for the following endpoints: decreased hindlimb strength in female rats (Daughtrey et al. 1997; quantitative data obtained from unpublished report by Gill 1989), increased incidence of altered gait in female rats (Daughtrey et al. 1997; quantitative data obtained from unpublished report by Gill 1989), and decreased fetal weights in mouse offspring (Bevan et al. 1997a). An adequate model was not identified for increased relative liver weight (Dodd and Kintigh 1989) because models failed to meet conventional goodness-of-fit criteria using either the full datasets or with the highest dose dropped. The datasets used for BMD modeling are presented in Tables A-2, A-3, and A-4, the model predictions are presented in Tables A-5, A-6, and A-7, and the fits of the selected models are presented in Figures A-1, A-2, and A-3. Neurological data from Dodd and Kintigh (1989) and Vergnes and Chun (1994) were inadequate for BMD modeling (incidence data not reported), and nasal and tracheal inflammation data from Texaco Inc. (1981) were inadequate for BMD modeling because the endpoint was only evaluated in control and high-exposure animals.

Table A-2. Neurological Endpoints in Female Rats Following Inhalation Exposure to Methyl *tert*-Butyl Ether (MTBE) for 6 Hours

	Concentration (ppm)			
	0	800	4,000	8,000
Altered gait Incidence (percent incidence)	1/8 (13%)	2/8 (25%)	6/8[a] (75%)	8/8[b] (100%)
Hind limb grip strength (kg) Mean±SD (n)	0.40±0.079 (8)	0.38±0.082 (8)	0.35±0.051[a] (8)	0.28±0.084[b] (8)

[a]p<0.05.
[b]p<0.01.

(n) = number of animals; SD = standard deviation

Source: Gill 1989 (unpublished report associated with published study by Daughtrey et al. 1997)

Table A-3. Fetal Weights in Mouse Offspring Following Maternal Inhalation Exposure to Methyl *tert*-Butyl Ether (MTBE) on GDs 6–15 (6 Hours/Day)

	Concentration (ppm)			
	0	1,000	4,000	8,000
Fetal body weight/litter (%) Mean±SD (n)	1.4±0.1 (27)	1.4±0.1 (29)	1.3±0.1[a] (26)	1.1±0.1[a] (26)

[a]p<0.01.

GD = gestation day; (n) = number of animals; SD = standard deviation

Source: Bevan et al. 1997a

Table A-4. Liver Weights in Female Mice Following Maternal Inhalation Exposure to Methyl *tert*-Butyl Ether (MTBE) for 13 Days (6 Hours/Day)

	Concentration (ppm)			
	0	2,000	4,000	8,000
Relative liver weight (percent body weight) Mean±SD (n)	5.830±0.4339 (5)	6.719±0.2502[a] (5)	6.644±0.1258[a] (5)	7.141±0.1970[a] (5)

[a]p<0.01.

(n) = number of animals per group; SD = standard deviation

Source: Dodd and Kintigh 1989

Table A-5. Model Predictions for Increased Incidence of Altered Gait in Female Rats Following Inhalation Exposure to Methyl *tert*-Butyl Ether (MTBE) for 6 Hours (Gill 1989)

Model	DF	χ^2	χ^2 Goodness-of-fit p-value[a]	Scaled residuals[b] Dose below BMC	Dose above BMC	Overall largest	AIC	BMC_{10} (ppm)	$BMCL_{10}$ (ppm)
Dichotomous Hill	1	0.41	0.52	0.45	-0.0001	0.45	30.44	3257.91	176.07
Gamma[c]	1	0.34	0.56	0.25	-0.32	0.39	30.50	886.02	180.30
LogLogistic[d]	1	0.41	0.52	0.45	0.0004	0.45	30.44	3139.72	175.99
Multistage (3-degree)[e]	1	0.02	0.88	-0.04	0.07	0.11	30.06	635.32	189.94
Multistage (2-degree)[e]	1	0.13	0.72	-0.08	0.15	0.25	30.21	757.08	186.31
Multistage (1-degree)[e]	2	0.77	0.68	0.23	-0.48	0.64	29.18	287.81	168.16
Weibull[c]	1	0.22	0.64	0.30	-0.18	0.30	30.30	1023.27	184.47
Logistic	2	0.18	0.92	-0.07	0.18	0.31	28.29	772.71	446.91
LogProbit[d]	1	0.41	0.52	0.45	-0.0001	0.45	30.44	2873.77	181.50
Probit[f]	**2**	**0.08**	**0.96**	-0.07	**0.14**	0.20	**28.14**	**732.29**	**453.69**

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Scaled residuals at doses immediately below and above the BMC; also the largest residual at any dose.
[c]Power restricted to ≥1.
[d]Slope restricted to ≥1.
[e]Betas restricted to ≥0.
[f]Selected model. All models provided an adequate fit to the data. BMCLs were sufficiently close (differed by <3-fold). Therefore, the model with the lowest AIC was selected (Probit).

AIC = Akaike Information Criterion; BMC = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMCL = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); DF = degrees of freedom; ND = not determined, goodness-of-fit criteria, p<0.10

Figure A-1. Fit of Probit Model to Incidence Data for Altered Gait in Female Rats Following Inhalation Exposure to Methyl *tert*-Butyl Ether (MTBE) for 6 Hours (Gill 1989)

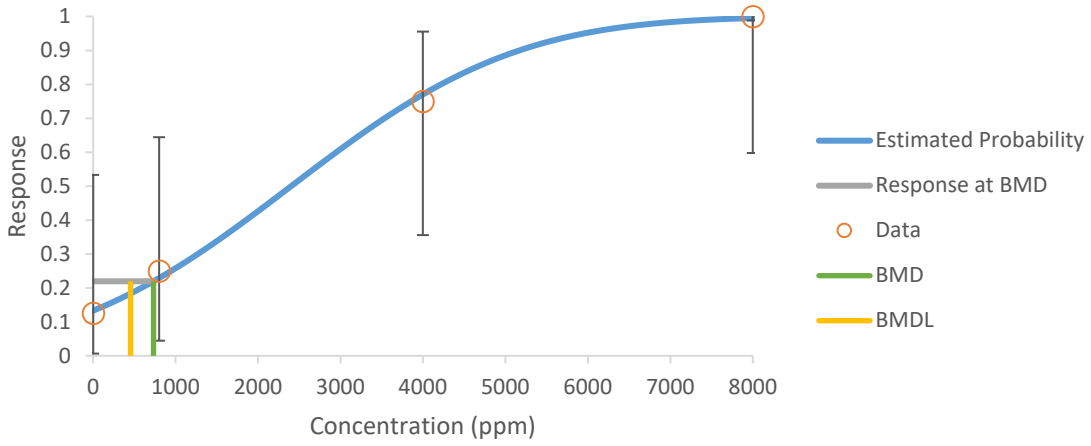


Table A-6. Results from Benchmark Dose (BMD) Analysis (Constant Variance) for Decreased Hindlimb Grip Strength in Female Rats Following Inhalation Exposure to Methyl *tert*-Butyl Ether (MTBE) for 6 Hours (Gill 1989)

Model	Test for significant difference p-value[a]	Test for variance p-value[b]	Test for means p-value[c]	Scaled residuals[d]			AIC	BMC_{SD1} (ppm)	$BMCL_{SD1}$ (ppm)
				Dose below BMC	Dose above BMC	Overall largest			
Exponential (model 2)[e]	0.04	0.52	0.84	0.48	-0.25	0.48	-72.71	4,674.24	2,881.25
Exponential (model 3)[e]	0.04	0.52	0.65	0.13	-0.04	-0.34	-70.86	5,470.60	2,915.30
Exponential (model 4)[e]	0.04	0.52	0.84	0.48	-0.25	0.48	-72.71	4,673.45	2,881.24
Exponential (model 5)[e]	0.04	0.52	0.65	0.13	-0.04	-0.34	-70.86	5,471.28	2,915.30
Hill[e]	0.04	0.52	0.57	0.00001	-0.00002	0.40	-70.74	4,263.15	3,835.62
Polynomial (3-degree)[e]	0.04	0.52	0.74	0.07	-0.01	-0.26	-70.95	5,613.91	3,310.10
Polynomial (2-degree)[e]	0.04	0.52	0.72	0.10	-0.02	-0.28	-70.93	5,512.37	3,305.67
Power[e]	0.04	0.52	0.68	0.15	-0.04	-0.32	-70.89	5,442.41	3,298.62
Linear[f]	**0.04**	**0.52**	**0.89**	**0.36**	**-0.15**	**0.36**	**-72.83**	**4,932.21**	**3,285.54**

[a]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[b]Values <0.05 fail to meet conventional goodness-of-fit criteria.
[c]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[d]Scaled residuals at doses immediately below and above the BMC; also the largest residual at any dose.
[e]Restricted model.
[f]Recommended model. The constant variance model provided an adequate fit to the data. All models provided adequate fits to the means. The BMCLs were sufficiently close (<3-fold); therefore, the model with the lowest AIC was selected (Linear).

AIC = Akaike Information Criterion; BMC = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMCL = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., $_{05}$ = exposure concentration associated with a 5% relative deviation); SD = standard deviation

Figure A-2. Fit of Linear Model to Data for Hindlimb Grip Strength in Female Rats Following Inhalation Exposure to Methyl *tert*-Butyl Ether (MTBE) for 6 Hours (Gill 1989)

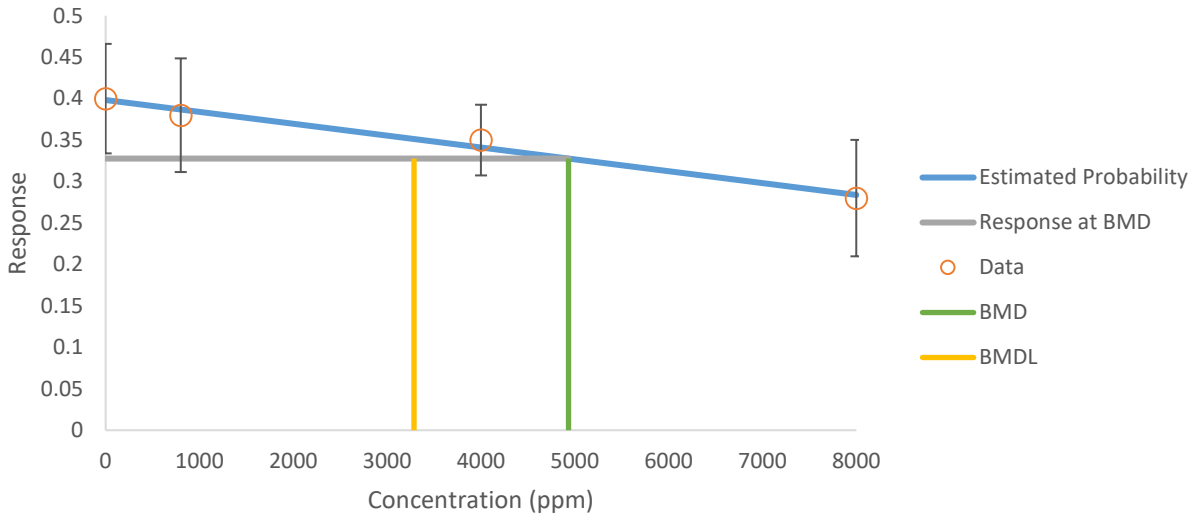


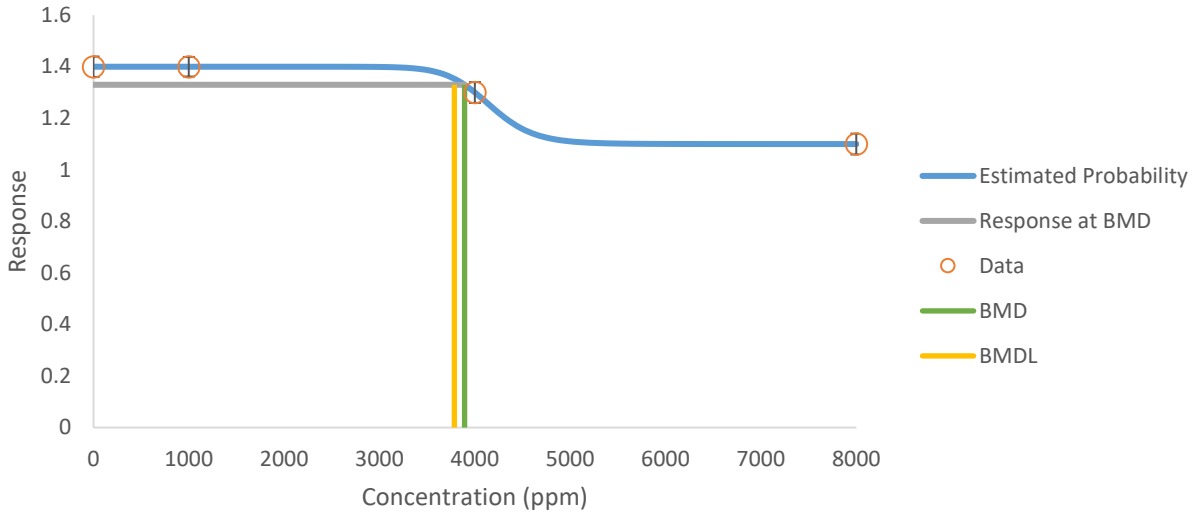
Table A-7. Results from Benchmark Dose (BMD) Analysis (Constant Variance) for Decreased Fetal Weights in Mouse Offspring Following Maternal Inhalation Exposure to Methyl *tert*-Butyl Ether (MTBE) on GDs 6–15 (6 Hours/Day) (Bevan et al. 1997a)

Model	Test for significant difference p-value[a]	Test for variance p-value[b]	Test for means p-value[c]	Scaled residuals[d]			AIC	BMC_{RD5} (ppm)	$BMCL_{RD5}$ (ppm)
				Dose below BMC	Dose above BMC	Overall largest			
Exponential (model 2)[e]	<0.0001	0.99999947	0.03	0.77	1.73	1.73	-181.89	ND	ND
Exponential (model 3)[e]	<0.0001	0.99999947	0.68	0.31	-0.10	0.31	-186.78	3,169.10	2,196.78
Exponential (model 4)[e]	<0.0001	0.99999947	0.03	0.77	1.73	1.73	-181.89	ND	ND
Exponential (model 5)[e]	<0.0001	0.99999947	ND	0.31	-0.10	0.31	-184.78	ND	ND
Hill[e,f]	**<0.0001**	**0.99999947**	**1.0**	**-0.0002**	**0.0003**	**0.0003**	**-186.94**	**3,891.16**	**3,784.02**
Polynomial (3-degree)[e]	<0.0001	0.99999947	0.51	0.51	-0.23	0.51	-186.51	3,108.30	2,015.59
Polynomial (2-degree)[e]	<0.0001	0.99999947	0.51	0.51	-0.23	0.51	-186.51	3,108.92	2,055.76
Power[e]	<0.0001	0.99999947	0.64	0.35	-0.13	0.35	-186.73	3,143.02	2,142.47
Linear	<0.0001	0.99999947	0.07	0.68	1.47	1.47	-183.73	ND	ND

[a]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[b]Values <0.05 fail to meet conventional goodness-of-fit criteria.
[c]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[d]Scaled residuals at doses immediately below and above the BMC; also the largest residual at any dose.
[e]Restricted model.
[f]Recommended model. The constant variance model provided an adequate fit to the data. The Exponential 3, Hill, 2- and 3-degree polynomial, and power models provided adequate fits to the means. The BMCLs were sufficiently close (<3-fold); therefore, the model with the lowest AIC was selected (Hill).

AIC = Akaike Information Criterion; BMC = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMCL = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., $_{05}$ = exposure concentration associated with a 5% relative deviation); GD = gestation day; ND = not determined; value did not compute or the model failed to meet the conventional goodness of fit criteria

Figure A-3. Fit of Hill Model to Data for Fetal Weights in Mouse Offspring Following Maternal Inhalation Exposure to Methyl tert-Butyl Ether (MTBE)on Gestation Days 6–15 (6 Hours/Day) (Bevan et al. 1997a)



The candidate PODs for neurological, respiratory, hepatic, and developmental effects are summarized in Table A-8. The lowest PODs were identified for neurological effects, with adjusted BMCL/NOAEL values of 100–114 ppm. Therefore, neurological effects were selected as the critical effect.

Table A-8. Summary of Candidate Effects and POD Values Considered for Derivation of an Acute Inhalation MRL for Methyl *tert*-Butyl Ether (MTBE)

Species	Duration	Effect	Candidate POD (ppm)	POD type	Reference
Neurological effects					
Fischer-344 rat	13 days 6 hours/day	Hypoactivity	500	$LOAEL_{ADJ}$	Dodd and Kintigh 1989
CD-1 mouse	13 days 6 hours/day	Hypoactivity	500	$LOAEL_{ADJ}$	Dodd and Kintigh 1989
CD-1 mouse	2 days 6 hours/day	Hypoactivity, decreased startle effect	100	$NOAEL_{ADJ}$	Vergnes and Chun 1994
Fischer-344 rat	6 hours	Altered gait in females[a]	114	$BMCL_{ADJ}$	Daughtrey et al. 1997; Gill 1989[b]
Fischer-344 rat	6 hours	Decreased limb strength in females	821	$BMCL_{ADJ}$	Daughtrey et al. 1997; Gill 1989[a]

Table A-8. Summary of Candidate Effects and POD Values Considered for Derivation of an Acute Inhalation MRL for Methyl *tert*-Butyl Ether (MTBE)

Species	Duration	Effect	Candidate POD (ppm)	POD type	Reference
Respiratory effects					
Sprague-Dawley rat	9 days 5 days/week 6 hours/day	Inflammation of nasal mucosa and trachea	179	$LOAEL_{ADJ}$	Texaco Inc. 1981
Hepatic effects					
CD-1 mouse	13 days 6 hours/day	Increased relative liver weight in females	500	$LOAEL_{ADJ}$	Dodd and Kintigh 1989
Developmental effects					
CD-1 mouse	10 days (GDs 6–15) 6 hours/day	Decreased fetal weights	946	$BMCL_{ADJ}$	Bevan et al. 1997a

[a]Selected study/endpoint for derivation of acute inhalation MRL.
[b]Gill (1989) is the unpublished report associated with Daughtrey et al. (1997). Raw data for benchmark dose modeling was acquired from Gill (1989) (not available in published report).

BMC = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; $BMCL_{ADJ}$ = 95% lower confidence limit on the BMC (adjusted for continuous exposure); GD = gestation day; $LOAEL_{ADJ}$ = lowest observed adverse effect level (adjusted for continuous exposure); MRL = Minimal Risk Level; NA = not applicable; ND = not determined; $NOAEL_{ADJ}$ = no-observed-adverse-effect level (adjusted for continuous exposure); POD = point of departure

Selection of the Principal Study: The $BMCL_{ADJ}$ of 114 ppm for neurological effects (altered gait) in female rats observed by Daughtrey et al. (1997) following a 6-hour exposure to MTBE was selected as the POD for the provisional acute-duration inhalation MRL. Data for this study are also available in the unpublished report by Gill (1989). This POD was selected over the $NOAEL_{ADJ}$ of 100 ppm for neurological effects reported by Vergnes and Chun (1994) because the selected study was designed to examine potential neurological effects following acute inhalation exposure to MTBE, including clinical signs, a functional observation battery (FOB), and motor activity, while Vergnes and Chun (1994) only evaluated clinical signs in the context of an *in vivo* genotoxicity assay. Additionally, the selected study included more animals per dose than Vergnes and Chun (1994). Therefore, there is higher confidence in the neurological POD from the study by Daughtrey et al. (1997). Additionally, quantitative data adequate for BMD modeling were only available for Daughtrey et al. (1997) (from the associated unpublished report by Gil 1989).

Summary of the Principal Study:

Daughtrey WC, Gill MW, Pritts IM, et al. 1997. Neurotoxicological evaluation of methyl tertiary-butyl ether in rats. J Appl Toxicol 17 Suppl 1:S57-S64.

Gill MW. 1989. Methyl tertiary butyl ether single exposure vapor inhalation neurotoxicity study in rats. Union Carbide Corporation. Submitted to the U.S. Environmental Protection Agency under TSCA Section 4. 602-823. OTS0528043. 409813440.

Daughtrey et al. (1997) exposed Fischer 344 rats to MTBE vapor for 6 hours at concentrations of 0, 800, 4,000, or 8,000 ppm. Groups were comprised of 22 males and 22 females. Groups of 14 male and 14 female rats were evaluated for motor activity prior to and within 1 hour following a single 6-hour

exposure. The length of the test sessions was either 90 minutes (pre-exposure) or 5 hours (post-exposure). The remaining eight rats/sex/group were given an FOB of tests (piloerection, respiratory pattern, gait, urination, startle response, pupil size, pupil response, catatonic pose, fore and hind paw grip strength, treadmill, inclined screen turn, toe pinch, time to tail flick, rectal temperature, and hind leg splay) prior to exposure and at 1, 6, and 24 hours after exposure. Data for this study are also available in the unpublished report by Gill (1989).

No rats died prematurely. No body weight effects were noted. No clinical signs of overt toxicity were observed. In the FOB, evidence of transient CNS depression was observed at the 1-hour observation at ≥4,000 ppm; no effects were observed at the 6- or 24-hour observations. Altered gait (ataxia, duck walk) and decreased body temperature were observed in females at ≥4,000 ppm and males at 8,000 ppm. Decreased grip strength was observed in females only at ≥4,000 ppm. Other significant behavioral findings in males and/or females at 8,000 ppm included decreased muscle tone, decreased treadmill performance, hindlimb splay, and labored respiration. Lacrimation was also observed but was attributed to the irritative nature of MTBE vapors. No significant behavioral observations were found in the 800-ppm group during the FOB. In motor activity testing, a biphasic result was observed in both sexes at 8,000 ppm, with a significant 60–67% reduction in motor activity at 10 minutes followed by significant increases up to 17-fold between 30 and 60 minutes, compared to controls. No significant findings were observed at 4,000 ppm. Significant changes in motor behavior at 800 ppm were observed only at 10 minutes and included a 24% increase in males and a 16% decrease in females. These findings were not considered biologically relevant due to lack of dose-response, low magnitude of effect, and differential findings in males versus females. Motor activity testing during the initial 180 minutes of the dark phase showed a statistically significant decrease in activity during the first hour of darkness only at 8,000 ppm (magnitude of effect not reported by the study authors).

Selection of the Point of Departure for the MRL: The $BMCL_{10}$ of 454 ppm for neurological effects (altered gait) in female rats was selected as the POD. This value represents the lowest available POD for the critical effect (neurotoxicity) from an acute comprehensive neurological study (Daughtrey et al. 1997). This value was selected over the NOAEL of 400 ppm based on clinical signs in the context of an *in vivo* genotoxicity assay by Vergnes and Chun (1994) due to higher confidence in the value derived from the more comprehensive study by Daughtrey et al. (1997).

Calculations

Intermittent Exposure: The $BMCL_{10}$ of 454 ppm was adjusted from intermittent exposure to account for a continuous exposure scenario:

$$BMCL_{ADJ} = 454 \text{ ppm} \times (6 \text{ hours}/24 \text{ hours}) = 114 \text{ ppm}.$$

Human Equivalent Concentration: While several PBPK models have been developed for MTBE, further refinement is needed to decrease uncertainty in estimated exposure levels, particularly for humans (see Sections 3.1.5 and 6.2 for more details). Therefore, a human equivalent concentration (HEC) for extrarespiratory effects was calculated by multiplying the $BMCL_{ADJ}$ by the ratio of animal:human blood gas partition coefficients, using a reported rat blood gas partition coefficient of 11.5 (Rao and Ginsberg 1997) and the midpoint of the range of human blood gas partition coefficients (17.7–19.6) reported by Rao and Ginsberg (1997) and Kim et al. (2007):

$BMCL_{HEC}$ = $BMCL_{ADJ}$ x ratio of animal:human blood gas partition coefficients
$BMCL_{HEC} = 114 \text{ ppm} \times (11.5/18.7)$
$BMCL_{HEC} = 114 \text{ ppm} \times (0.615)$
$BMCL_{HEC} = 70.1 \text{ ppm}$

Uncertainty Factor: The $BMCL_{HEC}$ is divided by a total uncertainty factor (UF) of 30.

- 3 for extrapolation from animals to humans after dosimetric adjustment
- 10 for human variability

Provisional MRL = $BMCL_{HEC} \div UF$
$70.1 \text{ ppm} \div (3 \times 10) = 2 \text{ ppm}$

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Selection of a neurological effect as the critical effect following acute inhalation exposure is supported by consistent observation of CNS depressive effects following inhalation exposure to concentrations ≥2,000 ppm following acute-, intermediate-, and chronic-duration studies (Bevan et al. 1997a, 1997b; Bird et al. 1997; Dodd and Kintigh 1989; Lington et al. 1997; Moser et al. 1996; MTBE Committee 1990a; Vergnes and Chun 1994; Vergnes and Morabit 1989). Additionally, some studies have reported effects consistent with transient CNS depression in humans exposed to MTBE in fuel, including headache, nausea or vomiting, dizziness, and a feeling of spaciness or disorientation (Alaska DHSS 1992a, 1992b; CDC 1993a; Moolenaar et al. 1994; Wisconsin DHSS 1995). When using the neurological NOAEL of 400 ppm from Vergnes and Chun (1994), the provisional MRL calculates to the same value.

Agency Contacts (Chemical Managers): Jennifer Przybyla

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Methyl *tert*-Butyl Ether (MTBE)
CAS Numbers: 1634-04-4
Date: January 2022
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Intermediate
MRL: 1 ppm (provisional)
Critical Effect: CNS depression and elevated liver weight
Reference: Bevan et al. 1997b; Bird et al. 1997
Point of Departure: NOAEL of 400 ppm ($NOAEL_{HEC}$ of 43.9 ppm)
Uncertainty Factor: 30
LSE Graph Key: 27, 29
Species: Rat

MRL Summary: A provisional intermediate-duration inhalation MRL of 1 ppm was derived for MTBE based on CNS depression in rats and mice and elevated liver weight in rats exposed to concentrations ≥3,000 ppm for 6 hours/day, 5 days/week for 4–19 weeks; a NOAEL of 400 ppm was identified (Bevan et al. 1997b; Bird et al. 1997). The MRL is based on the NOAEL of 400 ppm, which was adjusted to continuous duration exposure and converted to a $NOAEL_{HEC}$ of 43.9 ppm and divided by a total uncertainty factor of 30 (3 for extrapolation from animals to humans after dosimetric adjustment and 10 for human variability).

Selection of the Critical Effect: Available intermediate-duration inhalation studies report numerous MTBE-related effects, with NOAEL and LOAEL values of 400 and 3,000 ppm, respectively (see Table A-9). Effects observed at ≥3,000 ppm included neurological effects in rats and mice, hepatic effects in male and female rats and female mice, endocrine (adrenal) effects in rats, and decreased neonatal weights in F1 and F2 rat offspring. Renal effects in male rats were also observed at exposure levels ≥3,000 ppm; however, these effects were not considered an appropriate basis for the MRL because available toxicity and mechanistic studies indicate that renal effects in males are partially attributable to α2u-globulin, which is not relevant for human health (Ahmed 2001; Bogen and Heilman 2015; McGregor 2006; Phillips et al. 2008). Additionally, the adversity of elevated adrenal gland weight in female rats at ≥3,000 ppm in the absence of histopathological alterations at concentrations up to 8,000 ppm, reported in Bird et al. (1997), is unclear. Only one study reported adrenal lesions in female mice (loss of zona reticularis) at 8,000 ppm, in the absence of altered adrenal weight (Moser et al. 1998); however, no histopathological evidence of damage to the adrenal gland was observed in intermediate-duration inhalation studies in rats at concentrations up to 8,000 ppm (Greenough et al. 1980; Lington et al. 1997). Therefore, only neurological, hepatic, and developmental effects were further considered for MRL derivation.

Table A-9. Summary of Relevant NOAEL and LOAEL Values Following Intermediate Inhalation to Methyl *tert*-Butyl Ether (MTBE)

Species	Duration	NOAEL (ppm)	LOAEL (ppm)	Effect	Reference[a]
Neurological effects					
Fischer-344 rat	28 days 5 days/week 6 hours/day	400	3,000 (serious LOAEL)	Ataxia, hypoactivity, loss of startle reflex, blepharospasm	Bird et al. 1997; Chun and Kintigh 1993

Table A-9. Summary of Relevant NOAEL and LOAEL Values Following Intermediate Inhalation to Methyl *tert*-Butyl Ether (MTBE)

Species	Duration	NOAEL (ppm)	LOAEL (ppm)	Effect	Reference[a]
Sprague-Dawley rat	2 generations ~14–19 weeks/ generation 5 days/week 6 hours/day	400	3,000	Hypoactivity, blepharospasm, lack of startle reflex in F0 and F1 adults	Bevan et al. 1997b; Neeper-Bradley 1991
CD-1 mouse	28 days 5 days/week 6 hours/day	400	3,000 (serious LOAEL)	Ataxia, hypoactivity, loss of startle reflex	Bird et al. 1997; Chun and Kintigh 1993
Fischer-344 rat	13 weeks 5 days/week 6 hours/day	800	4,000	Transient hypoactivity	Lington et al. 1997
Hepatic effects					
Fischer-344 rat	28 days 5 days/week 6 hours/day	400	3,000	Increased relative liver weight in males and females	Bird et al. 1997; Chun and Kintigh 1993
Sprague-Dawley rats	2 generations ~14–19 weeks/ generation 5 days/week 6 hours/day	400	3,000	Increased relative liver weight in F1 adult males	Bevan et al. 1997b
CD-1 mouse	28 days 5 days/week 6 hours/day	400	3,000	Increased relative liver weight in females	Bird et al. 1997; Chun and Kintigh 1993
Fischer-344 rat	13 weeks 5 days/week 6 hours/day	ND	800	Increased relative liver weight in males	Lington et al. 1997
Endocrine effects					
Fischer-344 rat	28 days 5 days/week 6 hours/day	400	3,000	Increased relative adrenal gland weight in females	Bird et al. 1997; Chun and Kintigh 1993
Fischer-344 rat	13 weeks 5 days/week 6 hours/day	800	4,000	Increased relative adrenal gland weight	Lington et al. 1997
Developmental effects					
Sprague-Dawley rats	2 generations ~14–19 weeks/ generation 5 days/week 6 hours/day	400	3,000	Decreased F1 and F2 offspring body weight during lactation	Bevan et al. 1997b; Neeper-Bradley 1991

[a]Both published and unpublished studies are cited when unpublished data were referred to for additional information.

LOAEL = lowest observed adverse effect level; ND = not determined; NOAEL = no-observed-adverse-effect level

In order to identify the most sensitive POD, BMD modeling was attempted for critical neurological and developmental endpoints in Table A-9 when data were amenable to modeling. The data were fit to all

available continuous models in EPA's BMDS (version 3.1.2) using a BMR of 1 standard deviation (liver weight) or 5% relative deviation (developmental body weight). Adequate model fit was judged by three criteria: goodness-of-fit statistics (p-value >0.1), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined BMR. Among all of the models providing adequate fit to the data, the lowest BMCL (95% lower confidence limit on the BMC) was selected as the POD when the difference between the BMCLs estimated from these models was >3-fold; otherwise, the BMCL from the model with the lowest AIC was chosen.

Suitable models were identified for the following endpoints: increased relative liver weight in female mice (Bird et al. 1997; quantitative data obtained from unpublished report by Chun and Kintigh 1993), increased relative liver weight in male rats (Lington et al. 1997), increased relative liver weight in adult F1 males (Bevan et al. 1997b), and decreased female F1 body weight (postnatal day [PND] 14) and F2 body weight (PND 21) (Bevan et al. 1997b; quantitative data obtained from unpublished report by Neeper-Bradley 1991). No adequate models were identified for increased relative liver weight in male or female rats (Bird et al. 1997; quantitative data obtained from unpublished report by Chun and Kintigh 1993) because they failed to meet conventional goodness-of-fit criteria using either the full dataset or with the highest dose dropped. BMD modeling could not be conducted on neurological data because the dataset provides limited information on the dose-response between the extremes of 0% incidence in controls and low-concentration groups and 100% incidence at the LOAEL. The datasets used for BMD modeling are presented in Tables A-10, A-11, and A-12, the model predictions are presented in Tables A-13, A-14, A-15, A-16, and A-17, and the fits of the selected models are presented in Figures A-4, A-5, A-6, A-7, and A-8.

Table A-10. Relative Liver Weights in Rats and Mice Following Inhalation Exposure for 28 Days (5 Days/Week, 6 Hours/Day)

	Concentration (ppm)			
	0	400	3,000	8,000
Male rat relative liver weight (% BW) Mean±SD (n)	3.756±0.2057 (10)	3.844±0.0959 (10)	4.094±0.2473[a] (10)	4.393±0.2749[a] (10)
Female rat relative liver weight (% BW) Mean±SD (n)	3.556±0.0854 (10)	3.606±0.2525 (10)	3.869±0.1446[a] (10)	3.916±0.1347[b] (10)
Female mouse relative liver weight (% BW) Mean±SD (n)	5.428±0.4886 (10)	5.334±0.4029 (10)	5.895±0.4654[a] (9)	6.120±0.3768[a] (10)

[a]p<0.05.
[b]p<0.01.

BW = body weight; (n) = number of animals; SD = standard deviation

Source: Chun and Kintigh 1993 (unpublished report associated with published study by Bird et al. 1997)

Table A-11. Relative Liver Weights in Male Rats Following Inhalation Exposure for 13 Weeks (5 Days/Week, 6 Hours/Day)

	Concentration (ppm)			
	0	800	4,000	8,000
Male rat relative liver weight (% BW) Mean±SD (n)	3.15±0.16 (15)	3.39±0.16 (15)	3.78±0.26[a] (15)	4.37±0.19[a] (15)

[a]p≤0.05.

BW = body weight; (n) = number of animals; SD = standard deviation

Source: Lington et al. 1997

Table A-12. Body and Liver Weights in Rat Offspring in a 2-Generation Inhalation Exposure Study (5 Days/Week, 6 Hours/Day)

	Concentration (ppm)			
	0	400	3,000	8,000
F1 female body weight on PND 14 (g) Litter mean±SD (n)	25.43±2.808 (22)	25.43±2.456 (22)	22.94±3.452[a] (25)	22.16±2.845[b] (20)
F2 body weight on PND 21 (g) Litter mean±SD (n)	45.67±2.707 (22)	44.25±3.479 (22)	41.29±4.178[b] (22)	38.28±8.844[b] (21)
Adult F1 male relative liver weight (%) Mean±SD (n)	3.42±0.29 (25)	3.49±0.32 (25)	3.76±0.37[b] (25)	4.31±0.42[b] (25)

[a]p<0.05.
[b]p<0.01.

(n) = number of animals; PND = postnatal day; SD = standard deviation

Sources: Bevan et al. 1997b; Neeper-Bradley 1991

Table A-13. Results from Benchmark Dose (BMD) Analysis (Constant Variance) of Relative Liver Weight in Female Mice Following Inhalation Exposure to Methyl *tert*-Butyl Ether (MTBE) for 28 Days (5 Days/Week, 6 Hours/Day) (Chun and Kintigh 1993)

Model	Test for significant difference p-value[a]	Test for variance p-value[b]	Test for means p-value[c]	Scaled residuals[d]			AIC	BMC_{1SD} (ppm)	$BMCL_{1SD}$ (ppm)
				Dose below BMC	Dose above BMC	Overall largest			
Exponential (model 2)[e]	0.003	0.84	0.21	1.40	-0.42	1.40	50.62	4,690.99	3,388.88
Exponential (model 3)[e]	0.003	0.84	0.21	1.40	-0.42	1.40	50.62	4,690.86	3,388.89
Exponential (model 4)[e,f]	**0.003**	**0.84**	**0.28**	**-0.82**	**0.30**	**-0.82**	**50.68**	**2,250.54**	**847.07**
Exponential (model 5)[e]	0.003	0.84	ND	-0.36	-0.0002	-0.36	51.77	ND	ND
Hill[e]	0.003	0.84	ND	-0.36	0.0008	-0.36	51.77	ND	ND
Polynomial (3-degree)[e]	0.003	0.84	0.23	1.34	-0.43	1.34	50.44	4,505.24	3,188.10
Polynomial (2-degree)[e]	0.003	0.84	0.23	1.34	-0.43	1.34	50.44	4,505.24	3,188.10
Power[e]	0.003	0.84	0.23	1.34	-0.43	1.34	50.44	4,505.24	3,188.10
Linear	0.003	0.84	0.23	1.34	-0.43	1.34	50.44	4,505.24	3,188.10

[a]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[b]Values <0.05 fail to meet conventional goodness-of-fit criteria.
[c]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[d]Scaled residuals at doses immediately below and above the BMC; also the largest residual at any dose.
[e]Restricted model.
[f]Recommended model. The constant variance model provided an adequate fit to the data. All models except Exponential 5 and Hill models provided adequate fits to the means. The BMCLs differed by >3-fold; therefore, the model with the lowest BMCL was selected (Exponential 4).

AIC = Akaike Information Criterion; BMC = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMCL = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., $_{1SD}$ = exposure concentration associated with 1 standard deviation); ND = not determined; value did not compute or the model failed to meet the conventional goodness of fit criteria; SD = standard deviation

Figure A-4. Fit of Exponential 4 Model to Data for Relative Liver Weight in Female Mice Following Inhalation Exposure to Methyl *tert*-Butyl Ether (MTBE) in for 28 Days (5 Days/Week, 6 Hours/Day) (Chun and Kintigh 1993)

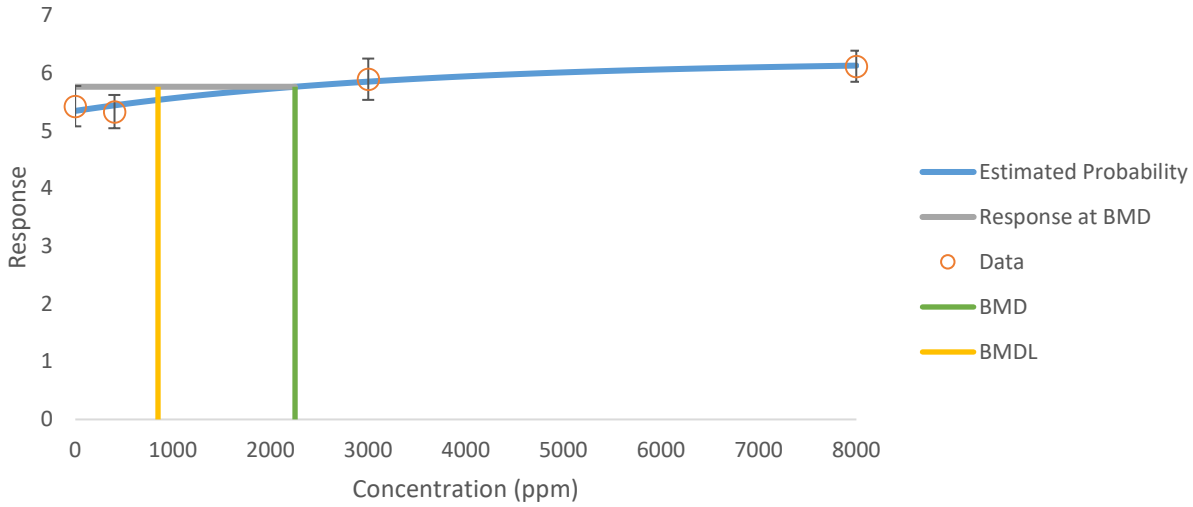


Table A-14. Results from Benchmark Dose (BMD) Analysis (Constant Variance) of Relative Liver Weight in Male Rats Following Inhalation Exposure to Methyl *tert*-Butyl Ether (MTBE) for 13 Weeks (5 Days/Week, 6 Hours/Day) (Lington et al. 1997)

Model	Test for significant difference p-value[a]	Test for variance p-value[b]	Test for means p-value[c]	Scaled residuals[d]			AIC	BMC_{1SD} (ppm)	$BMCL_{1SD}$ (ppm)
				Dose below BMC	Dose above BMC	Overall largest			
Exponential (model 2)[e]	<0.0001	0.16	0.13	1.30	0.41	-1.44	-18.79	1,541.78	1,320.85
Exponential (model 3)[e]	<0.0001	0.16	0.13	1.30	0.41	-1.44	-18.79	1,541.78	1,320.85
Exponential (model 4)[e]	<0.0001	0.16	0.08	1.33	-0.50	1.33	-17.95	ND	ND
Exponential (model 5)[e]	<0.0001	0.16	0.08	1.33	-0.50	1.33	-17.95	ND	ND
Hill[e]	<0.0001	0.16	0.08	1.33	-0.50	1.33	-17.95	ND	ND
Polynomial (3-degree)[e]	<0.0001	0.16	0.21	1.34	-0.18	1.34	-19.80	1,338.80	1,136.61
Polynomial (2-degree)[e]	<0.0001	0.16	0.21	1.34	-0.18	1.34	-19.80	1,338.80	1,136.61
Power[e,f]	<0.0001	0.16	0.21	1.34	-0.18	1.34	**-19.80**	**1,338.80**	**1,136.62**
Linear	<0.0001	0.16	0.21	1.34	-0.18	1.34	-19.80	1,338.80	1,136.61

[a]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[b]Values <0.05 fail to meet conventional goodness-of-fit criteria.
[c]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[d]Scaled residuals at doses immediately below and above the BMC; also the largest residual at any dose.
[e]Restricted model.
[f]Recommended model. The constant variance model provided an adequate fit to the data. All models except Exponential 4 and 5 and Hill models provided adequate fits to the means. The BMDLs were sufficiently close (<3-fold); therefore, the model with the lowest AIC was selected (Power).

AIC = Akaike Information Criterion; BMC = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMCL = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., $_{1SD}$ = exposure concentration associated with 1 standard deviation); NA = not applicable; ND = not determined; value did not compute or the model failed to meet the conventional goodness of fit criteria; SD = standard deviation

Figure A-5. Fit of Power Model to Data for Relative Liver Weight in Male Rats Following Inhalation Exposure to Methyl *tert*-Butyl Ether (MTBE) in for 13 Weeks (5 Days/Week, 6 Hours/Day) (Lington et al. 1997)

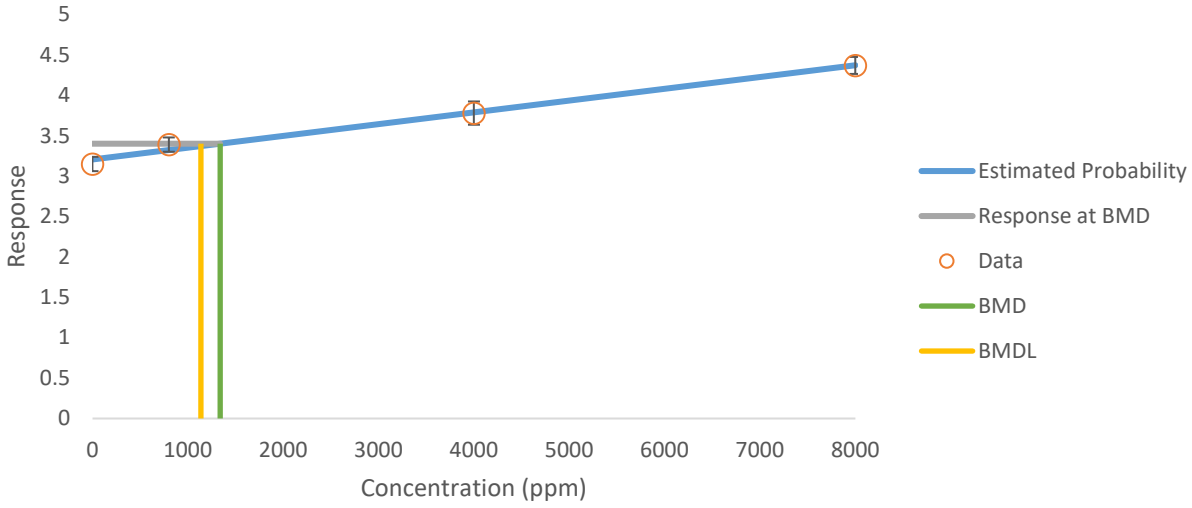


Table A-15. Results from Benchmark Dose (BMD) Analysis (Constant Variance) of Decreased F1 Body Weights in Female Rat Offspring on PND 14 Following Inhalation Exposure to Methyl *tert*-Butyl Ether (MTBE) in a 2-Generation Study (5 Days/Week, 6 Hours/Day) (Neeper-Bradley 1991)

Model	Test for significant difference p-value[a]	Test for variance p-value[b]	Test for means p-value[c]	Scaled residuals[d]			AIC	BMC_{RD5} (ppm)	$BMCL_{RD5}$ (ppm)
				Dose below BMC	Dose above BMC	Overall largest			
Exponential (model 2)[e]	0.0008	0.41	0.18	0.65	-1.54	-1.54	449.55	2,756.32	1,965.74
Exponential (model 3)[e]	0.0008	0.41	0.18	0.65	-1.54	-1.54	449.55	2,756.40	1,964.15
Exponential (model 4)[e,f]	**0.0008**	**0.41**	**0.49**	**0.52**	**-0.21**	**0.52**	**448.58**	**1,055.78**	**368.83**
Exponential (model 5)[e]	0.0008	0.41	ND	0.003	0.0005	0.003	450.11	2,224.88	411.23
Hill[e]	0.0008	0.41	ND	0.05	-0.004	0.05	450.11	1,616.28	399.61
Polynomial (3-degree)[e]	0.0008	0.41	0.15	0.69	-1.61	-1.61	449.85	2,936.70	2,148.46
Polynomial (2-degree)[e]	0.0008	0.41	0.15	0.69	-1.61	-1.61	449.85	2,936.61	2,148.46
Power[e]	0.0008	0.41	0.15	0.69	-1.61	-1.61	449.85	,2936.60	2,148.47
Linear	0.0008	0.41	0.15	0.69	-1.61	-1.61	449.85	2,936.51	2,148.45

[a]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[b]Values <0.05 fail to meet conventional goodness-of-fit criteria.
[c]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[d]Scaled residuals at doses immediately below and above the BMC; also the largest residual at any dose.
[e]Restricted model.
[f]Recommended model. The constant variance model provided an adequate fit to the data. All models except Exponential 5 and Hill models provided adequate fits to the means. The BMCLs differed by >3-fold; therefore, the model with the lowest BMCL was selected (Exponential 4).

AIC = Akaike Information Criterion; BMC = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMCL = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., $_{05}$ = exposure concentration associated with a 5% relative deviation); ND = not determined; value did not compute or the model failed to meet the conventional goodness of fit criteria; PND = postnatal day; RD = relative deviation

Figure A-6. Fit of Exponential 4 Model to Data for Female F1 Body Weights in Female Rat Offspring on Postnatal Day 14 Following Inhalation Exposure to Methyl *tert*-Butyl Ether (MTBE) in a 2-Generation Study (5 Days/Week, 6 Hours/Day) (Neeper-Bradley 1991)

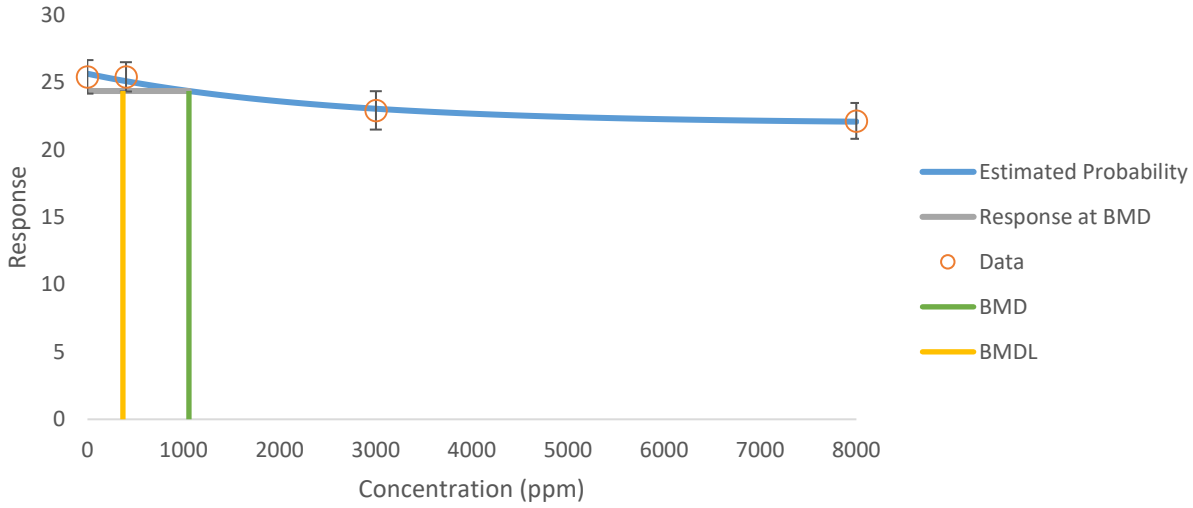


Table A-16. Results from Benchmark Dose (BMD) Analysis of Decreased F2 Body Weights in Rat Offspring on PND 21 Following Inhalation Exposure to Methyl *tert*-Butyl Ether (MTBE) in a 2-Generation Study (5 Days/Week, 6 Hours/Day) (Neeper-Bradley 1991)

Model	Test for significant difference p-value[a]	Test for variance p-value[b]	Test for means p-value[c]	Scaled residuals[d]			AIC	BMC_{RD5} (ppm)	$BMCL_{RD5}$ (ppm)
				Dose below BMC	Dose above BMC	Overall largest			
Constant variance									
Linear	<0.0001	<0.0001	0.48	-0.22	-0.85	-0.85	540.71	ND	ND
Nonconstant variance									
Exponential (model 2)[e]	<0.0001	0.63	0.002	-0.84	-0.30	1.83	518.14	ND	ND
Exponential (model 3)[e]	<0.0001	0.63	0.002	-0.84	-0.30	1.83	518.14	ND	ND
Exponential (model 4)[e]	<0.0001	0.63	0.0005	-0.85	-0.13	1.73	520.06	ND	ND
Exponential (model 5)[e]	<0.0001	0.63	0.0005	-0.85	-0.07	1.68	520.05	ND	ND
Hill[e]	<0.0001	0.63	0.20	-0.67	-0.22	-0.67	508.53	1,645.07	739.31
Polynomial (3-degree)[e,f]	**<0.0001**	**0.63**	**0.28**	**-0.65**	**-0.80**	**0.93**	**507.39**	**2,211.03**	**1,633.77**
Polynomial (2-degree)[e]	<0.0001	0.63	0.28	-0.65	-0.80	0.93	507.39	2,211.03	1,633.79
Power[e]	<0.0001	0.63	0.28	-0.65	-0.80	0.93	507.39	2,211.03	1,633.78
Linear	<0.0001	0.63	0.28	-0.65	-0.80	0.93	507.39	2,211.03	1,633.79

[a]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[b]Values <0.05 fail to meet conventional goodness-of-fit criteria.
[c]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[d]Scaled residuals at doses immediately below and above the BMC; also the largest residual at any dose.
[e]Restricted model.
[f]Recommended model. The constant variance did not provide an adequate fit to the data. With nonconstant variance applied, the Hill, 2- and 3- degree polynomial, power, and linear models provided adequate fit to the means. The BMDLs were sufficiently close (<3-fold). The fit models all had identical AIC values, so of those models, the model with the lowest BMCL was selected (3-degree Polynomial model).

AIC = Akaike Information Criterion; BMC = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMCL = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., $_{05}$ = exposure concentration associated with 5% extra risk); ND = not determined; models failed to meet conventional goodness-of-fit criteria; PND = postnatal day; RD = relative deviation

Figure A-7. Fit of Polynomial (3-Degree) Model to Data for F2 Body Weights in Rat Offspring on Postnatal Day 21 Following Inhalation Exposure to Methyl *tert*-Butyl Ether (MTBE) in a 2-Generation Study (5 Days/Week, 6 Hours/Day) (Neeper-Bradley 1991)

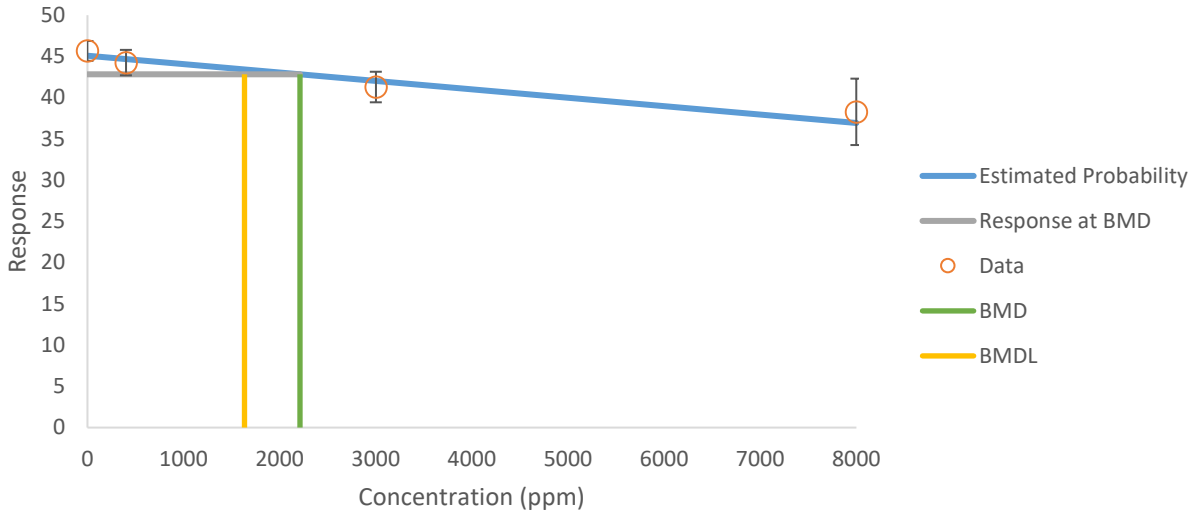


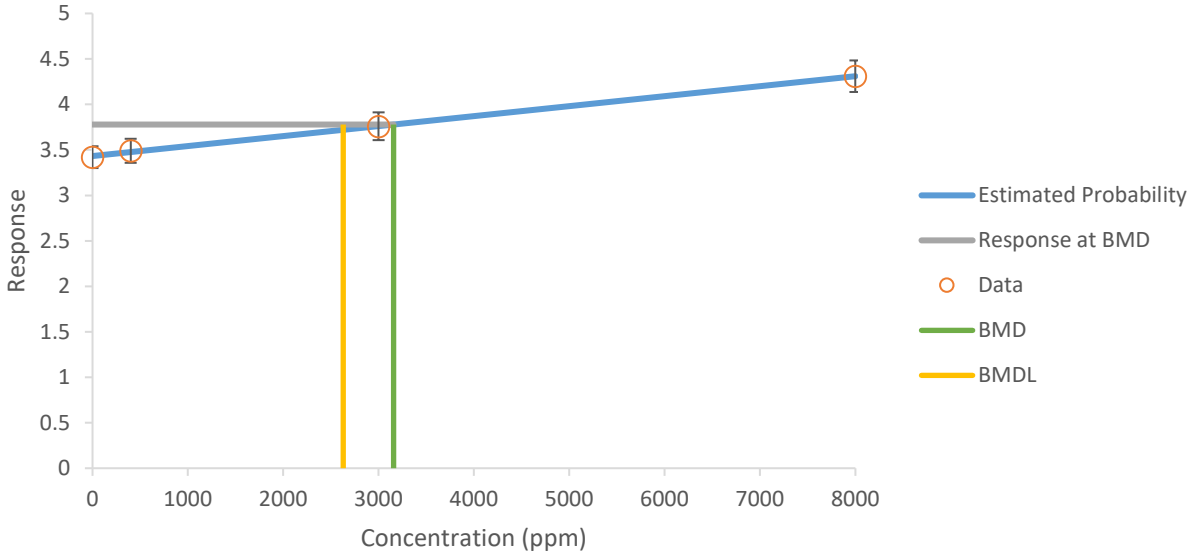
Table A-17. Results from Benchmark Dose (BMD) Analysis (Constant Variance) of Relative Liver Weight in Adult F1 Male Rats Following Inhalation Exposure to Methyl *tert*-Butyl Ether (MTBE) in a 2-Generation Study (5 Days/Week, 6 Hours/Day) (Bevan et al. 1997b)

Model	Test for significant difference p-value[a]	Test for variance p-value[b]	Test for means p-value[c]	Scaled residuals[d] Dose below BMC	Scaled residuals[d] Dose above BMC	Scaled residuals[d] Overall largest	AIC	BMC_{1SD} (ppm)	$BMCL_{1SD}$ (ppm)
Exponential (model 2)[e]	<0.0001	0.265	0.924	0.21	-0.08	-0.29	77.88	3,388.81	2,869.25
Exponential (model 3)[e]	<0.0001	0.265	0.924	0.21	-0.08	-0.29	77.88	3,388.81	2,869.25
Exponential (model 4)[e]	<0.0001	0.265	0.790	-0.05	0.009	0.20	79.79	3,132.15	2,598.05
Exponential (model 5)[e]	<0.0001	0.265	0.790	-0.04	0.005	0.20	79.79	3,140.15	2,611.77
Hill[e]	<0.0001	0.265	ND	$1.84x10^{-6}$	0.0002	-0.50	82.23	ND	ND
Polynomial (3-degree)[e]	<0.0001	0.265	0.965	-0.02	-0.002	0.20	77.79	3,157.23	2,629.03
Polynomial (2-degree)[e]	<0.0001	0.265	0.965	-0.02	-0.002	0.20	77.79	3,157.23	2,629.03
Power[e]	<0.0001	0.265	0.965	-0.02	-0.002	0.20	77.79	3,157.23	2,629.07
Linear[f]	**<0.0001**	**0.265**	**0.965**	**-0.02**	**-0.002**	**0.20**	**77.79**	**3,157.23**	**2,629.03**

[a]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[b]Values <0.05 fail to meet conventional goodness-of-fit criteria.
[c]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[d]Scaled residuals at doses immediately below and above the BMC; also the largest residual at any dose.
[e]Restricted model.
[f]Recommended model. The constant variance model provided an adequate fit to the data. All models except the Hill model provided adequate fits to the means. The BMDLs were sufficiently close (<3-fold). Several models had the same lowest AIC value (Linear, Power, Polynomial 2 and 3), and the Polynomial models converged upon the Linear model. Between the Power and the Linear model, the model with the (slightly) lower BMCL was selected (Linear).

AIC = Akaike Information Criterion; BMC = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMCL = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., $_{1SD}$ = exposure concentration associated with 1 standard deviation); ND = not determined; value did not compute or the model failed to meet the conventional goodness of fit criteria; SD = standard deviation

Figure A-8. Fit of Linear Model to Data for Relative Liver Weight in Adult F1 Male Rats Following Inhalation Exposure to Methyl tert-Butyl Ether (MTBE) in a 2-Generation Study (5 Days/Week, 6 Hours/Day) (Bevan et al. 1997b)



The candidate PODs are summarized in Table A-18. The most sensitive candidate PODs for all three critical effects (neurological, hepatic, developmental) were comparable (adjusted NOAEL/BMCL values of 65.9–71.4 ppm). Based on consistent evidence across several studies, neurological and hepatic effects were selected as co-critical effects. Decreased PND 14 F1 body weight in females (Bevan et al. 1997b) was not selected as a co-critical effect due to inconsistent findings across postnatal time periods and sexes; additionally, the BMCL for the F2 generation was much higher, further suggesting inconsistencies in the data.

Table A-18. Summary of Candidate Effects and POD Values Considered for Derivation of an Intermediate Inhalation MRL for Methyl *tert*-Butyl Ether (MTBE)

Species	Duration	Effect	Candidate POD (ppm)	POD type	Reference[a]
Neurological effects					
Fischer-344 rat	28 days 5 days/week 6 hours/day	Ataxia, hypoactivity, loss of startle reflex, blepharospasm[b]	71.4	$NOAEL_{ADJ}$	Bird et al. 1997; Chun and Kintigh 1993
Sprague-Dawley rat	2 generations ~14–19 weeks/generation 5 days/week 6 hours/day	Hypoactivity, blepharospasm, lack of startle reflex in F0 and F1 adults[b]	71.4	$NOAEL_{ADJ}$	Bevan et al. 1997b; Neeper-Bradley 1991

Table A-18. Summary of Candidate Effects and POD Values Considered for Derivation of an Intermediate Inhalation MRL for Methyl *tert*-Butyl Ether (MTBE)

Species	Duration	Effect	Candidate POD (ppm)	POD type	Reference[a]
CD-1 mouse	28 days 5 days/week 6 hours/day	Ataxia, hypoactivity, loss of startle reflex[b]	71.4	$NOAEL_{ADJ}$	Bird et al. 1997; Chun and Kintigh 1993
Fischer-344 rat	13 weeks 5 days/week 6 hours/day	Transient hypoactivity at ≥4,000 ppm; ataxia at 8,000 ppm	143	$NOAEL_{ADJ}$	Lington et al. 1997
Hepatic effects					
Fischer-344 rat	28 days 5 days/week 6 hours/day	Increased relative liver weight in males and females[b]	71.4	$NOAEL_{ADJ}$	Bird et al. 1997; Chun and Kintigh 1993
Sprague-Dawley rats	2 generations ~14–19 weeks/ generation 5 days/week 6 hours/day	Increased relative liver weight in F1 adult males	467	$BMCL_{ADJ}$	Bevan et al. 1997b
CD-1 mouse	28 days 5 days/week 6 hours/day	Increased relative liver weight in females	151	$BMCL_{ADJ}$	Bird et al. 1997; Chun and Kintigh 1993
Fischer-344 rat	13 weeks 5 days/week 6 hours/day	Increased relative liver weight in males	203	$BMCL_{ADJ}$	Lington et al. 1997
Developmental effects					
Sprague-Dawley rats	2 generations ~14–19 weeks/ generation 5 days/week 6 hours/day	Decreased body weight in F1 females on PND 14	65.9	$BMCL_{ADJ}$	Bevan et al. 1997b; Neeper-Bradley 1991
Sprague-Dawley rats	2 generations ~14–19 weeks/ generation 5 days/week 6 hours/day	Decreased body weight in F2 pups on PND 21	292	$BMCL_{ADJ}$	Bevan et al. 1997b; Neeper-Bradley 1991

[a]Both published and unpublished studies are cited when unpublished data were referred to for additional information and/or raw data for benchmark dose modeling.
[b]Selected studies/endpoints for derivation of intermediate inhalation MRL.

BMC = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; $BMCL_{ADJ}$ = 95% lower confidence limit on the BMC (adjusted for continuous exposure); MRL = Minimal Risk Level; $NOAEL_{ADJ}$ = no-observed-adverse-effect level (adjusted for continuous exposure); PND = postnatal day; POD = point of departure

Selection of the Principal Studies: The 2-generation study in rats (Bevan et al. 1997b; Neeper-Bradley 1991) and the 28-day day studies in rats and mice (Bird et al. 1997; Chun and Kintigh 1993) were selected as co-principal studies based on identical PODs ($NOAEL_{ADJ}$ of 71.4 ppm) for CNS depression and elevated liver weight.

Summary of the Principal Studies:

Bevan C, Neeper-Bradley TL, Tyl RW, et al. 1997b. Two-generation reproductive toxicity study of methyl tertiary-butyl ether (MTBE) in rats. J Appl Toxicol 17 Suppl 1:S13-S19.

Neeper-Bradley TL. 1991. Two-generation reproduction study of inhaled methyl tert-butyl ether in CD (Sprague-Dawley) rats (final report) with attachments and cover letter dated 081691. MTBE Task Force. Submitted to the U.S. Environmental Protection Agency under TSCA Section 4. OTS0534056. 40-9113465. 42098 G8-2.
https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/OTS0540108.xhtml. January 17, 2020.

Bevan et al. (1997b) exposed Sprague-Dawley rats (25/sex/group) to MTBE at concentrations of 0, 400, 3,000, or 8,000 ppm via whole-body inhalation for 6 hours/day, 5 days/week for 10 weeks prior to mating. Exposure continued through the 21-day mating period (males were then randomly allocated to co-house with one female for 7 days maximum until mating was confirmed; after a 7-day period, unmated females were placed with a different male for the remainder of the 21-day mating period). Day of copulation was designated as GD 0. Male exposure continued until the last litter they sired was delivered, at which point they were sacrificed. Females were exposed during the mating period, gestation, lactation (GD 5), and weaning on PND 21. Females were sacrificed after the weaning of their offspring. The total exposure period was 16 weeks in F0 males and 17–19 weeks in F0 females. Birth was recorded as PND 0. On PND 28, at least one F1 rat/sex/litter was selected at random to continue exposure for up to 8 weeks prior to mating for generation of the F2 litter. Mating, exposure, and sacrifice schedule for F1 parental animals followed the same schedule as F0 parental animals. Parental rats were observed for viability twice daily and for clinical signs once daily. Male body weights were recorded weekly. Female body weights were recorded weekly prior to mating and then on GDs 0, 7, 14, and 20 after mating. Food consumption was recorded weekly for both sexes. After mating, female food consumption was recorded at 3–4-day intervals throughout gestation. All parental adults were examined grossly. Reproductive endpoints evaluated in both generations included number of sperm-positive females, number pregnant, number of live litters, gestation length, male and female mating indices, male and female fertility indices, and gestational index. At necropsy, the liver was weighed in F1 parental animals. Histopathological examination was conduction on the following tissues in F0 control and 8,000-ppm groups: pituitary, testes, epididymides, prostate and seminal vesicles, vagina, uterus, ovaries, respiratory tract (with nasal turbinates), and gross lesions. Only the livers from control and 8,000-ppm groups were examined for histopathological changes in F1 parental animals. Litters were examined twice a day for general appearance and any deaths. Offspring were counted, sexed, weighed, and examined for abnormalities on PNDs 0, 1, 4, 7, 14, 21, and 28. Live birth and survival indices were calculated. On PND 4, each litter was reduced to four females and four males via random selection. Culled pups were euthanized and examined for external malformations. Those with observed abnormalities were given a gross postmortem examination. Data for this study are also available in the unpublished report by Neeper-Bradley (1991).

All F0 parental animals survived until scheduled sacrifice. Hypoactivity, blepharospasms, and lack of startle reflex were observed at ≥3,000 ppm; ataxia was observed at 8,000 ppm. Periocular encrustation and ocular discharge were observed at 8,000 ppm as well (attributed to irritative nature of vapor; see dermal entry). There were no clinical signs of toxicity observed in the 400-ppm group. Body weight was significantly reduced throughout the 10-week premating exposure period for F0 males at 8,000 ppm group, with a 12% reduction the end of the premating period. Body weight gain was also decreased in F0

males at 8,000 ppm from week 1 to 7 of premating exposure (magnitude not reported), and an 8–13% decrease in food consumption was observed from week 1 to 3. Body weights for F0 males were not reported once mating began. In F0 females, body weights were similar to controls prior to mating, during mating, and during gestation. During lactation, a significant 2-fold increase in body weight gain was observed at 8,000 ppm; the biological significance of this increase in unclear especially since food consumption was significantly reduced in this group from PND 7 to 14. No exposure-related changes were observed in reproductive parameters. No exposure-related changes in gross or microscopic histology were observed in the F0 generation.

All F1 parental animals survived until scheduled sacrifice. Hypoactivity, blepharospasms, and lack of startle reflex were observed at ≥3,000 ppm; ataxia was observed at 8,000 ppm. Periocular encrustation and ocular discharge were observed at 8,000 ppm as well (attributed to irritative nature of vapor). There were no clinical signs of toxicity observed in the 400-ppm group. Body weight gain was reduced throughout the 8-week premating exposure period for F1 males at 8,000 ppm group, with a significant 13–14% decrease during weeks 1 and 2. Final body weight was significantly reduced by 11%. While body weights were significantly reduced for F1 females during the premating exposure period, body weights were lower at the beginning of the exposure period and body weight gains were comparable across groups. Similar to F0 dams, a significant 4-fold increase in body weight gain was observed at 8,000 ppm; the biological significance of this increase in unclear, especially since food consumption was significantly reduced in this group from PND 7 to 14. No exposure-related changes were observed in reproductive parameters. Absolute liver weight was significantly increased at 8,000 ppm in F1 males and females by 12 and 27%, respectively. Relative liver weight was also significantly increased at 8,000 ppm in F1 males and females by 26%. Relative liver weight was significantly increased in F1 males by 10% at 3,000 ppm as well. No exposure-related changes were observed at gross necropsy, and no exposure-related liver lesions were noted.

No exposure-related changes were observed in litter survival parameters for F1 or F2 generations. Exposure-related changes in F1 pups included decreased weights at 8,000 ppm from PND 14 to 28 in both sexes and at 3,000 ppm on PND 14 in females. In addition, body weight gain was reduced in the 3,000- and 8,000-ppm exposed groups on PNDs 7–14 and 14–21. In F2 pups, body weights were significantly reduced at 8,000 ppm from PND 7 to 28 in both sexes and at 3,000 ppm in males from PND 14 to 28. No exposure-related changes were observed at gross necropsy of pups.

Bird MG, Burleigh-Flayer HD, Chun JS, et al. 1997. Oncogenicity studies of inhaled methyl tertiary-butyl ether (MTBE) in CD-1 mice and F-344 rats. J Appl Toxicol 17 Suppl 1:S45-S55.

Chun JS, Kintigh WJ. 1993. Methyl tertiary butyl ether: Twenty-eight day vapor inhalation study in rats and mice. Union Carbide. Submitted to the MTBE Health Effects Testing Task Force. BRRC Report 93N1241.

Bird et al. (1997) exposed groups of Fischer-344 rats (10/sex/group) to MTBE at concentrations of 0, 400, 3,000, or 8,000 ppm via whole-body inhalation for 6 hours/day, 5 days/week for at least 4 weeks for 23 or 24 exposures (main experiment). Additional groups of rats (5/sex/group) were similarly exposed to 0 or 8,000 ppm for 24 exposures and maintained for 19 days following the last exposure (recovery experiment) or were to 0, 400, 3,000, or 8,000 ppm for 23 exposures to evaluate cell proliferation in the renal tubules (cell proliferation experiment). All rats were examined for clinical signs of toxicity and body weight changes during the study. Clinical blood chemistry parameters (urea nitrogen, creatinine, calcium, phosphorus, sodium, potassium, and chloride) were evaluated only in the 0 or 8,000 ppm groups prior to sacrifice. Urine samples from all exposure groups were evaluated for osmolality, pH, total volume, lactate dehydrogenase, ALP, N-acetyl-beta-D-glucosaminidase, total protein, and protein fraction. Complete necropsy, organ weight determinations (liver, kidneys, uterus, lungs, brain, spleen,

thyroid, and adrenals), and measurement of the length and width of the brain were performed on all rats except those in the cell proliferation experiment. Histological examinations were limited to the liver and kidneys. The livers were examined microscopically in the 0 and 8,000 ppm groups only, while the kidneys were examined microscopically in all groups. In addition, slides from all male rat kidneys were examined for protein accumulation in the tubular epithelial cells by Mallory's Heidenhain technique and for α2u-globulin accumulation using immunostaining with an antibody to α2u-globulin. Data are also available for this study in the unpublished report by Chun and Kintigh (1993).

No exposure-related mortality was observed. Clinical signs consisted of ataxia, hypoactivity, lack of startle response, and blepharospasm in rats during exposures to 3,000 and 8,000 ppm, and ataxia in rats following exposures to 8,000 ppm. Body weight loss (about 2%) occurred in male rats exposed to 8,000 ppm during the first week. Decreased body weight gain was seen throughout the study in male rats exposed to 8,000 ppm, with percentages of decreased body weight gain of 24–35% from exposure days 1–19 to 1–33. Decreased body weight gain was observed in female rats exposed to 8,000 ppm only during the first 2 weeks of exposure. No exposure-related effects on clinical chemistry parameters were found in rats. Urinalysis and urine chemistry evaluations revealed increased urine volume and decreased urinary pH in male and female rats at 8,000 ppm, but there was no other indication of renal damage. Exposure-related organ weight changes were observed in the kidneys, liver, adrenal glands, and spleen. Statistically significant organ weight changes in male rats at 3,000 ppm were limited to an 8 and 13% increase in absolute and relative liver weight, respectively. At 8,000 ppm, statistically significant organ weight changes included a 10% increase in absolute and relative liver weight; an 8% decrease in relative kidney weight; 45 and 53% increases in absolute and relative adrenal weight, respectively; and 18 and 13% decreases in absolute and relative spleen weight, respectively. In females, statistically significant organ weight changes at 3,000 ppm included 9 and 8% increases in absolute and relative liver weight, respectively; 11 and 8% increases in absolute and relative kidney weight, respectively; and 14 and 8% increases in absolute and relative adrenal weight, respectively. At 8,000 ppm, statistically significant organ weight changes in female rats included 17 and 10% increases in absolute and relative liver weight, respectively; a 4% increase in relative kidney weight; 21 and 23% increases in absolute and relative adrenal weight, respectively; and a 6% decrease in relative spleen weight. No gross or histopathological effects were noted in the organs and tissues examined. Although more protein accumulation in male rats exposed to 3,000 and 8,000 ppm was observed, no evidence of α2u-globulin accumulation was found. These results suggest that a mechanism other than α2u-globlin accumulation (perhaps the accumulation of another protein unique to male rats) may be responsible for increased susceptibility in male rats.

Bird et al. (1997) also exposed groups of CD-1 mice (10/sex/group) to MTBE at concentrations of 0, 400, 3,000, or 8,000 ppm via whole-body inhalation for 6 hours/day, 5 days/week for at least 4 weeks for 20 or 21 exposures (main experiment). Additional groups (5/sex/group) were similarly exposed to 0 or 8,000 ppm for 23 exposures and maintained for 21 days following the last exposure (recovery experiment). Animals were evaluated for body weight and clinical signs of toxicity. Select organ weights were recorded (liver, brain, spleen, thyroid). Histopathological evaluations were conducted on liver, kidney, and thyroid. At the end of the exposure period, brains from all male and female mice of the main experiment were homogenized to determine the levels of calcium and magnesium. Special blood chemistry evaluation of total T3, total T4, TSH, total bile acid, and estradiol were conducted. Data are also available for this study in the unpublished report by Chun and Kintigh (1993).

No exposure-related mortality was observed. Clinical signs consisted of ataxia, hypoactivity, and lack of startle response during exposures to 3,000 and 8,000 ppm and ataxia following exposures to 8,000 ppm. No exposure-related clinical signs were observed during the recovery period. No body weight effects were noted. Absolute and relative liver weights were elevated in females at ≥3,000 ppm, and centrilobular hypertrophy was observed in males at 8,000 ppm. Decreased absolute and relative spleen weight was observed in females at 8,000 ppm. However, the spleen was not examined histologically. No

exposure-related effects on brain weight were found. No exposure-related effects on brain calcium and magnesium levels were found. Special blood chemistry evaluation of total T3, total T4, TSH, total bile acid, and estradiol revealed that an increase in total T4 and TSH occurred in male mice at 8,000 ppm. However, these increases were not considered to be biologically significant due to the absence of histological evidence of thyroid lesions.

Selection of the Point of Departure for the MRL: The NOAEL of 400 ppm for CNS depression and elevated liver weights in rats and mice was selected as the POD because it is the identified lowest POD for the critical effects (neurotoxicity, hepatotoxicity) identified in the co-principal studies.

Calculations

Intermittent Exposure: The NOAEL of 400 ppm was adjusted from intermittent exposure to account for a continuous exposure scenario:

$NOAEL_{ADJ}$ = 400 ppm x 6 hours/24 hours x 5 days/7 days = 71.4 ppm

Human Equivalent Concentration: While several PBPK models have been developed for MTBE, further refinement is needed to decrease uncertainty in estimated exposure levels, particularly for humans (see Sections 3.1.5 and 6.2 for more details). Therefore, HEC values for extrarespiratory effects were calculated by multiplying the $NOAEL_{ADJ}$ by the ratio of animal:human blood gas partition coefficients. For rats, the reported rat blood gas partition coefficient of 11.5 (Rao and Ginsberg 1997) and the midpoint of the range of human blood gas partition coefficients (17.7–19.6) reported by Rao and Ginsberg (1997) and Kim et al. (2007) were used:

Rat $NOAEL_{HEC}$ = $NOAEL_{ADJ}$ x ratio of rat:human blood gas partition coefficients
Rat $NOAEL_{HECP}$ = 71.4 ppm x (11.5/18.7)
Rat $NOAEL_{HEC}$ = 71.4 ppm x 0.615 = 43.9 ppm

For mice, the default the animal:human blood gas partition coefficient of 1 was used (mouse blood gas partition coefficient is unknown):

Mouse $NOAEL_{HEC}$ = $NOAEL_{ADJ}$ x ratio of mouse:human blood gas partition coefficients
Mouse $NOAEL_{HEC}$ = 71.4 ppm x 1 (default value) = 71.4 ppm

Uncertainty Factor: The rat $NOAEL_{HEC}$ (most conservative HEC value) is divided by a total uncertainty factor (UF) of 30.

- 3 for extrapolation from animals to humans after dosimetric adjustment
- 10 for human variability

Provisional MRL = $NOAEL_{HEC}$ ÷ UFs
43.9 ppm ÷ (3 x 10) = 1 ppm

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Selection of a neurological effect as a co-critical effect following intermediate-duration inhalation exposure is supported by consistent observation of CNS-depressive effects following inhalation exposure to concentrations ≥2,000 ppm following acute-, intermediate-, and chronic-duration studies (Bevan et al. 1997a, 1997b; MTBE Committee 1990a; Bird et al. 1997; Dodd and Kintigh 1989; Lington et al. 1997; Moser et al. 1996; Vergnes and Chun 1994; Vergnes and Morabit 1989). Results from epidemiological studies also support CNS depression as a co-critical effect. Taxi drivers and health care workers who routinely

traveled via motor vehicles experience greater incidence of MTBE-related symptoms, including headache, spaciness, and nausea, compared to a lesser exposed referent group (exposure levels not reported) (Alaska DHSS 1992a). Workers exposed to automobile exhaust (median MTBE blood concentrations were 0.05 and 0.08 µg/L for nonsmokers and smokers, respectively) experienced a greater incidence of dizziness and headaches compared to controls who were not occupationally exposed to MTBE (MTBE blood concentrations were below the limit of detection for control smokers and nonsmokers) (CDC 1993a). Ecological studies show that residents in areas participating in oxyfuel programs had increased risk of symptoms associated with MTBE exposure compared to those living in areas not participating in the oxyfuel program (Moolenaar et al. 1994; Wisconsin DHSS 1995). Some studies did not show an association between MTBE and neurological effects. For instance, healthy males exposed to up to 50 ppm of MTBE while performing light physical activity did not self-report any neurological effects (Johanson et al. 1995); however, this exposure scenario and population may not be representative of the general population. For more information, see Section 2.15.

Selection of elevated liver weight as a co-critical effect following intermediate-duration inhalation exposure is supported by consistent observation of elevated liver weights in rats and mice following inhalation exposure to concentrations ≥2,000 ppm following acute-, intermediate-, and chronic-duration studies (Bevan et al. 1997a, 1997b; Bird et al. 1997; Dodd and Kintigh 1989; Lington et al. 1997; Moser et al. 1996), with evidence of centrilobular hypertrophy in mice at 8,000 ppm (Bird et al. 1997; Moser et al. 1996).

Agency Contacts (Chemical Managers): Jennifer Przybyla

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Methyl *tert*-Butyl Ether (MTBE)
CAS Numbers: 1634-04-4
Date: January 2022
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Chronic
MRL: 1 ppm (provisional)
Critical Effect: Renal effects
Reference: Bird et al. 1997; Chun et al. 1992
Point of Departure: NOAEL of 400 ppm ($NOAEL_{HEC}$ of 43.9 ppm)
Uncertainty Factor: 30
LSE Graph Key: 42
Species: Rat

MRL Summary: A chronic-duration provisional inhalation MRL of 1 ppm was derived for MTBE based on renal effects (increased kidney weight and increased incidence and severity of chronic progressive nephropathy) in female rats exposed to concentrations ≥3,000 ppm for 6 hours/day, 5 days/week for 24 months; a NOAEL of 400 ppm was identified (Bird et al. 1997). The MRL is based on the NOAEL of 400 ppm, which was adjusted to continuous duration exposure and converted to a $NOAEL_{HEC}$ of 43.9 ppm and divided by a total uncertainty factor of 30 (3 for extrapolation from animals to humans after dosimetric adjustment and 10 for human variability).

Selection of the Critical Effect: Available chronic-duration inhalation studies report relevant MTBE-related effects at 3,000 ppm (renal effects in female rats, hepatic effects in rats and mice) and 8,000 pm (CNS effects) (see Table A-19). Renal effects were also observed in male rats at ≥400 ppm; however, the higher incidence and greater severity of chronic progressive nephropathy at lower exposure concentrations in male rats compared with female rats may be due to the exacerbation of this syndrome by the accumulation of α2u-globulin, which is not relevant for human health (Ahmed 2001; Bogen and Heilman 2015; McGregor 2006; Phillips et al. 2008). Because enhancement of chronic progressive nephropathy, which led to increased mortality and decreased survival time in males, is associated with α2u-globulin accumulation in male rats only, these endpoints in male rats are not considered for MRL derivation. However, since female rats also had enhanced chronic progressive nephropathy not associated with α2u-globulin accumulation, renal effects in female rats were considered relevant. Therefore, hepatic and female rat renal effects were further considered for MRL derivation.

Table A-19. Summary of NOAEL and LOAEL Values Following Chronic Inhalation to Methyl *tert*-Butyl Ether (MTBE)

Species	Duration	NOAEL (ppm)	LOAEL (ppm)	Effect	Reference[a]
Neurological effects					
Fischer-344 rat	24 months 5 days/week 6 hours/day	3,000	8,000 (serious LOAEL)	Ataxia, prostration, salivation	Bird et al. 1997; Chun et al. 1992

Table A-19. Summary of NOAEL and LOAEL Values Following Chronic Inhalation to Methyl *tert*-Butyl Ether (MTBE)

Species	Duration	NOAEL (ppm)	LOAEL (ppm)	Effect	Reference[a]
Renal effects					
Fischer-344 rat	24 months 5 days/week 6 hours/day	400	3,000	Increased relative kidney weight and incidence and severity of CPN in females	Bird et al. 1997; Chun et al. 1992
Hepatic effects					
Fischer-344 rat	24 months 5 days/week 6 hours/day	400	3,000	Increased relative liver weight in females	Bird et al. 1997; Chun et al. 1992

[a]Both published and unpublished studies are cited when unpublished data were referred to for additional information

CPN = chronic progressive nephropathy; LOAEL = lowest observed adverse effect level; NOAEL = no-observed-adverse-effect level

In order to identify the most sensitive POD, BMD modeling was attempted for critical hepatic and female rat renal endpoints in Table A-19 when data were amenable to modeling. The data were fit to all available continuous models in EPA's BMDS (version 3.1.2) using a BMR of 1 standard deviation for continuous data or 10% extra risk for dichotomous data. Adequate model fit was judged by three criteria: goodness-of-fit statistics (p-value >0.1), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined BMR. Among all of the models providing adequate fit to the data, the lowest BMCL (95% lower confidence limit on the BMC) was selected as the POD when the difference between the BMCLs estimated from these models was >3-fold; otherwise, the BMCL from the model with the lowest AIC was chosen.

Suitable models were identified for increased relative liver weight in female rats (Bird et al. 1997; quantitative data obtained from unpublished report by Chun et al. 1992). Adequate models were not identified for increased relative kidney weight in female rats because they failed to meet conventional goodness-of-fit criteria (Bird et al. 1997; quantitative data obtained from unpublished report by Chun et al. 1992). Incidence data for lesions associated with chronic progressive nephropathy in female rats were not suitable for BMD modeling due to non-monotonic responses and/or high incidence in control (e.g., tubular proteinosis, glomerulosclerosis, interstitial nephritis, and fibrosis). Therefore, ATSDR used the NOAEL/LOAEL approach for the renal endpoints. The datasets used for BMD modeling are presented in Table A-20, the model predictions are presented in Table A-21, and the fit of the selected model (for the dataset with suitable models) is presented in Figure A-9.

Table A-20. Relative Liver and Kidney Weights in Female Rats Following Inhalation Exposure to Methyl *tert*-Butyl Ether (MTBE) for 24 Months (5 Days/Week, 6 Hours/Day)

	Concentration (ppm)			
	0	400	3,000	8,000
Relative liver weight (% BW) Mean±SD (n)	3.867±0.6629 (30)	3.725±0.5096 (27)	4.654±0.6379[a] (23)	5.508±1.3994[a] (25)
Relative kidney weight (% BW) Mean±SD (n)	0.907±0.2578 (30)	0.827±0.1427 (27)	1.072±0.2354[b] (23)	1.168±0.2564[a] (25)

[a]p<0.01.
[b]p<0.05.

BW = body weight; (n) = number of animals; SD = standard deviation

Source: Chun et al. 1992 (unpublished report associated with published study by Bird et al. 1997)

Table A-21. Results from Benchmark Dose (BMD) Analysis of Relative Liver Weight in Female Rats Following Inhalation Exposure to Methyl *tert*-Butyl Ether (MTBE) for 24 Months (5 Days/Week, 6 Hours/Day) (Chun et al. 1992)

Model	Test for significant difference p-value[a]	Test for variance p-value[b]	Test for means p-value[c]	Scaled residuals[d]			AIC	BMC_{1SD} (ppm)	$BMCL_{1SD}$ (ppm)
				Dose below BMC	Dose above BMC	Overall largest			
Full dataset									
Constant variance									
Linear	<0.0001	<0.0001	0.294	1.05	-0.32	1.05	271.72	ND	ND
Nonconstant variance									
Exponential (model 2)[e]	<0.0001	0.105	0.087	-1.40	1.45	1.45	246.34	ND	ND
Exponential (model 3)[e]	<0.0001	0.105	0.087	-1.40	1.45	1.45	246.34	ND	ND
Exponential (model 4)[e]	<0.0001	0.105	0.031	-1.38	1.05	-1.38	248.13	ND	ND
Exponential (model 5)[e]	<0.0001	0.105	ND	-0.83	0.71	-0.83	247.65	ND	ND
Hill[e]	<0.0001	0.105	ND	-0.83	0.71	-0.83	247.65	ND	ND
Polynomial (3-degree)[e]	<0.0001	0.105	0.031	-1.37	1.11	-1.37	248.11	ND	ND
Polynomial (2-degree)[e]	<0.0001	0.105	0.031	-1.37	1.11	-1.37	248.11	ND	ND
Power[e]	<0.0001	0.105	0.035	-1.32	1.33	1.33	247.90	ND	ND
Linear	<0.0001	0.105	0.098	-1.37	1.07	-1.37	246.12	ND	ND

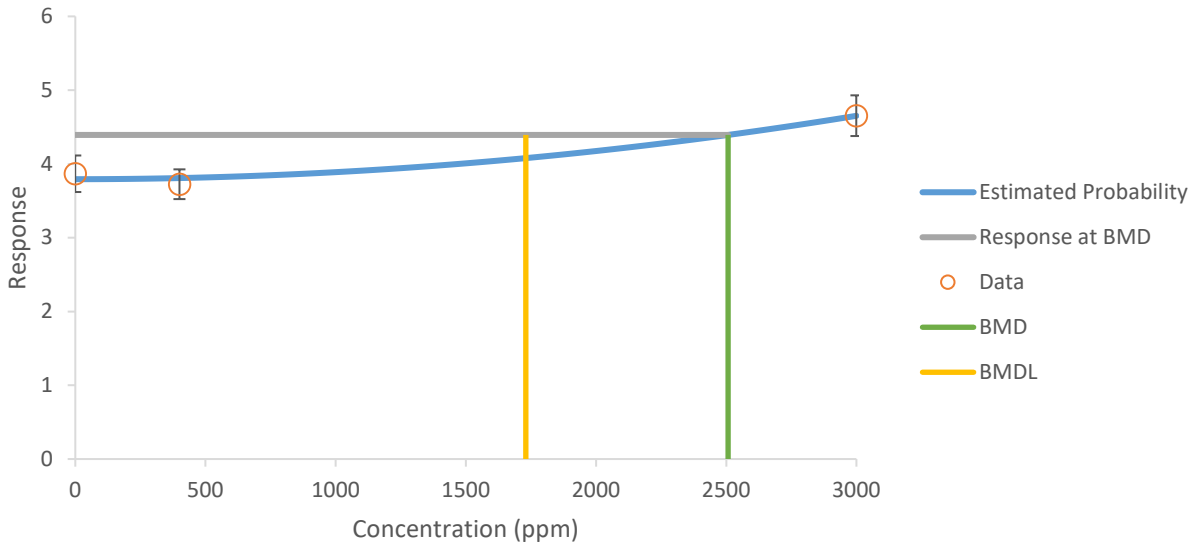
Table A-21. Results from Benchmark Dose (BMD) Analysis of Relative Liver Weight in Female Rats Following Inhalation Exposure to Methyl *tert*-Butyl Ether (MTBE) for 24 Months (5 Days/Week, 6 Hours/Day) (Chun et al. 1992)

Model	Test for significant difference p-value[a]	Test for variance p-value[b]	Test for means p-value[c]	Scaled residuals[d]			AIC	BMC_{1SD} (ppm)	$BMCL_{1SD}$ (ppm)
				Dose below BMC	Dose above BMC	Overall largest			
Highest dose dropped									
Constant variance									
Exponential (model 2)[e]	<0.0001	0.351	0.116	-1.19	0.14	-1.19	152.78	2130.86	1659.46
Exponential (model 3)[e]	<0.0001	0.351	ND	-0.65	-0.002	-0.65	153.12	ND	ND
Exponential (model 4)[e]	<0.0001	0.351	ND	-1.24	0.18	-1.24	155.00	ND	ND
Exponential (model 5)[e]	<0.0001	0.351	<0.0001	-0.65	-4.54×10^{-7}	-0.65	155.12	ND	ND
Hill[e]	<0.0001	0.351	<0.0001	-0.65	-5.99×10^{-6}	-0.65	155.12	ND	ND
Polynomial (2-degree)[e,f]	**<0.0001**	**0.351**	**0.322**	**-0.72**	**0.01**	**-0.72**	**151.30**	**2,507.18**	**1,730.29**
Power[e]	<0.0001	0.351	ND	-0.65	3.16×10^{-6}	-0.65	153.12	ND	ND
Linear	<0.0001	0.351	0.101	-1.25	0.18	-1.25	153.00	2,072.63	1,564.61

[a]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[b]Values <0.05 fail to meet conventional goodness-of-fit criteria.
[c]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[d]Scaled residuals at doses immediately below and above the BMC; also the largest residual at any dose.
[e]Restricted model.
[f]Recommended model. The constant variance model did not provide an adequate fit to the full dataset. With nonconstant variance applied, none of the models provided an adequate fit to the means. With the highest dose dropped, the constant variance model provided an adequate fit the data. Only the Exponential 2, Polynomial 2, and Linear models provided an adequate fit to the means. BMCLs were sufficiently close (differed by <3-fold). Therefore, the model with the lowest AIC was selected (2nd degree Polynomial).

AIC = Akaike Information Criterion; BMC = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMCL = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., $_{1SD}$ = exposure concentration associated with 1 standard deviation); ND = not determined; value did not compute or the model failed to meet the conventional goodness of fit criteria; SD = standard deviation

Figure A-9. Fit of 2nd Degree Polynomial Model to Data for Relative Liver Weight in Female Rats Following Inhalation Exposure to Methyl *tert*-Butyl Ether (MTBE) for 24 Months (5 Days/Week, 6 Hours/Day) (Chun et al. 1992)



The candidate PODs are summarized in Table A-22. The lowest POD was identified for renal effects in female rats, with a NOAEL value of 400 ppm. Therefore, renal effects in female rats were selected as the critical effect.

Table A-22. Summary of Candidate Effects and POD Values Considered for Derivation of a Chronic Inhalation MRL for Methyl *tert*-Butyl Ether (MTBE)

Species	Duration	Effect	Candidate POD (ppm)	POD type	Reference[a]
Renal effects					
Fischer-344 rat	24 months 5 days/week 6 hours/day	Increased relative kidney weight and incidence and severity of CPN in females[b]	71.4	$NOAEL_{ADJ}$	Bird et al. 1997; Chun et al. 1992
Hepatic effects					
Fischer-344 rat	24 months 5 days/week 6 hours/day	Increased relative liver weight in females	309	$BMCL_{ADJ}$	Bird et al. 1997; Chun et al. 1992

[a]Both published and unpublished studies are cited when unpublished data were referred to for additional information and/or raw data for benchmark dose modeling
[b]Selected study/endpoint for derivation of chronic inhalation MRL.

BMC = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; $BMCL_{ADJ}$ = 95% lower confidence limit on the BMC (adjusted for continuous exposure); MRL = Minimal Risk Level; $NOAEL_{ADJ}$ = no-observed-adverse-effect level (adjusted for continuous exposure); POD = point of departure

Selection of the Principal Study: The 24-month study in rats by Bird et al. (1997) is selected as the principal study based on renal effects in female rats because this study provides the lowest POD for the identified critical effect. Data are also available for this study in the unpublished report by Chun et al. (1992).

Summary of the Principal Study:

Bird MG, Burleigh-Flayer HD, Chun JS, et al. 1997. Oncogenicity studies of inhaled methyl tertiary-butyl ether (MTBE) in CD-1 mice and F-344 rats. J Appl Toxicol 17 Suppl 1:S45-S55.

Chun JS, Burleigh-Flayer HD, Kintigh WJ. 1992. Final report, methyl tertiary butyl ether: Vapor inhalation oncogenicity study in Fischer 344 rats, with cover letter dated 11/19/92. MTBE Task Force. Submitted to the U.S. Environmental Protection Agency under TSCA Section 4. OTS0558686. 42098 G9-3. https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/OTS0558686.xhtml. January 20, 2020.

Bird et al. (1997) exposed groups of Fischer 344 rats (50/sex/group) to MTBE vapor at concentrations of 0, 400, 3,000, or 8,000 ppm via whole-body inhalation for 6 hours/day, 5 days/week for 24 months. Animals were observed individually for mortality and clinical signs of toxicity every day. Body weights were measured weekly up to week 13 and then measured every other week. Blood was collected at 12 months and prior to sacrifice for hematology and serum chemistry analyses in rats from the control and 8,000-ppm groups. In female rats, corticosterone levels were measured in 10 rats/group at sacrifice. In male rats, corticosterone levels were measured from 10 animals each in the control and 8,000-ppm groups at week 81, 10 animals from the 3,000-ppm group at week 94, and 10 animals from the 400-ppm group at week 104. Urinalysis was conducted at termination. Gross necropsy was carried out for all animals after 24 months of exposure, including those that had died prematurely. The brain, liver, kidneys, lungs, spleen, adrenal glands, and testes were weighed. Tissues of all major organ systems were collected for histopathological evaluation from control and 8,000-ppm exposed rats, as well as all rats that died or were sacrificed moribund. In males, the liver, kidneys, testes, and gross lesions were also examined microscopically in the 400- and 3,000-ppm groups. For females, the liver and gross lesions of the 400- and 3,000-ppm groups were examined. Data are also available for this study in the unpublished report by Chun et al. (1992).

Male rats in the 3,000- and 8,000-ppm exposed groups had increased mortality rates and decreased mean survival times with the major cause of death being chronic progressive nephropathy. Due to this, male rats in the 3,000- and 8,000-ppm exposed groups were terminated early at weeks 97 and 82, respectively. Slight, but not significant, increases in mortality and/or decreases in survival time were also observed in males at 400 ppm and females at 3,000 and 8,000 ppm; these were also attributed to chronic progressive nephropathy. Bird et al. (1997) qualitatively reported an increase in clinical signs of neurotoxicity such as blepharospasm, hypoactivity, ataxia, and lack of startle reflex at 3,000 and 8,000 ppm, with increased salivation in males of these groups, and prostration at 8,000 ppm. However, statistics performed for this review (Fisher's Exact Probability Test) of incidence data provided by Chun et al. (1992) for rats showing blepharospasm, hypoactivity, salivation, ataxia, and prostration at least once during the chronic study indicate that statistically significant changes were limited to prostration in females at 3,000 ppm (but not 8,000 ppm), increased incidence of ataxia in males and females at 8,000 ppm, and increased prostration and salivation in males at 8,000 ppm. Due to lack of dose-response, it is unclear if prostration observed in females is exposure-related. Quantitative startle reflex data could not be located for independent statistical review. The only non-neurological clinical sign noted was swollen periocular tissue in male rats at ≥3,000 ppm, which was attributed to irritative effect of direct vapor exposure rather than systemic toxicity. Based on statistics performed for this review (Fisher's Exact Probability Test) of incidence data provided by Chun et al. (1992), statistically significant increases were observed at 3,000 and 8,000 ppm. Body weight and body weight gain decreased in the 8,000-ppm group throughout the study. Upon

termination of males from the 8,000-ppm group at 82 weeks, body weight and body weight gain were decreased by 19 and 29%, respectively, compared to controls. At terminal sacrifice at 104 weeks, body weight and body weight gain in females from the 8,000-ppm group were reduced by 13 and 22%, respectively, compared to controls. No abnormalities were observed in hematological parameters of any MTBE exposed group. Serum corticosterone levels were increased by 2-fold in males from the 3,000-ppm group at week 97, but a 61% decrease was observed in males of the 8,000-ppm group at week 81. No other exposure-related changes were reported for clinical chemistry parameters. Statistical analysis for organ weights was not conducted for males exposed to 3,000 or 8,000 ppm due to early termination. In females, exposure-related and statistically significant changes in organ weight included a 20–45% increase in absolute and relative liver weights at ≥3,000 ppm and a 22–33% increase in relative kidney weight at ≥3,000 ppm.

Histopathological examination confirmed increased incidence and severity of changes associated with chronic progressive nephropathy in males at ≥400 ppm and females at ≥3,000 ppm, including glomerulosclerosis, tubular proteinosis, interstitial nephritis, and interstitial fibrosis. The most severe lesions were observed in male rats at 8,000 ppm. Additional lesions were observed in males, and considered secondary to nephropathy, including fibrous osteodystrophy, parathyroid hyperplasia, and mineralization within numerous tissues. Neoplastic lesions were observed in both the kidneys and testes. The incidence of renal tubular cell tumors was increased in male rats at ≥3,000 ppm, with a significant increase in combined incidence of adenomas and carcinomas for the 3,000-ppm group (8/50) compared to controls (1/50). Early mortality may have contributed to lack of significant increase at 8,000 ppm (3/50). No renal tubular cell tumors were found in males at 400 ppm. The incidence of testicular interstitial cell adenomas was increased significantly in at 3,000 ppm (41/50) and 8,000 ppm (47/50), compared to controls (32/50). However, observed incidences in the exposure groups were within historical controls and the control incidence was low compared to historical data. Since testicular tumors are the most common tumor in this strain of rat, and findings were within historical controls, these tumors were not considered exposure related.

Selection of the Point of Departure for the MRL: The NOAEL of 400 ppm for renal effects in female rats was selected as the POD, as it represents the lowest candidate POD. This POD is protective of local irritative effects on the eyes observed at ≥3,000 ppm and non-dose-related female prostration observed at 3,000 ppm only.

Calculations

Intermittent Exposure: The NOAEL of 400 ppm was adjusted from intermittent exposure to account for a continuous exposure scenario:

$NOAEL_{ADJ}$ = 400 ppm x 6 hours/24 hours x 5 days/7 days = 71.4 ppm.

Human Equivalent Concentration: While several PBPK models have been developed for MTBE, further refinement is needed to decrease uncertainty in estimated exposure levels, particularly for humans (see Sections 3.1.5 and 6.2 for more details). Therefore, a HEC value for extrarespiratory effects was calculated by multiplying the $NOAEL_{ADJ}$ by the ratio of animal:human blood gas partition coefficients, using reported rat blood gas partition coefficient of 11.5 (Rao and Ginsberg (1997) and the midpoint of the range of human blood gas partition coefficients (17.7–19.6) reported by Rao and Ginsberg (1997) and Kim et al. (2007):

$NOAEL_{HEC}$ = $NOAEL_{ADJ}$ x ratio of animal:human blood gas partition coefficients
$NOAEL_{HEC}$ = 71.4 ppm x (11.5/18.7)
$NOAEL_{HEC}$ = 71.4 ppm x (0.615) = 43.9 ppm

Uncertainty Factor: The $NOAEL_{HEC}$ is divided by a total uncertainty factor (UF) of 30.

- 3 for extrapolation from animals to humans after dosimetric adjustment
- 10 for human variability

Provisional MRL = $NOAEL_{HEC}$ ÷ UFs
43.9 ppm ÷ (3 x 10) = 1 ppm

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Selection of a renal effect in female rats as the critical effect following chronic inhalation exposure is supported by evidence of elevated kidney weights in female rats following exposure to ≥4,000 ppm for 13 weeks (Lington et al. 1997), and female mice following exposure to 8,000 ppm for 18 months (Bird et al. 1997).

Agency Contacts (Chemical Managers): Jennifer Przybyla

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Methyl *tert*-Butyl Ether (MTBE)
CAS Numbers: 1634-04-4
Date: January 2022
Profile Status: Draft for Public Comment
Route: Oral
Duration: Acute

MRL Summary: There are insufficient data to support derivation of an acute-duration oral MRL.

Rationale for Not Deriving an MRL: Available acute oral studies report MTBE-related effects at LOAELs in the range of 400–450 mg/kg/day, including neurological and male reproductive effects in rats (see Table A-23). Gastrointestinal effects were observed at ≥357 mg/kg/day, but effects are limited to qualitatively reported diarrhea, which may be due to irritative portal-of-entry effects associated with bolus gavage. This is supported by evidence of gastrointestinal effects only in gavage studies (Amoco 1992; Robinson et al. 1990) and not in drinking water studies, even after chronic exposure (Belpoggi et al. 1995, 1997; Bermudez et al. 2012; Dodd et al. 2013). Therefore, diarrhea was not considered for MRL derivation because it may not be a relevant endpoint for humans who are predominantly exposed via drinking water.

Of the candidate endpoints in Table A-23, none were considered adequate for MRL derivation. Reports of neurological effects at ≥400 mg/kg/day had limited qualitative and quantitative reporting, precluding use of these studies as the basis for the MRL. For male reproductive effects, adversity of decreased testes weight and increased serum luteinizing hormone (LH) in the absence of other testicular effects is unclear, particularly because neither of these effects were observed after 4 weeks of exposure using the same protocols at doses up to 1,600 mg/kg/day (Dong-mei et al. 2009; Li et al. 2008). Uncertainties in male reproductive effects following oral exposure preclude the use of these endpoints as the basis for the MRL.

Table A-23. Summary of NOAEL and LOAEL Values Following Acute Oral Exposure to Methyl *tert*-Butyl Ether (MTBE)

Species	Duration	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Neurological effects					
Fischer 344 rat	Once	40	400	Drowsiness	MTBE Committee 1990b
Sprague-Dawley rat	2 weeks	ND	450	Lethargy; transient ataxia in some animals	de Peyster et al. 2014
Male reproductive effects					
Sprague-Dawley rat	2 weeks	ND	400	Transient decreases in testes weight (not observed at 4 weeks)	Dong-mei et al. 2009

Table A-23. Summary of NOAEL and LOAEL Values Following Acute Oral Exposure to Methyl *tert*-Butyl Ether (MTBE)

Species	Duration	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Sprague-Dawley rat	2 weeks	ND	400	Transient increased serum LH (not observed at 4 weeks)	Li et al. 2008

LH = luteinizing hormone; LOAEL = lowest observed adverse effect level; ND = not determined; NOAEL = no-observed-adverse-effect level

Agency Contacts (Chemical Managers): Jennifer Przybyla

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Methyl *tert*-Butyl Ether (MTBE)
CAS Numbers: 1634-04-4
Date: January 2022
Profile Status: Draft for Public Comment
Route: Oral
Duration: Intermediate
MRL: 0.6 mg/kg/day (provisional)
Critical Effect: CNS effects (hypoactivity)
Reference: Amoco 1992
Point of Departure: NOAEL of 90 mg/kg/day ($NOAEL_{ADJ}$ of 64 mg/kg/day)
Uncertainty Factor: 100
LSE Graph Key: 16
Species: Rat

MRL Summary: A provisional intermediate-duration oral MRL of 0.6 mg/kg/day was derived for MTBE based on transient CNS depression (hypoactivity) in rats exposed to doses ≥440 mg/kg/day 5 days/week for 4 weeks; a NOAEL of 90 mg/kg/day was identified (Amoco 1992). The MRL is based on the NOAEL of 90 mg/kg/day, which was adjusted for intermittent exposure to a $NOAEL_{ADJ}$ of 64 mg/kg/day and divided by a total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Selection of the Critical Effect: Available intermediate-duration oral studies report the most sensitive MTBE-related effects at LOAELs in the range of 400–440 mg/kg/day, including neurological effects in rats (CNS depression) and reproductive effects in male rats (sperm effects and changes to seminiferous tubules) (see Table A-24). Both neurological and male reproductive effects were considered for MRL derivation.

Gastrointestinal effects were also observed in intermediate-duration oral studies at doses ≥100 mg/kg/day, but effects are limited to qualitatively reported diarrhea, which may be due to irritative portal-of-entry effects associated with bolus gavage. This is supported by evidence of gastrointestinal effects only in gavage studies (Amoco 1992; Robinson et al. 1990) and not in drinking water studies, even after chronic exposure (Belpoggi et al. 1995, 1997; Bermudez et al. 2012; Dodd et al. 2013). Therefore, diarrhea was not considered for MRL derivation because it may not be a relevant endpoint for humans who are predominantly exposed via drinking water. One study reported mild hepatic effects (elevated serum cholesterol) in rats following exposure to ≥100 mg/kg/day for 90 days (Robinson et al. 1990); this effect was not considered for MRL derivation due to unclear adversity in the absence of associated hepatic lesions (e.g., fatty liver). Renal effects in male rats were also observed at ≥209 mg/kg/day; however, renal effects in male rats were not considered an appropriate basis for the MRL because available toxicity and mechanistic studies indicate that renal effects in males are partially attributable to α2u-globulin, which is not relevant for human health (Ahmed 2001; Bogen and Heilman 2015; McGregor 2006; Phillips et al. 2008). One low-dose study reported altered zinc and glucose homeostasis at drinking water doses ≥0.15 mg/kg/day (Saeedi et al. 2017); however, this study evaluated a limited number of endpoints and other studies evaluating serum glucose levels at much higher doses report inconsistent findings (Robinson et al. 1990). Due to unknown adversity of the findings by Saeedi et al. (2017), this study was not considered for MRL derivation.

Table A-24. Summary of NOAEL and LOAEL Values Following Intermediate Oral Exposure to Methyl *tert*-Butyl Ether (MTBE)

Species	Duration	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Neurological effects					
Sprague-Dawley rat	4 weeks 5 days/week	90	440	Transient hypoactivity	Amoco 1992
Hepatic effects					
Sprague-Dawley rat	90 days	ND	100	Elevated serum cholesterol	Robinson et al. 1990
Reproductive effects					
Sprague-Dawley rat	4 weeks	ND	400	Increased abnormal sperm	Li et al. 2008
Sprague-Dawley rat	30 days	ND	400	Seminiferous tubule changes	Gholami et al. 2015

LOAEL = lowest observed adverse effect level; ND = not determined; NOAEL = no-observed-adverse-effect level;

In order to identify the most sensitive POD, BMD modeling was attempted for critical neurological and male reproductive endpoints in Table A-24 when data were amenable to modeling. The data were fit to all available continuous models in EPA's BMDS (version 3.1.2) using a BMR of 1 standard deviation (sperm deformity ratio) or 10% extra risk (hypoactivity). Adequate model fit was judged by three criteria: goodness-of-fit statistics (p value >0.1), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined BMR. Among all of the models providing adequate fit to the data, the lowest BMDL (95% lower confidence limit on the BMD) was selected as the POD when the difference between the BMDLs estimated from these models was >3-fold; otherwise, the BMDL from the model with the lowest AIC was chosen.

Suitable models were identified for increased sperm deformity in male rats (Li et al. 2008). A suitable model was not identified for CNS effects (hypoactivity in male rats) due to plateauing of effects at 440 and 1,750 mg/kg/day (Amoco 1992). The datasets used for BMD modeling are presented in Tables A-25 and A-26, the model predictions are presented in Table A-27, and the fit of the selected model is presented in Figure A-10. Data reporting for changes in the seminiferous tubules were inadequate for modeling because incidence data were not reported by Gholami et al. (2015).

Table A-25. Neurological Effects in Male Rats Following Gavage Exposure to Methyl *tert*-Butyl Ether (MTBE) for 4 Weeks (5 Days/Week)

	Dose (mg/kg/day)			
	0	90	440	1,750
Hypoactivity Incidence (percent incidence)	0/10 (0%)	0/10 (0%)	4/10[a] (40%)	4/10[a] (40%)

[a]p<0.05.

Source: Amoco 1992

Table A-26. Sperm Effects in Male Rats Following Gavage Exposure to Methyl *tert*-Butyl Ether (MTBE) for 4 Weeks

	Dose (mg/kg/day)			
	0	400	800	1,600
Sperm deformity ratio (percent) Mean±SD (n)	12.1±3.3 (8)	18.5±4.9[a] (7)	19.5±2.8[a] (9)	29.1±4.5[b] (9)

[a]p < 0.05.
[b]p < 0.01.

(n) = number of animals; SD = standard deviation

Source: Li et al. 2008

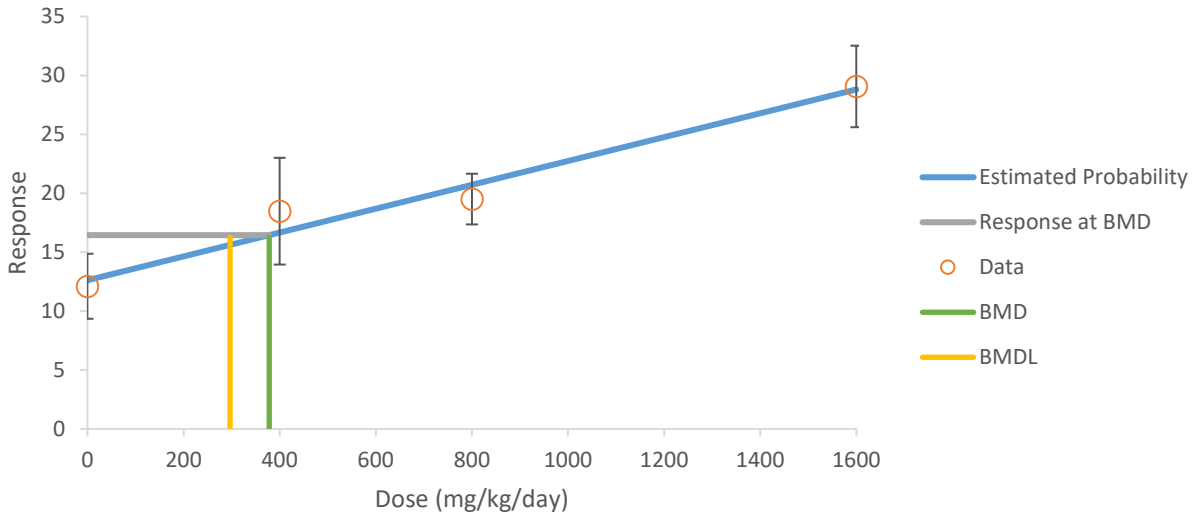
Table A-27. Results from Benchmark Dose (BMD) Analysis (Constant Variance) of Sperm Deformity Ratio (%) in Male Rats Following Gavage Exposure to Methyl *tert*-Butyl Ether (MTBE) for 4 Weeks (Li et al. 2008)

Model	Test for significant difference p-value[a]	Test for variance p-value[b]	Test for means p-value[c]	Scaled residuals[d]			AIC	BMD_{1SD} (mg/kg/day)	$BMDL_{1SD}$ (mg/kg/day)
				Dose below BMD	Dose above BMD	Overall largest			
Exponential (model 2)[e]	<0.0001	0.37	0.185	1.44	-0.26	1.44	188.87	522.63	431.56
Exponential (model 3)[e]	<0.0001	0.37	0.185	1.44	-0.26	1.44	188.87	522.63	431.56
Exponential (model 4)[e]	<0.0001	0.37	0.097	-0.37	1.25	1.25	190.26	ND	ND
Exponential (model 5)[e]	<0.0001	0.37	0.097	-0.37	1.25	1.25	190.26	ND	ND
Hill[e]	<0.0001	0.37	ND	-0.32	1.23	1.23	192.29	ND	ND
Polynomial (3-degree)[e]	<0.0001	0.37	0.103	-0.54	1.32	1.32	190.16	408.65	297.82
Polynomial (2-degree)[e]	<0.0001	0.37	0.098	1.29	-0.85	1.29	190.24	ND	ND
Power[e,f]	**<0.0001**	**0.37**	**0.252**	**-0.38**	**1.25**	**1.25**	**188.26**	**378.24**	**296.67**
Linear	<0.0001	0.37	0.252	-0.38	1.25	1.25	188.26	378.27	296.67

[a]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[b]Values <0.05 fail to meet conventional goodness-of-fit criteria.
[c]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[d]Scaled residuals at doses immediately below and above the BMD; also the largest residual at any dose.
[e]Restricted model.
[f]Recommended model (lowest AIC). The constant variance model provided an adequate fit to the data. The Exponential 2, Exponential 3, 3-degree polynomial, Power, and Linear models provided adequate fit to the means. Of these models, the BMDLs were sufficiently close (<3-fold); therefore, the model with the lowest AIC was selected (Power model).

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure dose associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{1SD}$ = exposure dose associated with a change of 1 standard deviation from the control); ND = not determined; value did not compute or the model failed to meet the conventional goodness of fit criteria;
SD = standard deviation

Figure A-10. Fit of the Power Model to Data for Sperm Deformity Ratio (%) in Male Rats Following Gavage Exposure to Methyl tert-Butyl Ether (MTBE) for 4 Weeks (Li et al. 2008)



The candidate PODs are summarized in Table A-28. The lowest POD was identified for neurological effects, with a $NOAEL_{ADJ}$ value of 64 mg/kg/day. Therefore, neurological effects were selected as the critical effect.

Table A-28. Summary of Candidate Effects and POD Values Considered for Derivation of an Intermediate Oral MRL for Methyl *tert*-Butyl Ether (MTBE)

Species	Duration	Effect	Candidate POD (ppm)	POD type	Reference
Neurological effects					
Sprague-Dawley rat	4 weeks 5 days/week	Transient hypoactivity[a]	64	$NOAEL_{ADJ}$	Amoco 1992
Reproductive effects					
Sprague-Dawley rat	4 weeks 7 days/week	Increased abnormal sperm	297	BMDL	Li et al. 2008
Sprague-Dawley rat	30 days 7 days/week	Seminiferous tubule changes	400	LOAEL	Gholami et al. 2015

[a]Selected study/endpoint for derivation of acute oral MRL.

BMD = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD; LOAEL = lowest-observed-adverse-effect level; MRL = Minimal Risk Level; $NOAEL_{ADJ}$ = no-observed-adverse-effect level (adjusted for continuous exposure); POD = point of departure

Selection of the Principal Study: The 4-week study in rats by Amoco (1992) was selected as the principal studies because it provided the lowest POD ($NOAEL_{ADJ}$ = 64 mg/kg/day) for the critical effect (neurotoxicity).

Summary of the Principal Study:

Amoco. 1992. 28-Day oral toxicity study of methyl tert-butyl ether in rats (final report) with cover letter dated 070192. Amoco Corporation. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0540108. 86-920000979. https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/OTS0540108.xhtml. January 17, 2020.

Amoco (1992) exposed Sprague-Dawley rats (10/sex/group) to undiluted MTBE at doses of 0, 90, 440, or 1,750 mg/kg/day via gavage 5 days/week for 4 weeks. The rats were observed for clinical signs of toxicity daily, and body weight was measured weekly. The rats were sacrificed at the end of the treatment period, blood was collected for serum chemistry and hematology determinations, organ weights were measured, and comprehensive gross necropsy was performed. Comprehensive histological examination (with the exception of the femur, bone marrow smear, tongue, larynx, mandibular lymph nodes, ear, nasal turbinate, mid-thoracic and lumbar spinal cord, vagina, exorbital lacrimal glands, and Harderian glands, unless grossly abnormal) was performed on control and high-dose rats. The kidneys (males only) and stomach from the low- and mid-dose groups were also examined microscopically because of signs of toxicity in these tissues in the high-dose group.

No deaths attributable to MTBE occurred. Transient exposure-related clinical signs observed during the first hour post-dosing throughout the study included salivation in males and females at ≥440 mg/kg/day, hypoactivity in males at ≥440 mg/kg/day, and ataxia in both sexes at 1,750 mg/kg/day. Salivation is likely a local irritative effect associated with gavage exposure, rather than a systemic CNS effect. No exposure-related changes in body weight were observed. No hematological changes were observed. Serum cholesterol was elevated in both males and females at 1,750 mg/kg/day, compared with controls; no other exposure-related changes in clinical chemistry were noted. No exposure-related absolute organ weight changes were observed. Relative organ weight effects included a 9 and 13% increase in relative liver weights in males and females, respectively, at 1,750 mg/kg/day; a 9 and 15% increase in relative kidney weight in males at 440 and 1,750 mg/kg/day, respectively; a 6–8% increase in relative kidney weight in females at 90 and 1,750 mg/kg/day; and a 23% increase in relative adrenal weight in males at 1,750 mg/kg/day. Incidence of submucosal edema of the squamous portion of the stomach was increased at 1,750 mg/kg/day in both sexes. In males, hyaline droplets in proximal convoluted tubules were observed at ≥440 mg/kg/day; no histopathological changes were observed in female kidneys. No other histopathological changes were observed.

Selection of the Point of Departure for the MRL: The NOAEL of 90 mg/kg/day for CNS depression (hypoactivity) in rats reported by Amoco (1992) was selected as the POD because it represents the lowest available POD for the critical effect (neurotoxicity).

Intermittent Exposure: The NOAEL of 90 mg/kg/day was adjusted from intermittent exposure to account for a continuous exposure scenario:

$NOAEL_{ADJ}$ = 90 mg/kg/day x (5 days/7 days) = 64 mg/kg/day.

Uncertainty Factor: The $NOAEL_{ADJ}$ is divided by a total uncertainty factor (UF) of 100:

- 10 for extrapolation from animals to humans;
- 10 for human variability

Provisional MRL = $NOAEL_{ADJ}$ ÷ (UFs x MF)
64 mg/kg/day ÷ (10 x 10) = 0.6 mg/kg/day

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Selection of a neurological effect as the critical effect following intermediate oral exposure is supported by consistent observation of CNS depressive effects following gavage exposure to acute or intermediate doses ≥400 mg/kg/day in rats (Amoco 1992; ARCO 1980; de Peyster et al. 2003, 2014; Dong-mei et al. 2009; MTBE Committee 1990b; Robinson et al. 1990) and 2,000 mg/kg/day in mice (de Peyster et al. 2008). Transient CNS depression was also consistently reported in animal inhalation studies (Bevan et al. 1997a, 1997b; Bird et al. 1997; Dodd and Kintigh 1989; Lington et al. 1997; Moser et al. 1996; MTBE Committee 1990a; Vergnes and Chun 1994; Vergnes and Morabit 1989) and has been reported in some humans exposed to MTBE in fuel (Alaska DHSS 1992a, 1992b; CDC 1993a; Moolenaar et al. 1994; Wisconsin DHSS 1995) or during intracystic therapy for gallstone dissolution (Allen et al. 1985a; Bonardi et al. 1986; Brandon et al. 1988; Di Padova et al. 1986; Eidsvoll et al. 1993; Kaye et al. 1990; McNulty et al. 1991; Murray et al. 1988; Neoptolemos et al. 1990; Ponchon et al. 1988; Saraya et al. 1990; Thistle et al. 1989; Tobio-Calo et al. 1992; van Sonnenberg et al. 1986; Williams et al. 1990). However, it is acknowledged that evidence for neurological findings following oral studies is not as robust as evidence following inhalation exposure due to lack of CNS depression in a chronic gavage study (Belpoggi et al. 1995, 1997) or in intermediate- or chronic-duration drinking water studies (Bermudez et al. 2012; Dodd et al. 2013). Since MTBE elimination is relatively rapid, lack of CNS depression in drinking water studies at similar overall doses may be due to dosing over time (as opposed to bolus gavage doses).

Agency Contacts (Chemical Managers): Jennifer Przybyla

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Methyl *tert*-Butyl Ether (MTBE)
CAS Numbers: 1634-04-4
Date: January 2022
Profile Status: Draft for Public Comment
Route: Oral
Duration: Chronic

MRL Summary: There are insufficient data to support derivation of a chronic-duration oral MRL.

Rationale for Not Deriving an MRL: Serious effects (death and cancer) were observed at ≥250 mg/kg/day, along with dysplastic proliferation of lymphoreticular tissue (possibly preneoplastic). The only adverse effects observed at doses below this serious LOAEL value are renal effects in male rats at drinking water doses ≥29 mg/kg/day (Bermudez et al. 2012); however, these effects were not considered an appropriate basis for the MRL because available toxicity and mechanistic studies indicate that renal effects in males are partially attributable to α2u-globulin, which is not relevant for human health (Ahmed 2001; Bogen and Heilman 2015; McGregor 2006; Phillips et al. 2008). Renal effects in female rats were not observed until chronic doses 4-fold higher than the identified serious LOAEL (1,042 mg/kg/day; Dodd et al. 2013). Therefore, a chronic oral MRL was not derived.

Agency Contacts (Chemical Managers): Jennifer Przybyla

APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR MTBE

The objective of the toxicological profile is to evaluate the potential for human exposure and the potential health hazards associated with inhalation, oral, or dermal/ocular exposure to MTBE.

B.1 LITERATURE SEARCH AND SCREEN

A literature search and screen was conducted to identify studies examining health effects, toxicokinetics, mechanisms of action, susceptible populations, biomarkers, chemical interactions, physical and chemical properties, production, use, environmental fate, environmental releases, and environmental and biological monitoring data for MTBE. ATSDR primarily focused on peer-reviewed articles without publication date or language restrictions. Non-peer-reviewed studies that were considered relevant to the assessment of the health effects of MTBE have undergone peer review by at least three ATSDR-selected experts who have been screened for conflict of interest. The inclusion criteria used to identify relevant studies examining the health effects of MTBE are presented in Table B-1.

Table B-1. Inclusion Criteria for the Literature Search and Screen

- Health Effects
  - Species
    - Human
    - Laboratory mammals
  - Route of exposure
    - Inhalation
    - Oral
    - Dermal (or ocular)
    - Parenteral (these studies will be considered supporting data)
  - Health outcome
    - Death
    - Systemic effects
    - Body weight effects
    - Respiratory effects
    - Cardiovascular effects
    - Gastrointestinal effects
    - Hematological effects
    - Musculoskeletal effects
    - Hepatic effects
    - Renal effects
    - Dermal effects
    - Ocular effects
    - Endocrine effects
    - Immunological effects
    - Neurological effects
    - Reproductive effects
    - Developmental effects
    - Other noncancer effects

Table B-1. Inclusion Criteria for the Literature Search and Screen

Cancer
Toxicokinetics
Absorption
Distribution
Metabolism
Excretion
PBPK models
Biomarkers
Biomarkers of exposure
Biomarkers of effect
Interactions with other chemicals
Potential for human exposure
Releases to the environment
Air
Water
Soil
Environmental fate
Transport and partitioning
Transformation and degradation
Environmental monitoring
Air
Water
Sediment and soil
Other media
Biomonitoring
General populations
Occupation populations

B.1.1 Literature Search

The current literature search was intended to update the 1996 toxicological profile for MTBE; thus, the literature search was restricted to studies published between January 1994 and February 2019. The following main databases were searched in February 2019:

- PubMed
- National Library of Medicine's TOXLINE
- Scientific and Technical Information Network's TOXCENTER

The search strategy used the chemical names, Chemical Abstracts Service (CAS) numbers, synonyms, Medical Subject Headings (MeSH) headings, and keywords for MTBE. The query strings used for the literature search are presented in Table B-2.

The search was augmented by searching the Toxic Substances Control Act Test Submissions (TSCATS), NTP website, and National Institute of Health Research Portfolio Online Reporting Tools Expenditures

and Results (NIH RePORTER) databases using the queries presented in Table B-3. Additional databases were searched in the creation of various tables and figures, such as the TRI Explorer, the Substance Priority List (SPL) resource page, and other items as needed. Regulations applicable to MTBE were identified by searching international and U.S. agency websites and documents.

Review articles were identified and used for the purpose of providing background information and identifying additional references. ATSDR also identified reports from the grey literature, which included unpublished research reports, technical reports from government agencies, conference proceedings and abstracts, and theses and dissertations.

Table B-2. Database Query Strings

Database search date	Query string
PubMed	
02/2019	((1634-04-4 [rn] OR (("2-Methoxy-2-methylpropane"[tw] OR "Methyl t-butyl ether"[tw] OR "Methyl tert butyl ether"[tw] OR "Methyl tertiary butyl ether"[tw] OR "MTBE"[tw] OR "t-Butyl methyl ether"[tw] OR "tert-Butyl methyl ether"[tw] OR "(tert-Butyl)methylether"[tw] OR "1,1-Dimethylethyl methyl ether"[tw] OR "2-Methoxy-2-methyl propane"[tw] OR "2-Methyl-2-methoxypropane"[tw] OR "Ether, methyl tert-butyl"[tw] OR "Ether, tert-butyl methyl"[tw] OR "Methyl 1,1-dimethylethyl ether"[tw] OR "Methyl-1,1-dimethylethyl ether"[tw] OR "Propane, 2-methoxy-2-methyl"[tw] OR "tert-Butoxymethane"[tw] OR "tert-Butyl-methyl-aether"[tw]) NOT medline[sb])) AND (1994 : 3000[dp] OR 1994 : 3000[mhda] OR 1994 : 3000[crdt] OR 1994 : 3000[edat])) OR (("2-Methoxy-2-methylpropane"[tw] OR "Methyl t-butyl ether"[tw] OR "Methyl tert butyl ether"[tw] OR "Methyl tertiary butyl ether"[tw] OR "MTBE"[tw] OR "t-Butyl methyl ether"[tw] OR "tert-Butyl methyl ether"[tw] OR "(tert-Butyl)methylether"[tw] OR "1,1-Dimethylethyl methyl ether"[tw] OR "2-Methoxy-2-methyl propane"[tw] OR "2-Methyl-2-methoxypropane"[tw] OR "Ether, methyl tert-butyl"[tw] OR "Ether, tert-butyl methyl"[tw] OR "Methyl 1,1-dimethylethyl ether"[tw] OR "Methyl-1,1-dimethylethyl ether"[tw] OR "Propane, 2-methoxy-2-methyl"[tw] OR "tert-Butoxymethane"[tw] OR "tert-Butyl-methyl-aether"[tw]) AND (("Methyl Ethers/toxicity"[mh] OR "Methyl Ethers/adverse effects"[mh] OR "Methyl Ethers/poisoning"[mh] OR "Methyl Ethers/pharmacokinetics"[mh]) OR ("Methyl Ethers"[mh] AND ("environmental exposure"[mh] OR ci[sh])) OR ("Methyl Ethers"[mh] AND toxicokinetics[mh:noexp]) OR ("Methyl Ethers/blood"[mh] OR "Methyl Ethers/cerebrospinal fluid"[mh] OR "Methyl Ethers/urine"[mh]) OR ("Methyl Ethers"[mh] AND ("endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh])) OR ("Methyl Ethers"[mh] AND ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("Methyl Ethers/antagonists and inhibitors"[mh]) OR ("Methyl Ethers/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("Methyl Ethers"[mh] AND cancer[sb]) OR ("Methyl Ethers/pharmacology"[majr])) AND (1994 : 3000[dp] OR 1994 : 3000[mhda] OR 1994 : 3000[crdt] OR 1994 : 3000[edat]))

Table B-2. Database Query Strings

Database search date	Query string
Toxline	
02/2019	Year of Publication: 1994 through 2019 (1634 -04-4[rn] OR "2-Methoxy-2-methylpropane" OR "Methyl t-butyl ether" OR "Methyl tert butyl ether" OR "Methyl tertiary butyl ether" OR "MTBE" OR "t-Butyl methyl ether" OR "tert-Butyl methyl ether" OR "(tert-Butyl)methylether" OR "1,1-Dimethylethyl methyl ether" OR "2-Methoxy-2-methyl propane" OR "2-Methyl-2-methoxypropane" OR "Ether, methyl tert-butyl" OR "Ether, tert-butyl methyl" OR "Methyl 1,1-dimethylethyl ether" OR "Methyl-1,1-dimethylethyl ether" OR "Propane, 2-methoxy-2-methyl" OR "tert-Butoxymethane" OR "tert-Butyl-methyl-aether") AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org]
Toxcenter	
02/2019	L1 6170 SEA FILE=TOXCENTER 1634-04-4 L2 5988 SEA FILE=TOXCENTER L1 NOT TSCATS/FS L3 4833 SEA FILE=TOXCENTER L2 NOT PATENT/DT L4 4528 SEA FILE=TOXCENTER L3 AND PY>=1994 ACT TOXQUERY/Q --------- L5 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) L6 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT) L7 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50) L8 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT L9 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?) L10 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?) L11 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?) L12 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE)) L13 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?) L14 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?) L15 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?) L16 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?) L17 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?) L18 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?) L19 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?)

Table B-2. Database Query Strings

Database search date	Query string
	L20 QUE (ENDOCRIN? AND DISRUPT?)
	L21 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?)
	L22 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)
	L23 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)
	L24 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?)
	L25 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)
	L26 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?)
	L27 QUE (NEPHROTOX? OR HEPATOTOX?)
	L28 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?)
	L29 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?)
	L30 QUE L5 OR L6 OR L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR L28 OR L29
	L31 QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE OR PORCINE OR MONKEY? OR MACAQUE?)
	L32 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE)
	L33 QUE L30 OR L31 OR L32
	L34 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?)
	L35 QUE L33 OR L34

	L36 1957 SEA FILE=TOXCENTER L4 AND L35
	L37 439 SEA FILE=TOXCENTER L36 AND MEDLINE/FS
	L38 273 SEA FILE=TOXCENTER L36 AND BIOSIS/FS
	L39 1227 SEA FILE=TOXCENTER L36 AND CAPLUS/FS
	L40 18 SEA FILE=TOXCENTER L36 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS)
	L41 1582 DUP REM L37 L38 L40 L39 (375 DUPLICATES REMOVED) ANSWERS '1-1582' FROM FILE TOXCENTER
	L*** DEL 439 S L36 AND MEDLINE/FS
	L*** DEL 439 S L36 AND MEDLINE/FS
	L42 439 SEA FILE=TOXCENTER L41
	L*** DEL 273 S L36 AND BIOSIS/FS
	L*** DEL 273 S L36 AND BIOSIS/FS
	L43 159 SEA FILE=TOXCENTER L41
	L*** DEL 1227 S L36 AND CAPLUS/FS
	L*** DEL 1227 S L36 AND CAPLUS/FS
	L44 969 SEA FILE=TOXCENTER L41
	L*** DEL 18 S L36 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS)

Table B-2. Database Query Strings

Database search date	Query string
	L*** DEL 18 S L36 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS) L45 15 SEA FILE=TOXCENTER L41 L46 1143 SEA FILE=TOXCENTER (L42 OR L43 OR L44 OR L45) NOT MEDLINE/FS D SCAN L46

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS via ChemView	
02/2019	Compounds searched: 1634-04-4
NTP	
02/2019	**NTP Site Search (http://ntpsearch.niehs.nih.gov/home), no date limit:** "1634-04-4" "Methyl t-butyl ether" "Methyl tert butyl ether" "Methyl tertiary butyl ether" "MTBE" "t-Butyl methyl ether" "tert-Butyl methyl ether" "2-Methoxy-2-methylpropane" "(tert-Butyl)methylether" "1,1-Dimethylethyl methyl ether" "2-Methoxy-2-methyl propane" "2-Methyl-2-methoxypropane" "Ether, methyl tert-butyl" "Ether, tert-butyl methyl" "Methyl 1,1-dimethylethyl ether" "Methyl-1,1-dimethylethyl ether" "Propane, 2-methoxy-2-methyl" "tert-Butoxymethane" "tert-Butyl-methyl-aether"
Regulations.gov	
02/2019	**Notices or rules:** 1634-04-4
NIH RePORTER	
12/2019	**Search in: Projects AdminIC: All, Fiscal Year: Active Projects** **Text Search:** "2-Methoxy-2-methylpropane" OR "Methyl t-butyl ether" OR "Methyl tert butyl ether" OR "Methyl tertiary butyl ether" OR "MTBE" OR "t-Butyl methyl ether" OR "tert-Butyl methyl ether" OR "(tert-Butyl)methylether" OR "1,1-Dimethylethyl methyl ether" OR "2-Methoxy-2-methyl propane" OR "2-Methyl-2-methoxypropane" OR "Ether, methyl tert-butyl" OR "Ether, tert-butyl methyl" OR "Methyl 1,1-dimethylethyl ether" OR "Methyl-1,1-dimethylethyl ether" OR "Propane, 2-methoxy-2-methyl" OR "tert-Butoxymethane" OR "tert-Butyl-methyl-aether" OR MTBE (Advanced), Search in: Projects Admin IC: All, Fiscal Year: Active Projects
Other	Identified throughout the assessment process

The February 2019 results were:

- Number of records identified from PubMed, TOXLINE, and TOXCENTER (after duplicate removal): 2,343
- Number of records identified from other strategies: 71
- Total number of records to undergo literature screening: 2,414

B.1.2 Literature Screening

A two-step process was used to screen the literature search to identify relevant studies on MTBE:

- Title and abstract screen
- Full text screen

Title and Abstract Screen. Within the reference library, titles and abstracts were screened manually for relevance. Studies that were considered relevant (see Table B-1 for inclusion criteria) were moved to the second step of the literature screening process. Studies were excluded when the title and abstract clearly indicated that the study was not relevant to the toxicological profile.

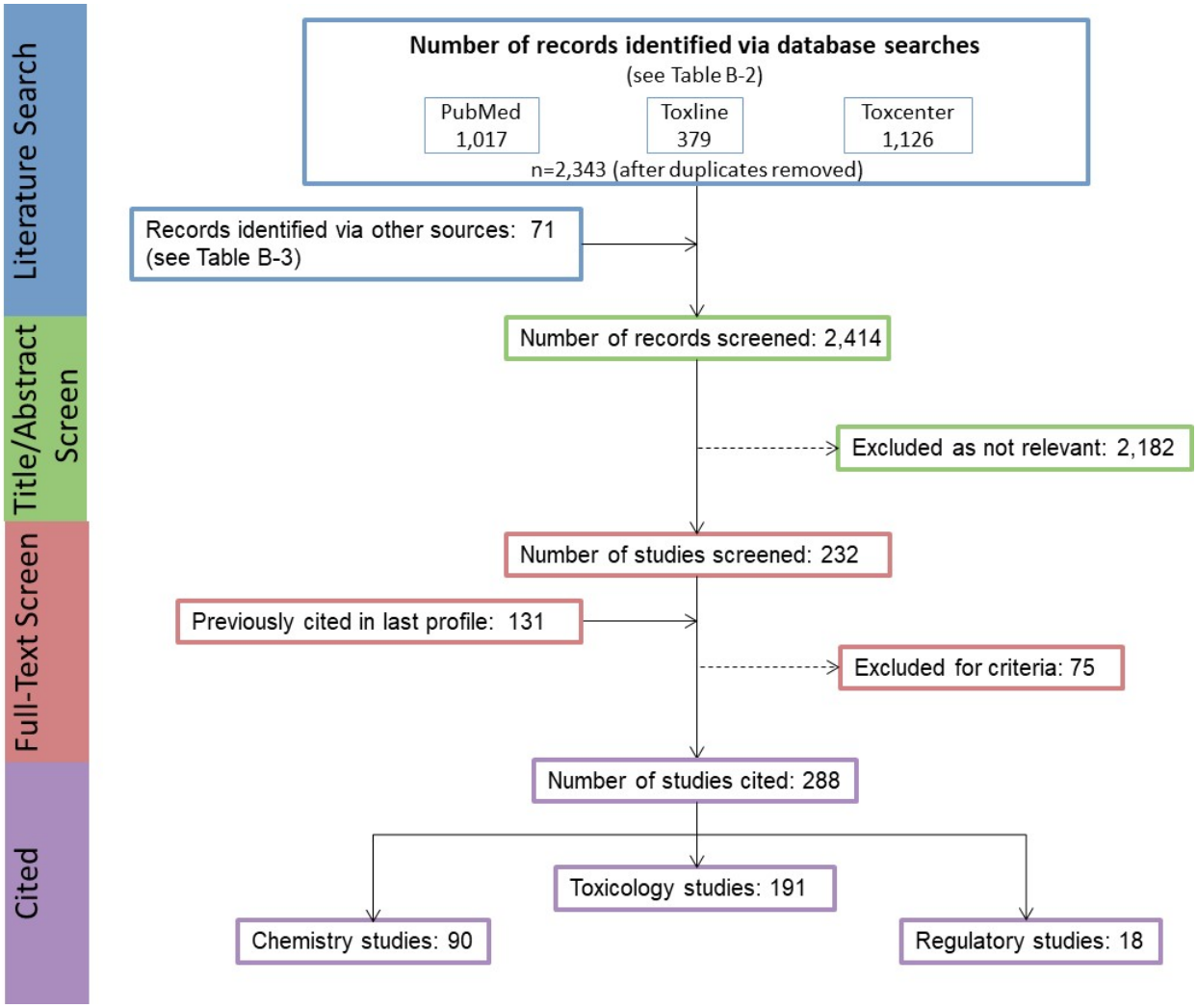
- Number of titles and abstracts screened: 2,414
- Number of studies considered relevant and moved to the next step: 232

Full Text Screen. The second step in the literature screening process was a full text review of individual studies considered relevant in the title and abstract screen step. Each study was reviewed to determine whether it was relevant for inclusion in the toxicological profile.

- Number of studies undergoing full text review: 232
- Number of studies cited in the pre-public draft of the toxicological profile: 131
- Total number of studies cited in the profile: 288

A summary of the results of the literature search and screening is presented in Figure B-1.

Figure B-1. February 2019 Literature Search Results and Screen for MTBE



APPENDIX C. USER'S GUIDE

Chapter 1. Relevance to Public Health

This chapter provides an overview of U.S. exposures, a summary of health effects based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information, and an overview of the minimal risk levels. This is designed to present interpretive, weight-of-evidence discussions for human health endpoints by addressing the following questions:

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

Minimal Risk Levels (MRLs)

Where sufficient toxicologic information is available, ATSDR derives MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a hazardous substance emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Section 1.2, Summary of Health Effects, contains basic information known about the substance. Other sections, such as Section 3.2 Children and Other Populations that are Unusually Susceptible and Section 3.4 Interactions with Other Substances, provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive endpoint which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a

substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables that are provided in Chapter 2. Detailed discussions of the MRLs are presented in Appendix A.

Chapter 2. Health Effects

Tables and ss for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species and MRLs to humans for noncancer endpoints. The LSE tables and figures can be used for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE tables and figures follow. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

TABLE LEGEND

See Sample LSE Table (page C-5)

(1) Route of exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically, when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure (i.e., inhalation, oral, and dermal). LSE figures are limited to the inhalation and oral routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures. Profiles with more than one chemical may have more LSE tables and figures.

(2) Exposure period. Three exposure periods—acute (<15 days), intermediate (15–364 days), and chronic (≥365 days)—are presented within each relevant route of exposure. In this example, two oral studies of chronic-duration exposure are reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Figure key. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 51 identified NOAELs and less serious LOAELs (also see the three "51R" data points in sample LSE Figure 2-X).

(4) Species (strain) No./group. The test species (and strain), whether animal or human, are identified in this column. The column also contains information on the number of subjects and sex per group. Chapter 1, Relevance to Public Health, covers the relevance of animal data to human toxicity and Section 3.1, Toxicokinetics, contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(5) Exposure parameters/doses. The duration of the study and exposure regimens are provided in these columns. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 51), rats were orally exposed to “Chemical X” via feed for 2 years. For a

more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Aida et al. 1992).

(6) Parameters monitored. This column lists the parameters used to assess health effects. Parameters monitored could include serum (blood) chemistry (BC), biochemical changes (BI), body weight (BW), clinical signs (CS), developmental toxicity (DX), food intake (FI), gross necropsy (GN), hematology (HE), histopathology (HP), immune function (IX), lethality (LE), neurological function (NX), organ function (OF), ophthalmology (OP), organ weight (OW), reproductive function (RX), urinalysis (UR), and water intake (WI).

(7) Endpoint. This column lists the endpoint examined. The major categories of health endpoints included in LSE tables and figures are death, body weight, respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, dermal, ocular, endocrine, immunological, neurological, reproductive, developmental, other noncancer, and cancer. "Other noncancer" refers to any effect (e.g., alterations in blood glucose levels) not covered in these systems. In the example of key number 51, three endpoints (body weight, hematological, and hepatic) were investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no adverse effects were seen in the organ system studied. The body weight effect reported in key number 51 is a NOAEL at 25.5 mg/kg/day. NOAELs are not reported for cancer and death; with the exception of these two endpoints, this field is left blank if no NOAEL was identified in the study.

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused an adverse health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific endpoint used to quantify the adverse effect accompanies the LOAEL. Key number 51 reports a less serious LOAEL of 6.1 mg/kg/day for the hepatic system, which was used to derive a chronic exposure, oral MRL of 0.008 mg/kg/day (see footnote "c"). MRLs are not derived from serious LOAELs. A cancer effect level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases. If no LOAEL/CEL values were identified in the study, this field is left blank.

(10) Reference. The complete reference citation is provided in Chapter 8 of the profile.

(11) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. For example, footnote "c" indicates that the LOAEL of 6.1 mg/kg/day in key number 51 was used to derive an oral MRL of 0.008 mg/kg/day.

FIGURE LEGEND

See Sample LSE Figure (page C-6)

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(12) Exposure period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the chronic exposure period are illustrated.

(13) Endpoint. These are the categories of health effects for which reliable quantitative data exist. The same health effect endpoints appear in the LSE table.

(14) Levels of exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(15) LOAEL. In this example, the half-shaded circle that is designated 51R identifies a LOAEL critical endpoint in the rat upon which a chronic oral exposure MRL is based. The key number 51 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 6.1 mg/kg/day (see entry 51 in the sample LSE table) to the MRL of 0.008 mg/kg/day (see footnote "c" in the sample LSE table).

(16) CEL. Key number 59R is one of studies for which CELs were derived. The diamond symbol refers to a CEL for the test species (rat). The number 59 corresponds to the entry in the LSE table.

(17) Key to LSE figure. The key provides the abbreviations and symbols used in the figure.

APPENDIX C

Table 2-X. Levels of Significant Exposure to [Chemical X] – Oral (1)

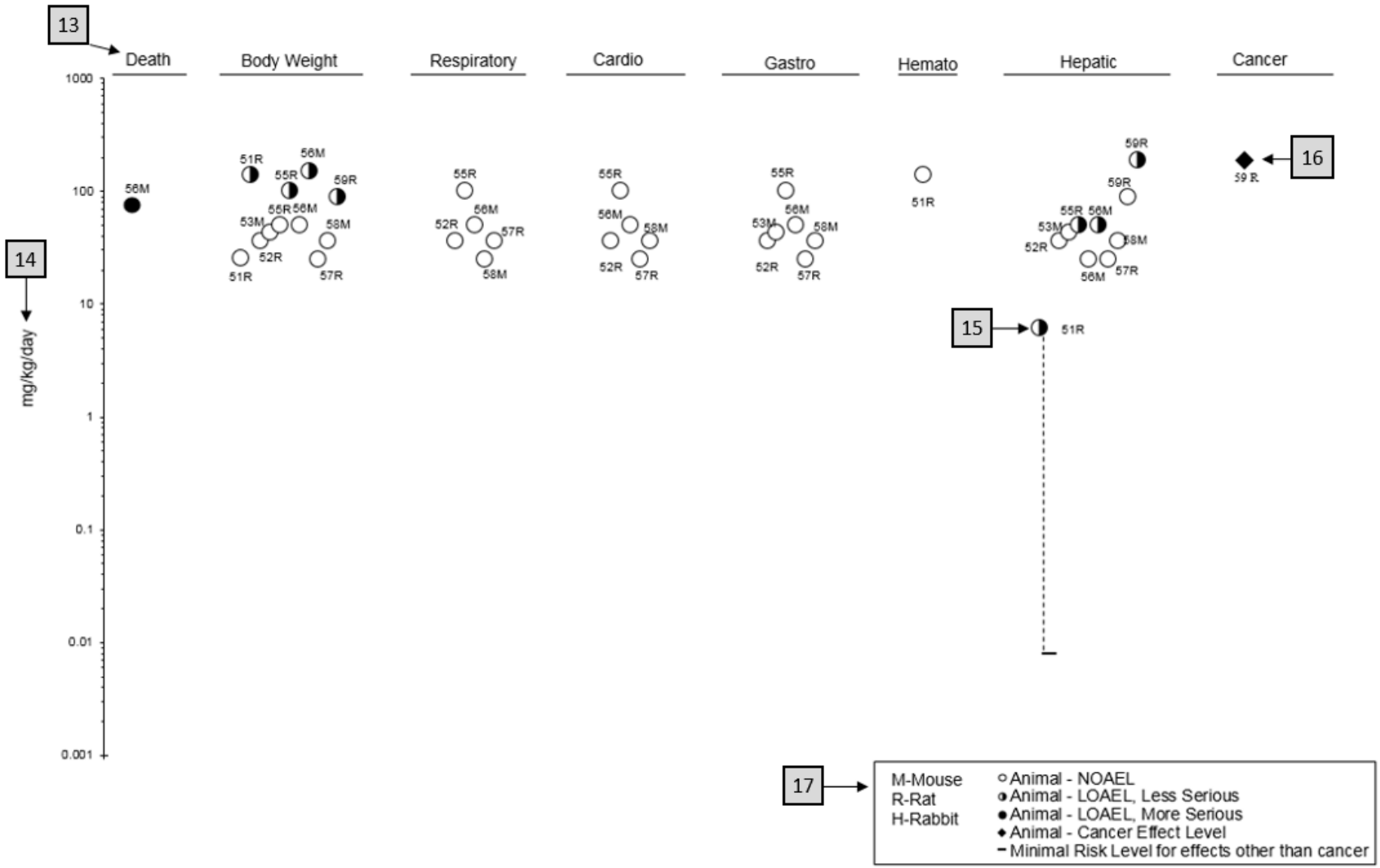
Figure key[a] (3)	Species (strain) No./group (4)	Exposure parameters (5)	Doses (mg/kg/day) (5)	Parameters monitored (6)	Endpoint (7)	NOAEL (mg/kg/day) (8)	Less serious LOAEL (mg/kg/day) (9)	Serious LOAEL (mg/kg/day) (9)	Effect
CHRONIC EXPOSURE (2)									
51	Rat (Wistar) 40 M, 40 F	2 years (F)	M: 0, 6.1, 25.5, 138.0 F: 0, 8.0, 31.7, 168.4	CS, WI, BW, OW, HE, BC, HP	Bd wt	25.5	138.0		Decreased body weight gain in males (23–25%) and females (31–39%)
					Hemato	138.0			
					Hepatic		6.1[c]		Increases in absolute and relative weights at ≥6.1/8.0 mg/kg/day after 12 months of exposure; fatty generation at ≥6.1 mg/kg/day in males and at ≥31.7 mg/kg/day in females, and granulomas in females at 31.7 and 168.4 mg/kg/day after 12, 18, or 24 months of exposure and in males at ≥6.1 mg/kg/day only after 24 months of exposure
Aida et al. 1992 (10)									
52	Rat (F344) 78 M	104 weeks (W)	0, 3.9, 20.6, 36.3	CS, BW, FI, BC, OW, HP	Hepatic	36.3			
					Renal	20.6	36.3		Increased incidence of renal tubular cell hyperplasia
					Endocr	36.3			
George et al. 2002									
59	Rat (Wistar) 58M, 58F	Lifetime (W)	M: 0, 90 F: 0, 190	BW, HP	Cancer		190 F		Increased incidence of hepatic neoplastic nodules in females only; no additional description of the tumors was provided
Tumasonis et al. 1985									

[a]The number corresponds to entries in Figure 2-x.

(11) [b]Used to derive an acute-duration oral minimal risk level (MRL) of 0.1 mg/kg/day based on the $BMDL_{05}$ of 10 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

[c]Used to derive a chronic-duration oral MRL of 0.008 mg/kg/day based on the $BMDL_{10}$ of 0.78 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Figure 2-X. Levels of Significant Exposure to [Chemical X] - Oral



APPENDIX D. QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances may find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Relevance to Public Health: The Relevance to Public Health Section provides an overview of exposure and health effects and evaluates, interprets, and assesses the significance of toxicity data to human health. A table listing minimal risk levels (MRLs) is also included in this chapter.

Chapter 2: Health Effects: Specific health effects identified in both human and animal studies are reported by type of health effect (e.g., death, hepatic, renal, immune, reproductive), route of exposure (e.g., inhalation, oral, dermal), and length of exposure (e.g., acute, intermediate, and chronic).
NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting.

Pediatrics:

Section 3.2 Children and Other Populations that are Unusually Susceptible
Section 3.3 Biomarkers of Exposure and Effect

ATSDR Information Center

Phone: 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY)
Internet: http://www.atsdr.cdc.gov

The following additional materials are available online:

Case Studies in Environmental Medicine are self-instructional publications designed to increase primary health care providers' knowledge of a hazardous substance in the environment and to aid in the evaluation of potentially exposed patients (see https://www.atsdr.cdc.gov/csem/csem.html).

Managing Hazardous Materials Incidents is a set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident (see https://www.atsdr.cdc.gov/MHMI/index.asp).

Fact Sheets (ToxFAQs™) provide answers to frequently asked questions about toxic substances (see https://www.atsdr.cdc.gov/toxfaqs/Index.asp).

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. Contact: NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015 • Web Page: https://www.cdc.gov/nceh/.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 395 E Street, S.W., Suite 9200, Patriots Plaza Building, Washington, DC 20201 • Phone: 202-245-0625 or 1-800-CDC-INFO (800-232-4636) • Web Page: https://www.cdc.gov/niosh/.

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. Contact: NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212 • Web Page: https://www.niehs.nih.gov/.

Clinical Resources (Publicly Available Information)

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: http://www.aoec.org/.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266 • Web Page: http://www.acoem.org/.

The American College of Medical Toxicology (ACMT) is a nonprofit association of physicians with recognized expertise in medical toxicology. Contact: ACMT, 10645 North Tatum Boulevard, Suite 200-111, Phoenix AZ 85028 • Phone: 844-226-8333 • FAX: 844-226-8333 • Web Page: http://www.acmt.net.

The Pediatric Environmental Health Specialty Units (PEHSUs) is an interconnected system of specialists who respond to questions from public health professionals, clinicians, policy makers, and the public about the impact of environmental factors on the health of children and reproductive-aged adults. Contact information for regional centers can be found at http://pehsu.net/findhelp.html.

The American Association of Poison Control Centers (AAPCC) provide support on the prevention and treatment of poison exposures. Contact: AAPCC, 515 King Street, Suite 510, Alexandria VA 22314 • Phone: 701-894-1858 • Poison Help Line: 1-800-222-1222 • Web Page: http://www.aapcc.org/.

APPENDIX E. GLOSSARY

Absorption—The process by which a substance crosses biological membranes and enters systemic circulation. Absorption can also refer to the taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure—Exposure to a chemical for a duration of ≤14 days, as specified in the Toxicological Profiles.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)—The amount of a chemical adsorbed by sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Benchmark Dose (BMD) or Benchmark Concentration (BMC)—is the dose/concentration corresponding to a specific response level estimate using a statistical dose-response model applied to either experimental toxicology or epidemiology data. For example, a BMD_{10} would be the dose corresponding to a 10% benchmark response (BMR). The BMD is determined by modeling the dose-response curve in the region of the dose-response relationship where biologically observable data are feasible. The BMDL or BMCL is the 95% lower confidence limit on the BMD or BMC.

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers—Indicators signaling events in biologic systems or samples, typically classified as markers of exposure, effect, and susceptibility.

Cancer Effect Level (CEL)—The lowest dose of a chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-control study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without the outcome.

Case Report—A report that describes a single individual with a particular disease or exposure. These reports may suggest some potential topics for scientific research, but are not actual research studies.

Case Series—Reports that describe the experience of a small number of individuals with the same disease or exposure. These reports may suggest potential topics for scientific research, but are not actual research studies.

Ceiling Value—A concentration that must not be exceeded.

Chronic Exposure—Exposure to a chemical for ≥365 days, as specified in the Toxicological Profiles.

Clastogen—A substance that causes breaks in chromosomes resulting in addition, deletion, or rearrangement of parts of the chromosome.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome, and who are disease-free at start of follow-up. Often, at least one exposed group is compared to one unexposed group, while in other cohorts, exposure is a continuous variable and analyses are directed towards analyzing an exposure-response coefficient.

Cross-sectional Study—A type of epidemiological study of a group or groups of people that examines the relationship between exposure and outcome to a chemical or to chemicals at a specific point in time.

Data Needs—Substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment.

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the response or amount of the response.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the effect occurs. Effects include malformations and variations, altered growth, and *in utero* death.

Epidemiology—The investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Excretion—The process by which metabolic waste products are removed from the body.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic, or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one-half of a quantity of a chemical from the body or environmental media.

Health Advisory—An estimate of acceptable drinking water levels for a chemical substance derived by EPA and based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Immediately Dangerous to Life or Health (IDLH)—A condition that poses a threat of life or health, or conditions that pose an immediate threat of severe exposure to contaminants that are likely to have adverse cumulative or delayed effects on health.

Immunotoxicity—Adverse effect on the functioning of the immune system that may result from exposure to chemical substances.

Incidence—The ratio of new cases of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure—Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

***In Vitro*—**Isolated from the living organism and artificially maintained, as in a test tube.

***In Vivo*—**Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO})—The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50})—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{Lo})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50})—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50})—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

Metabolism—Process in which chemical substances are biotransformed in the body that could result in less toxic and/or readily excreted compounds or produce a biologically active intermediate.

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a Minimal Risk Level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity—The state of being diseased; the morbidity rate is the incidence or prevalence of a disease in a specific population.

Mortality—Death; the mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations, which are changes in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a hazardous substance.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Although effects may be produced at this dose, they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An odds ratio that is greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) regulatory limit on the amount or concentration of a substance not to be exceeded in workplace air averaged over any 8-hour work shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests (insects or other organisms harmful to cultivated plants or animals).

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments, which, in general, do not represent real, identifiable anatomic regions of the body, whereas the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic endpoints. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—A type of physiologically based dose-response model that is comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information, including tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as blood:air partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which a group is followed over time and the pertinent observations are made on events occurring after the start of the study.

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation RfC is expressed in units of mg/m^3 or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily oral exposure of the human population to a potential hazard that is likely to be without risk of deleterious noncancer health effects during a lifetime. The oral RfD is expressed in units of mg/kg/day.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). RQs are (1) ≥1 pound or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a hazardous substance. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a hazardous substance.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, existing health condition, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio/Relative Risk—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio that is greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed group.

Short-Term Exposure Limit (STEL)—A STEL is a 15-minute TWA exposure that should not be exceeded at any time during a workday.

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which it is believed that nearly all workers may be repeatedly exposed, day after day, for a working lifetime without adverse effect. The TLV may be expressed as a Time-Weighted Average (TLV-TWA), as a Short-Term Exposure Limit (TLV-STEL), or as a ceiling limit (TLV-C).

Time-Weighted Average (TWA)—An average exposure within a given time period.

Toxicokinetic—The absorption, distribution, metabolism, and elimination of toxic compounds in the living organism.

Toxics Release Inventory (TRI)—The TRI is an EPA program that tracks toxic chemical releases and pollution prevention activities reported by industrial and federal facilities.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL), Reference Dose (RfD), or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis (3 being the approximate logarithmic average of 10 and 1).

Xenobiotic—Any substance that is foreign to the biological system.

APPENDIX F. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

AAPCC	American Association of Poison Control Centers
ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ACMT	American College of Medical Toxicology
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AEGL	Acute Exposure Guideline Level
AIC	Akaike's information criterion
AIHA	American Industrial Hygiene Association
ALT	alanine aminotransferase
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BCF	bioconcentration factor
BMD/C	benchmark dose or benchmark concentration
BMD_X	dose that produces a X% change in response rate of an adverse effect
$BMDL_X$	95% lower confidence limit on the BMD_X
BMDS	Benchmark Dose Software
BMR	benchmark response
BUN	blood urea nitrogen
C	centigrade
CAA	Clean Air Act
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
cm	centimeter
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DWEL	drinking water exposure level
EAFUS	Everything Added to Food in the United States
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
ERPG	emergency response planning guidelines
F	Fahrenheit
F1	first-filial generation
FDA	Food and Drug Administration
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FR	Federal Register

FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GGT	γ-glutamyl transferase
GRAS	generally recognized as safe
HEC	human equivalent concentration
HED	human equivalent dose
HHS	Department of Health and Human Services
HPLC	high-performance liquid chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	kilokilogram; 1 kilokilogram is equivalent to 1,000 kilograms and 1 metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Level of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
MRL	Minimal Risk Level
MS	mass spectrometry
MSHA	Mine Safety and Health Administration
Mt	metric ton
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NCEH	National Center for Environmental Health
ND	not detected
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences

NIOSH	National Institute for Occupational Safety and Health
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NTP	National Toxicology Program
OR	odds ratio
OSHA	Occupational Safety and Health Administration
PAC	Protective Action Criteria
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PEHSU	Pediatric Environmental Health Specialty Unit
PEL	permissible exposure limit
PEL-C	permissible exposure limit-ceiling value
pg	picogram
PND	postnatal day
POD	point of departure
ppb	parts per billion
ppbv	parts per billion by volume
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure level/limit
REL-C	recommended exposure level-ceiling value
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SD	standard deviation
SE	standard error
SGOT	serum glutamic oxaloacetic transaminase (same as aspartate aminotransferase or AST)
SGPT	serum glutamic pyruvic transaminase (same as alanine aminotransferase or ALT)
SIC	standard industrial classification
SLOAEL	serious lowest-observed-adverse-effect level
SMR	standardized mortality ratio
sRBC	sheep red blood cell
STEL	short term exposure limit
TLV	threshold limit value
TLV-C	threshold limit value-ceiling value
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey

USNRC	U.S. Nuclear Regulatory Commission
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result