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.

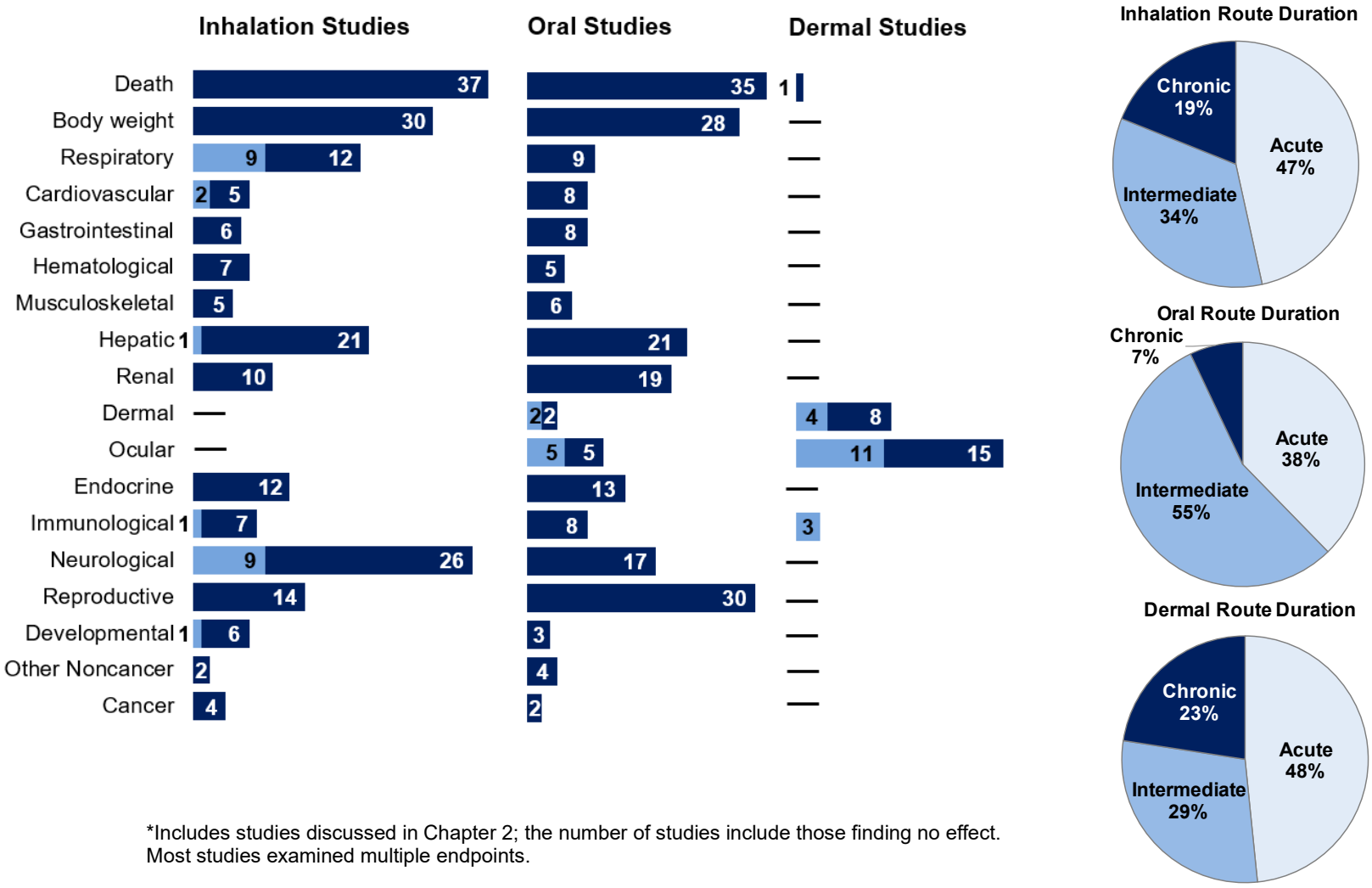
6.1 INFORMATION ON HEALTH EFFECTS

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 Methyl *tert*-Butyl Ether (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 an 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-duration oral exposure, available studies evaluating neurological endpoints were inadequate in design and/or reporting and male reproductive findings in adult animals were inconsistent between studies and exposure durations following oral exposure. Additional acute-duration 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 an 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 intermediate-duration inhalation MRL. The oral database is considered adequate to derive an intermediate-duration oral MRL; however, studies evaluating the critical effect (altered male reproductive development) are limited following oral exposure. The critical study (Zhu et al. 2022) did not identify a NOAEL, and the magnitude of serum testosterone decrease plateaued across all exposure doses. Due to this, there is some uncertainty in the shape of the model in the low-dose region of the curve. Therefore, additional studies evaluating male reproductive development in rats and mice following oral exposure to lower doses may reduce uncertainty in the intermediate-duration oral MRL.

Chronic-Duration MRLs. The inhalation database is adequate to derive a 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 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 oral 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 following adult exposure 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. Additional studies are needed to assess whether exposure to MTBE would result in developmental effects at dose levels not associated with maternal toxicity. Oral exposure studies are limited to a study involving paternal exposure and a limited number of studies evaluating male reproductive development following early postnatal exposure. Additional oral studies in multiple species may better define potential effects on the developing organism, especially the developing male reproductive system. 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 LDH (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 (see Table 4-2). 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). The most recent production volume of MTBE in the United States was 1,599 thousands of barrels occurring in December 2020, with the last reported export in late 2019 (EIA 2022). Therefore, it is unclear if MTBE is still being produced in the United States for export to other nations. TRI estimated that 230,947 pounds of MTBE were released from 127 facilities processing MTBE in 2021 (TRI21 2022). 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 2022).