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 mid-to-late 1980s, with peak usage in the late 1990s. 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.

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.

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. There were 88 laboratory animal toxicity studies with health effects data identified: 42 inhalation, 40 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.

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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)

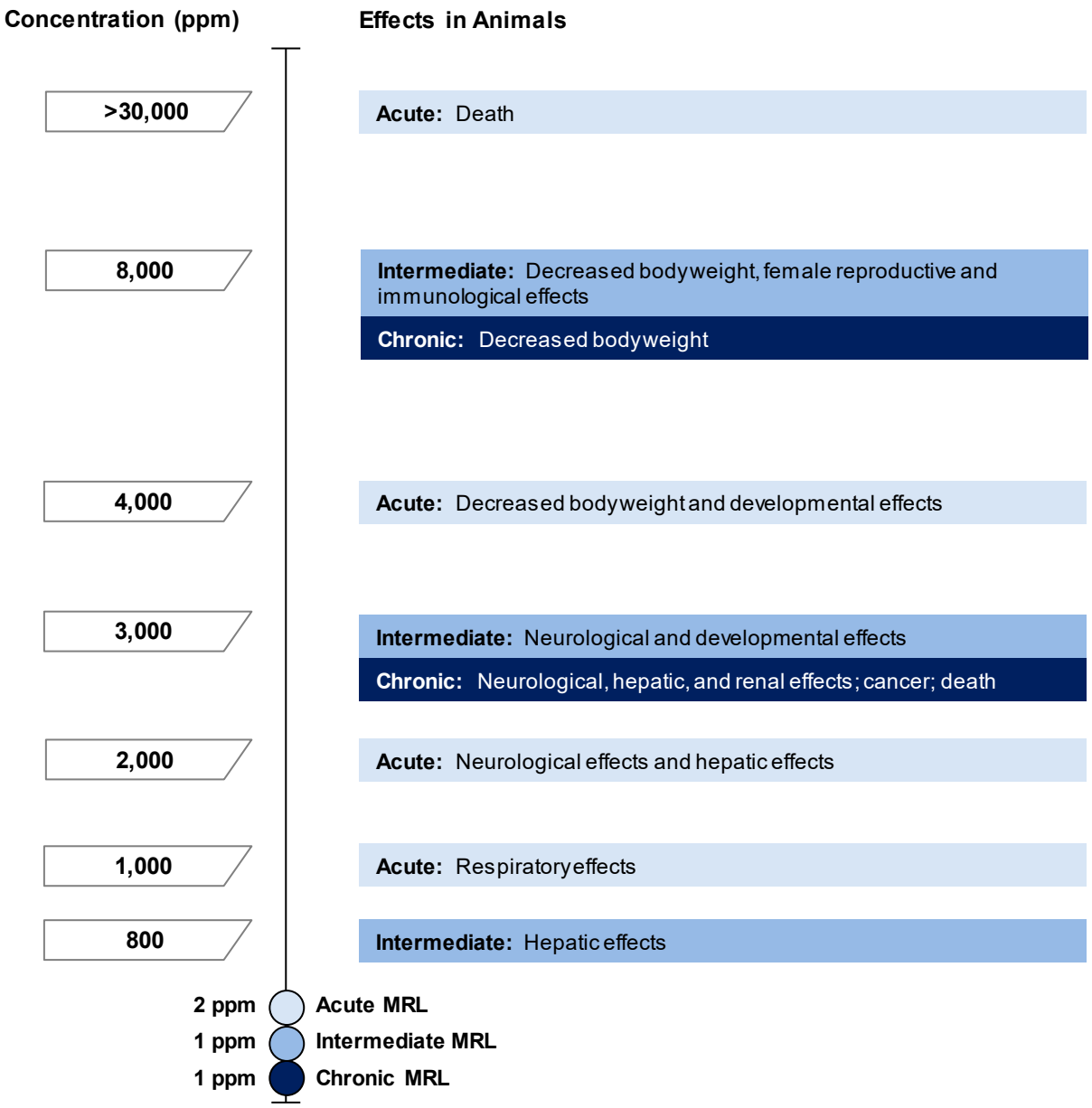
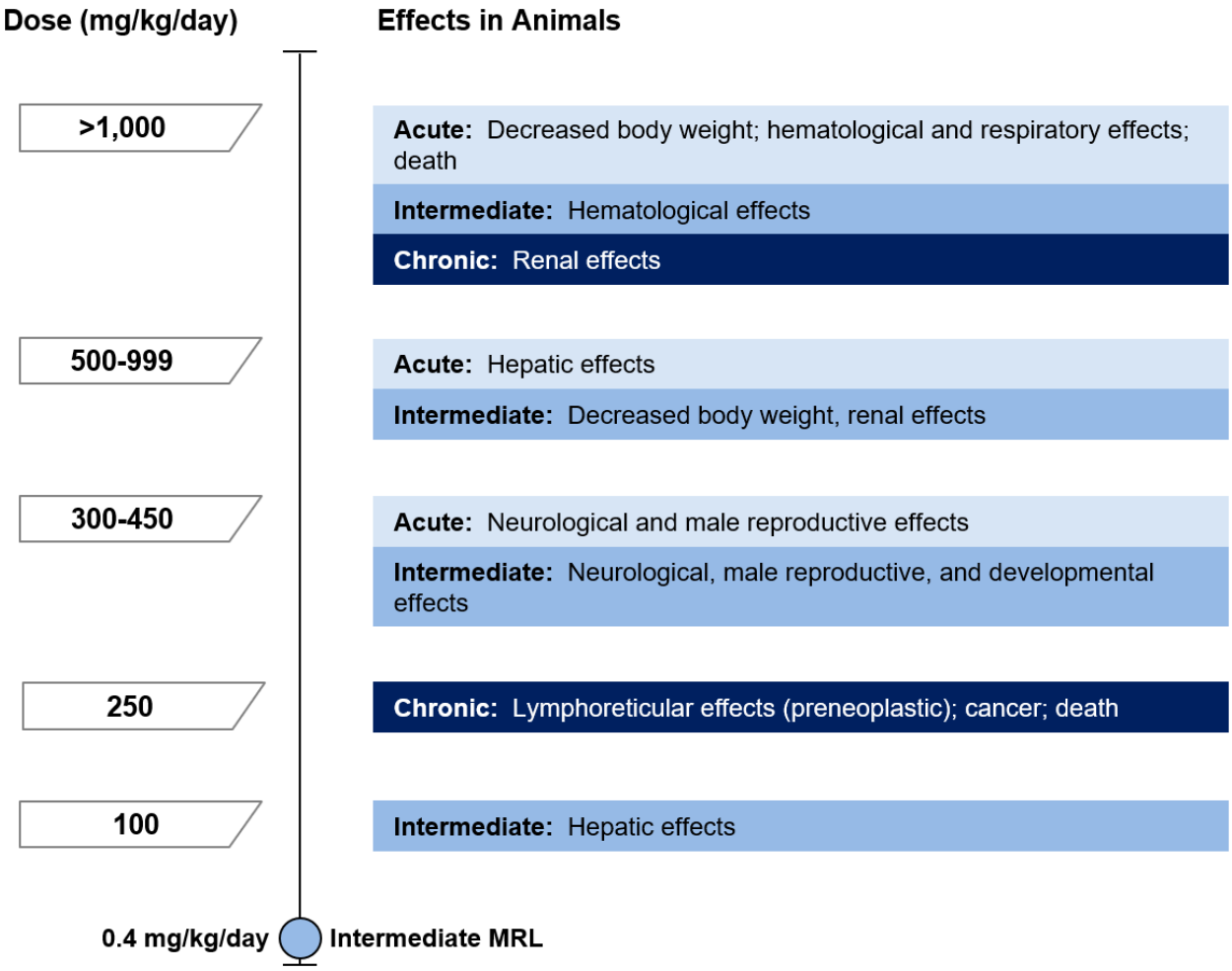


Figure 1-2. Health Effects Found in Animals Following Oral Exposure to Methyl *tert*-Butyl Ether (MTBE)



Respiratory Effects. Some occupational and population-based studies conducted in the early 1990s observed respiratory symptoms with introduction of MTBE into fuel during the oxyfuel program (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-duration 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-Mathews 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 conducted in the early 1990s observed effects consistent with transient CNS depression with introduction of MTBE into fuel during the oxyfuel program, 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-duration 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 to MTBE (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 following gestational exposure were available. One postnatal exposure study reported male

reproductive effects (decreased serum testosterone, decreased number and size of Leydig cells) in rats following prepubertal exposure to MTBE (Zhu et al. 2022).

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-duration 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-duration gavage exposure to MTBE (Belpoggi et al. 1995, 1997). No exposure-related tumors were observed following chronic-duration drinking water exposure in rats (Dodd et al. 2013).

The International Agency for Research on Cancer (IARC) has determined that MTBE is 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 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 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 and the developing organism 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.

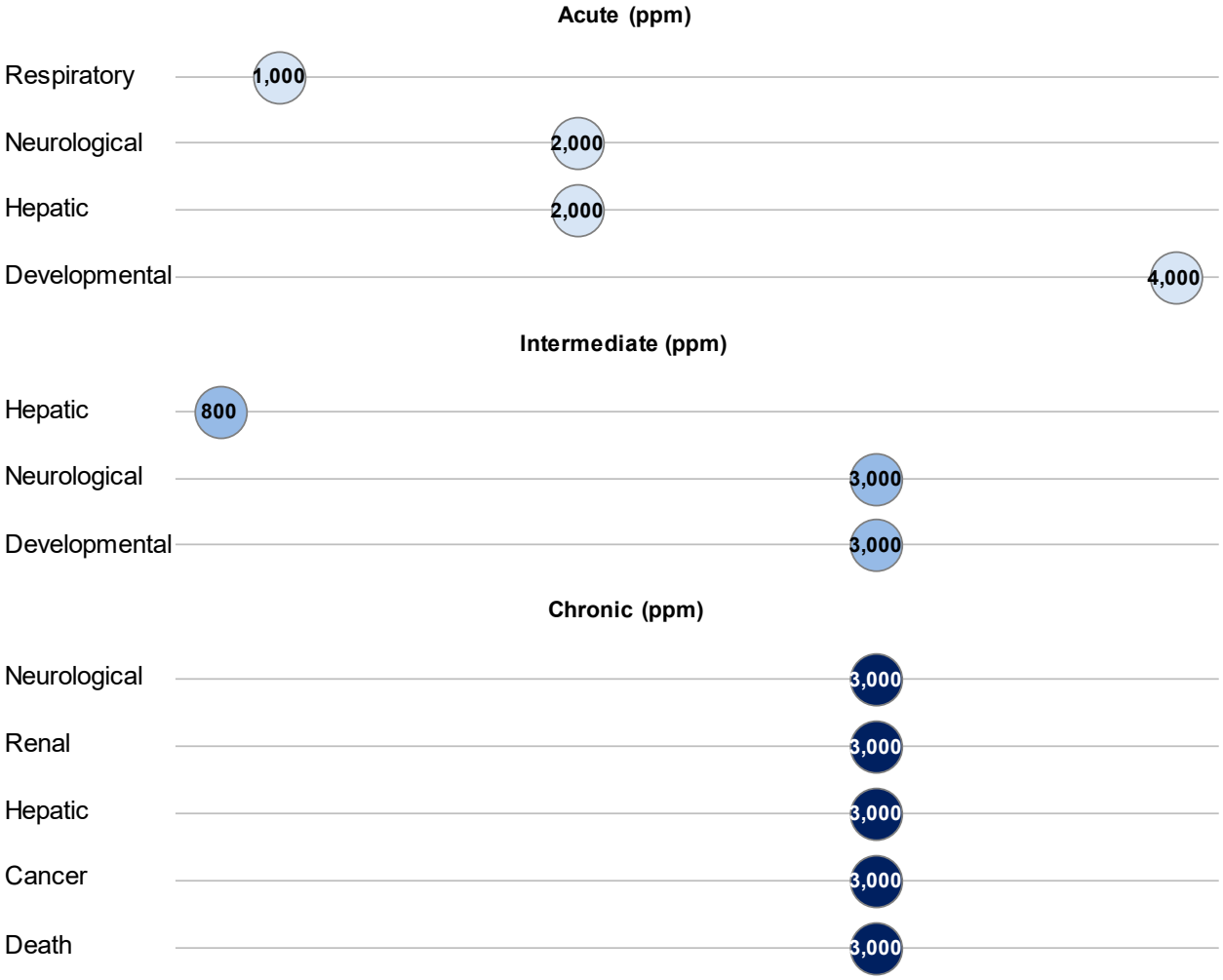


Figure 1-4. Summary of Sensitive Targets of Methyl *tert*-Butyl Ether (MTBE) – Oral

The hepatic, male reproductive, neurological, and lymphoreticular systems and the developing organism 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.

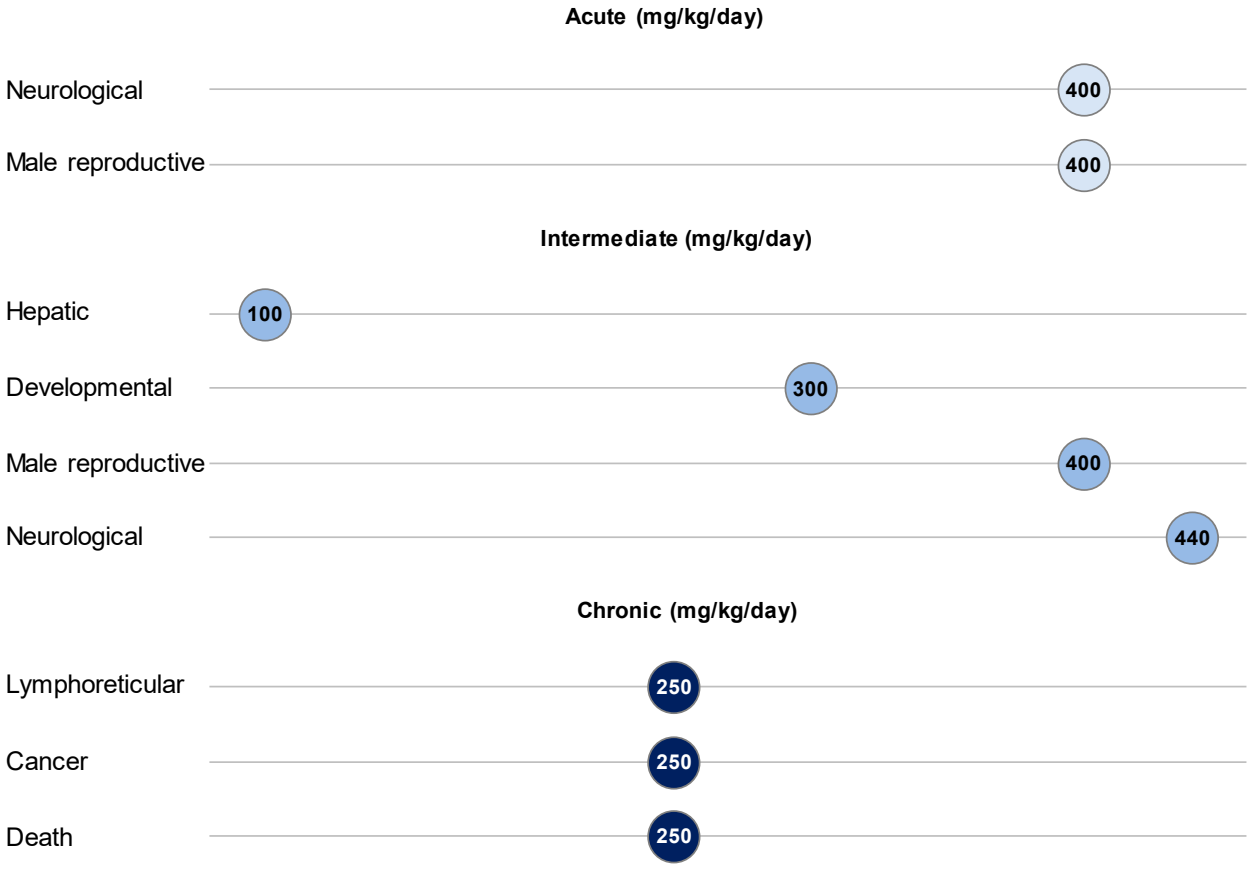


Table 1-1. Minimal Risk Levels (MRLs) for Methyl *tert*-Butyl Ether (MTBE)[a]

Exposure route	Exposure duration	MRL	Critical effect	POD type	POD value	Uncertainty/ modifying factor	Reference
Inhalation	Acute	**2 ppm** (7 mg/m^3)	Neurobehavior (altered gait)	$BMCL_{HEC}$	70.1	UF: 30	Daughtrey et al. 1997; Gill 1989[b]
	Intermediate	**1 ppm** (4 mg/m^3)	CNS depression and hepatic effects	$NOAEL_{HEC}$	43.9	UF: 30	Bevan et al. 1997b; Bird et al. 1997
	Chronic	**1 ppm** (4 mg/m^3)	Renal effects in females	$NOAEL_{HEC}$	43.9	UF: 30	Bird et al. 1997; Chun et al. 1992[c]
Oral	Acute	None	–	–	–	–	–
	Intermediate	**0.4 mg/kg/day**	Developmental (decreased serum testosterone following early postnatal exposure)	$BMDL_{1SD}$	36	UF: 100	Zhu et al. 2022
	Chronic	None	–	–	–	–	–

[a]See Appendix A for additional information.
[b]Gill (1989) is the unpublished report associated with Daughtrey et al. (1997). Raw data for BMD 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; BMC = benchmark concentration; BMCL = 95% lower confidence limit on the BMC; BMD = benchmark dose; BMDL = 95% lower confidence limit on the BMD; CNS = central nervous system; HEC = human equivalent concentration; NOAEL = no-observed-adverse-effect level; POD = point of departure; SD = standard deviation; UF = uncertainty factor