CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

Benzene is ubiquitous in the environment. It is a flammable organic compound and is formed from human activities and by natural processes. Benzene is slightly soluble in water and evaporates rapidly into air, with outdoor air concentrations ranging from 0.082 to 4.66 ppbv. The odor recognition threshold in air is 97 ppm. Therefore, populations can be exposed excessively to benzene without knowledge of the exposure or exposure-associated health hazards.

Benzene is widely distributed in the environment. The exposure scenario of most concern to the general public is low-level inhalation over long periods. This is because the general population is exposed to benzene mainly through inhalation of contaminated air, particularly in areas of heavy traffic and around gas stations, through inhalation of tobacco smoke from both active and passive smoking, and in some cases, from poorly ventilated indoor air. Smoking has been identified as the single most important source of benzene exposure for the estimated 40 million U.S. smokers. Smoking accounts for approximately half of the total benzene exposure of the general population. Individuals employed in industries that make or use benzene, or products containing benzene, are probably exposed to the highest concentrations of benzene. In addition, benzene is a common combustion product of wood and organic material, providing high inhalation exposure potential for firefighters. Of the general population, those residing around certain chemical manufacturing sites or living near waste sites containing benzene or near leaking fuel tanks may be exposed to concentrations of benzene that are higher than background air concentrations. In private residences, benzene levels in the air have been shown to be higher in houses with attached garages, where the inhabitants smoke inside the house, or where gas stoves or ovens are used.

Benzene may be present in food, beverages, and water; however, benzene is at low levels in these items and, therefore, not considered a major exposure. Benzene contamination of well water may occur from leakage of underground gasoline storage tanks and seepage from landfills and hazardous waste sites. People with contaminated tap water can be exposed from drinking the water or eating foods prepared with it. In addition, exposure can also occur via inhalation during showering, bathing, or cooking with contaminated tap water. Showering and bathing with benzene-contaminated water can also contribute to dermal exposure.

1.2 SUMMARY OF HEALTH EFFECTS

Exposure to benzene is associated with numerous adverse effects in several organ systems. This is due to highly reactive metabolites of benzene that are widely distributed throughout the body. However, the primary and most sensitive targets of benzene are the hematopoietic and immune systems. Hematotoxicity, immunotoxicity, and hematopoietic cancer (acute myelogenous leukemia or AML) are well-established health effects of benzene. The hematological effects of benzene were reported in workers in the early 1900s, with leukemia first reported in 1928 (Smith 2010). Since those initial reports, numerous studies have confirmed associations between occupational exposures to benzene and hematotoxicity, immunotoxicity, and leukemia, with support from several studies in laboratory animals. As illustrated in Figures 1-1 and 1-2, the most sensitive effects of benzene are on the hematological and immunological systems. A systematic review of these endpoints (Appendix C) resulted in the hazard identification conclusion that hematological effects are a known health effect for humans.

- ***Hematological:*** The primary effect of benzene on the hematological system is disruption of hematopoiesis (production of blood cells). The following hematological effects have been observed in humans and laboratory animals in association with exposure to benzene: (1) decreased numbers of peripheral blood cells (erythrocytes, thrombocytes, leukocytes); (2) decreased numbers of hematopoietic stem cells and progenitor cells in hematopoietic tissues (bone marrow, spleen); (3) decreased cellularity of hematologic tissues (bone marrow, spleen, thymus); and (4) histopathological changes to hematopoietic tissues (bone marrow, spleen, thymus).

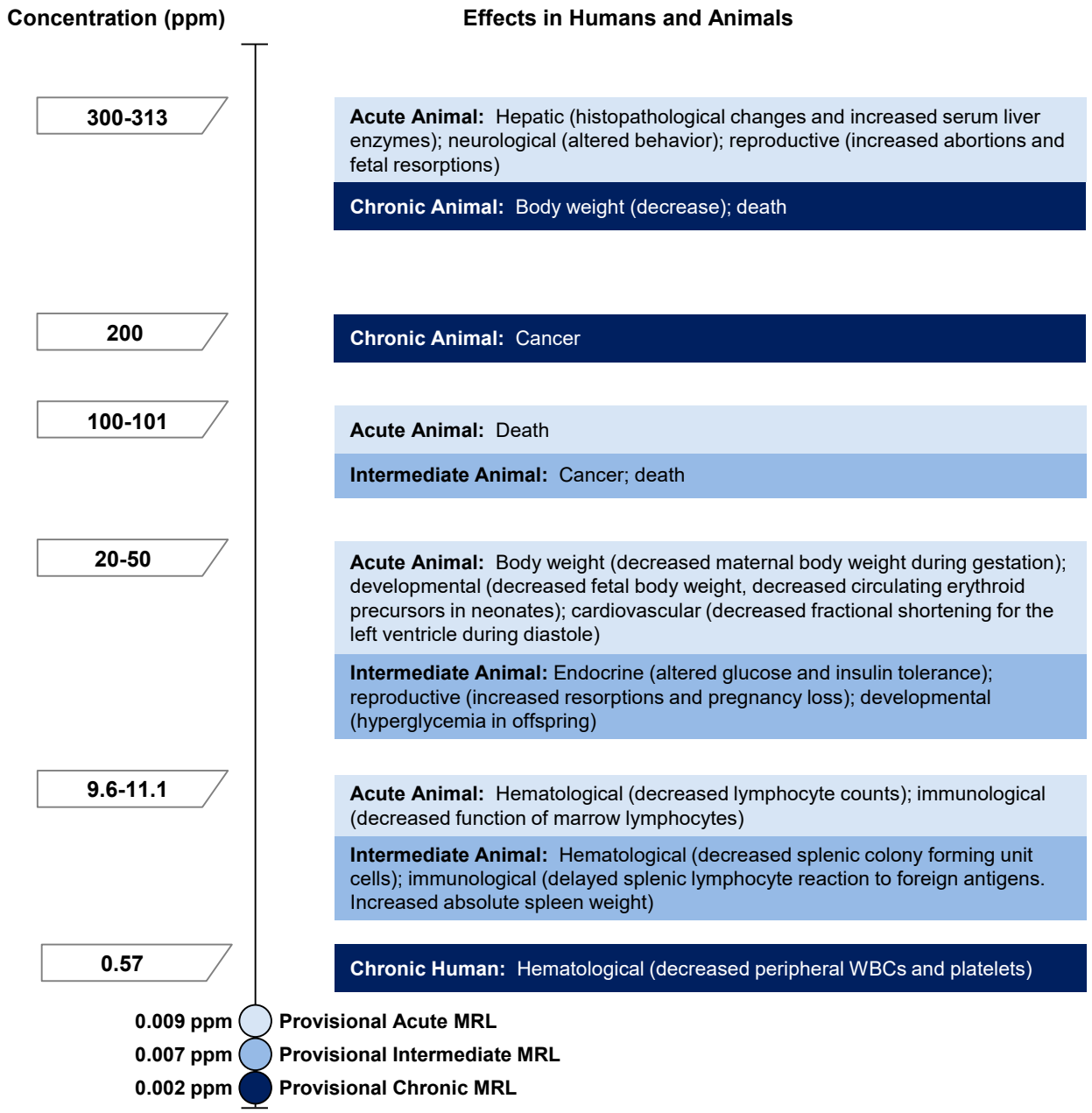
The systematic review identified immunological effects as a presumed health effect for humans.

- ***Immunological:*** Benzene may disrupt the immune system by decreasing the number of peripheral lymphocytes through the disruption of hemopoiesis, which contributes to immunosuppression. Studies conducted in laboratory animals have shown that exposure to benzene can alter immune responses to antigens, function of peripheral lymphocytes, and levels of circulating antibodies.

Studies evaluating developmental effects and cancer from benzene did not undergo formal systematic review; however, the following conclusions are drawn.

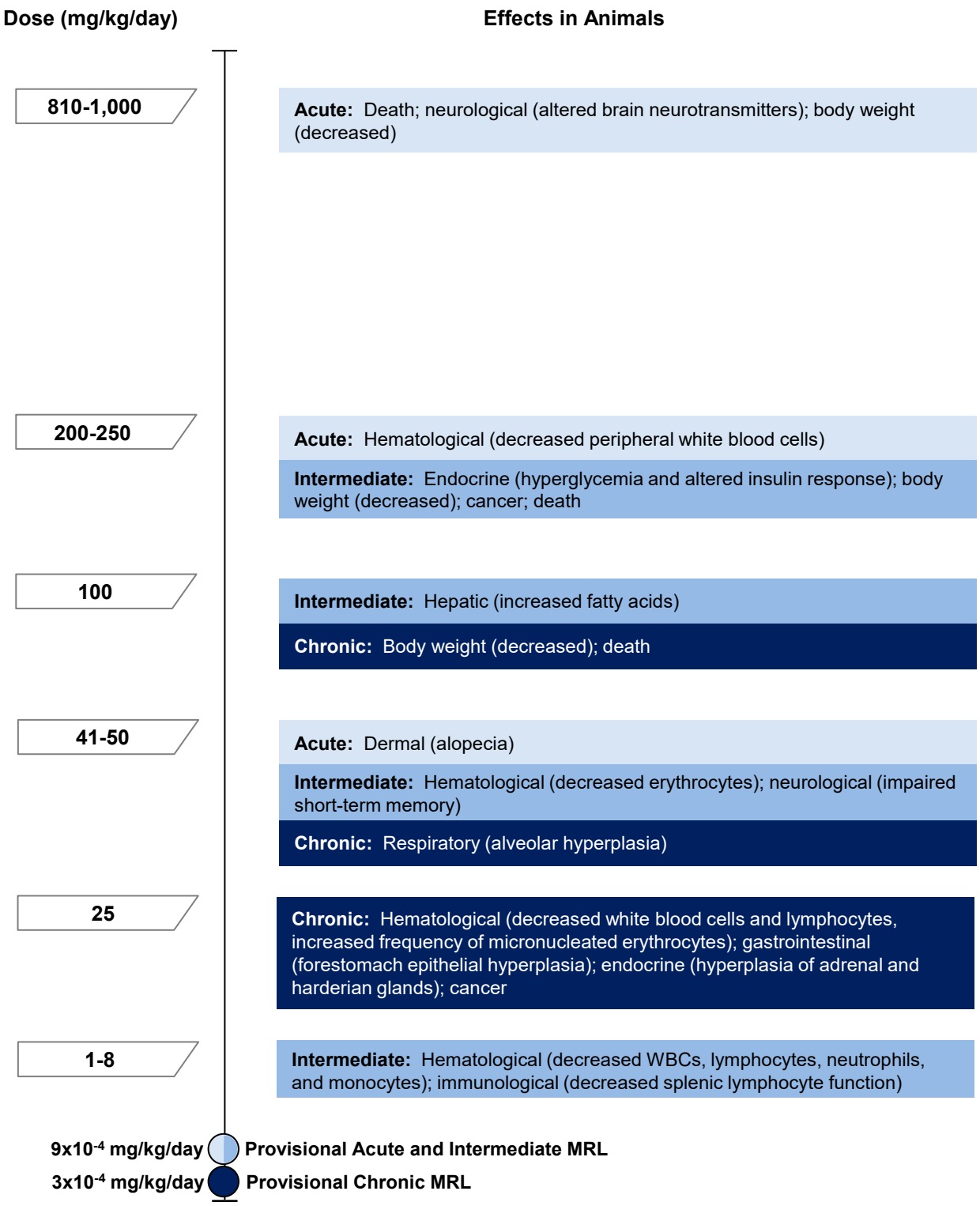
- ***Developmental:*** Results of developmental studies in laboratory animals have reported decreased fetal weight, increased skeletal variations, alterations in hematological parameters, neurodevelopmental effects, and altered glucose homeostasis. However, human data are inadequate to verify or refute findings in animals. Note that developmental effects were not considered for systematic review as the LOAEL values for developmental effects were higher than those for hematological effects.

Figure 1-1. Health Effects Found in Animals Following Inhalation Exposure to Benzene*



*Health effect displayed only at the most sensitive dose.

Figure 1-2. Health Effects Found in Animals Following Oral Exposure to Benzene*



*Health effect displayed only at the most sensitive dose.

- ***Cancer:*** Studies conducted in workers have shown that exposure to benzene is associated with increased risk of myelodysplastic syndromes and AML. Studies in laboratory animals show that exposure to benzene induced tumors at multiple sites in rats and mice, with a tendency towards induction of lymphomas in mice.

The Department of Health and Human Services (HHS) has determined that benzene is a known human carcinogen (NTP 2021). The International Agency Research on Cancer (IARC 2018) has classified benzene as a Group 1 (carcinogenic to humans) agent, and the U.S. Environmental Protection Agency (EPA) has classified benzene in Group A (known human carcinogen) (IRIS 2003).

1.3 MINIMAL RISK LEVELS (MRLs)

The inhalation database was considered adequate for derivation of an acute-, intermediate- and chronic-duration inhalation MRLs for benzene, with hematological and immunological effects as the most sensitive and well-studied effects. The toxicity of benzene following oral exposure has been much less studied compared to inhalation exposure. Available oral data identify hematological and immunological effects as the most sensitive. Adequate data are available to derive an intermediate-duration oral MRL. No adequate oral exposure studies were identified to derive acute- or chronic-duration oral MRLs. However, the intermediate-duration oral MRL was adopted for the acute-duration oral MRL. For the chronic-duration oral MRL, the intermediate-duration oral MRL was adopted with application of a modifying factor. For both the inhalation and oral databases, hematological effects are the most sensitive, as shown in Figures 1-3 and 1-4, respectively. The provisional MRLs are summarized in Table 1-1.

Figure 1-3. Summary of Sensitive Targets of Benzene – Inhalation

Available data indicate that the hematological and immunological systems are the most sensitive targets of benzene inhalation exposure.

Numbers in triangles and circles are the lowest LOAELs (ppm) among health effects in humans and animals, respectively.

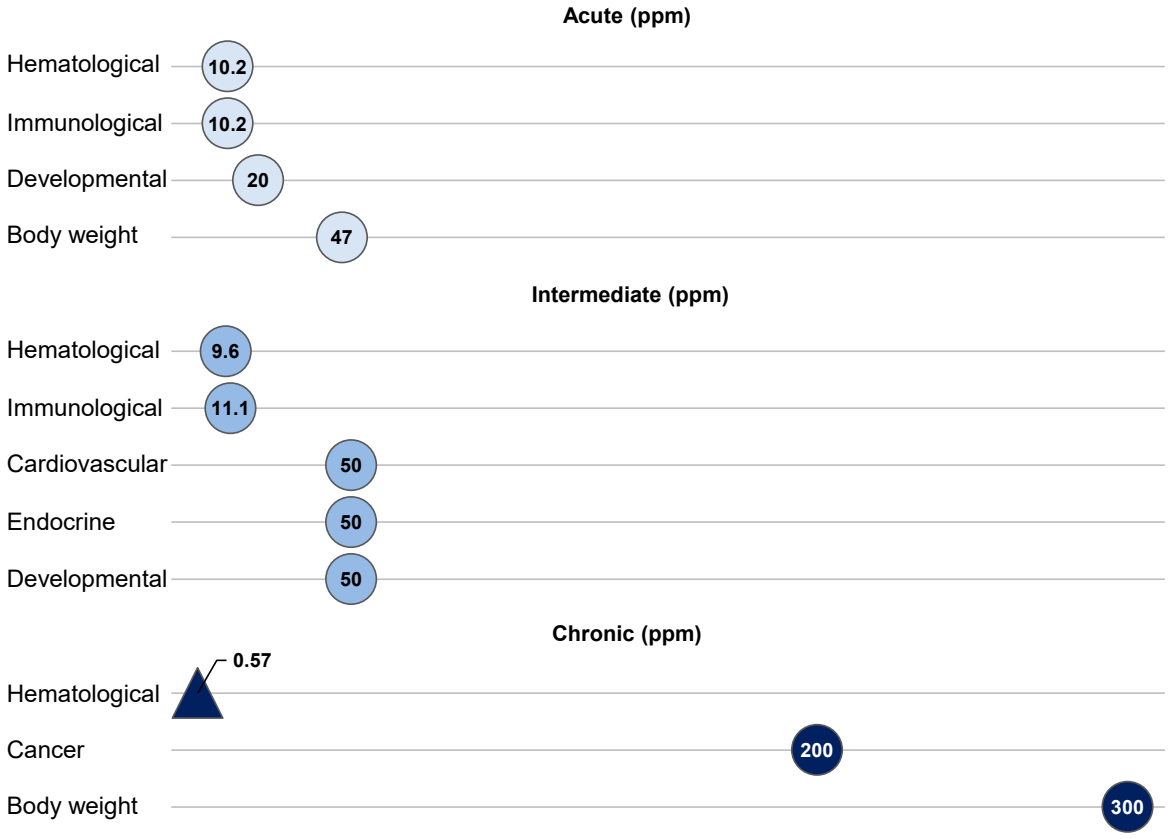


Figure 1-4. Summary of Sensitive Targets of Benzene – Oral

Available data indicate that the hematological system is the most sensitive target of benzene.
Numbers in circles are the lowest LOAELs (mg/kg/day) for all health effects in animals.
No reliable dose response data were available for humans.

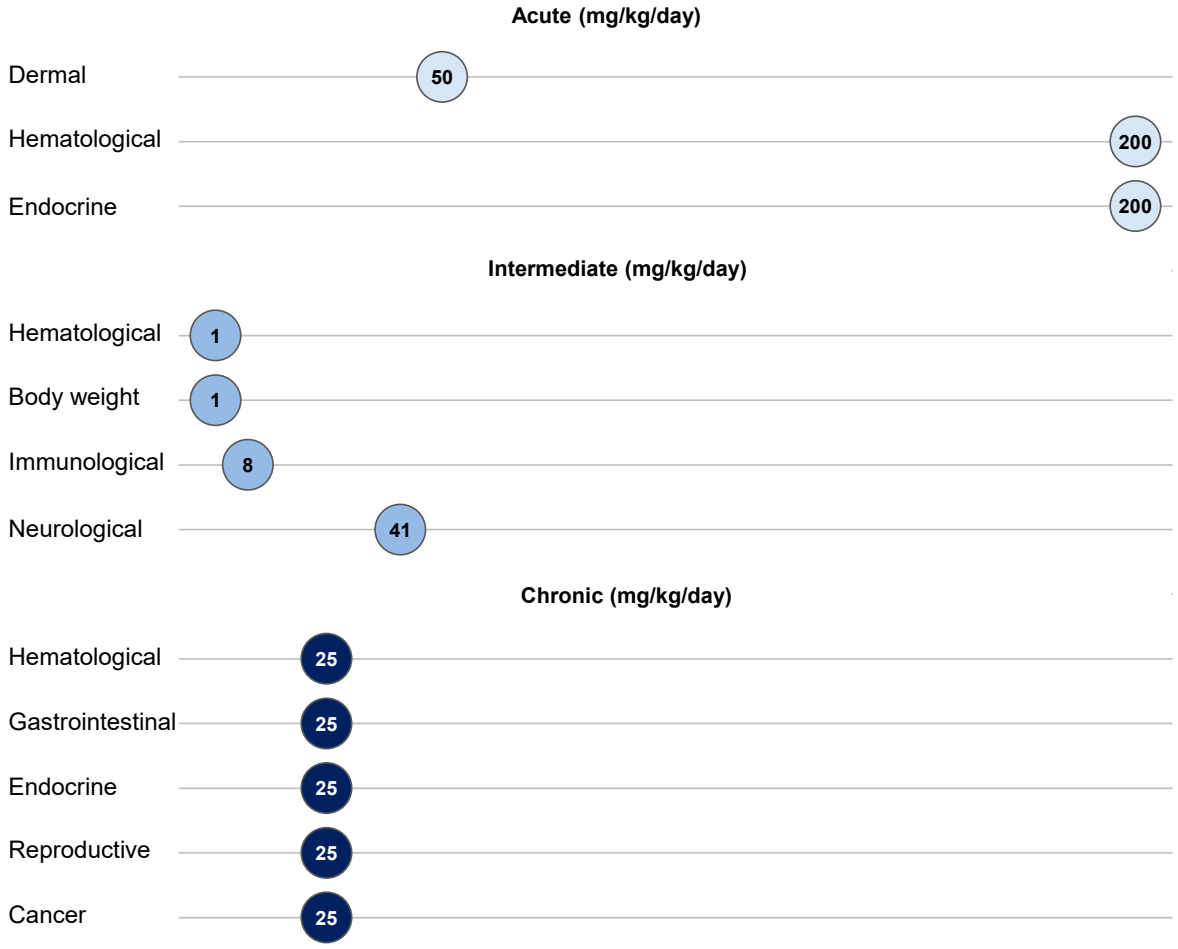


Table 1-1. Minimal Risk Levels (MRLs) for Benzene[a]

Exposure route	Exposure duration	Provisional MRL	Critical effect	POD type	POD value	Uncertainty/ modifying factor	Reference
Inhalation	Acute	**0.009 ppm** (0.03 mg/m^3)	Decreased number of peripheral lymphocytes and impaired function of marrow lymphocytes	$LOAEL_{HEC}$	2.55 ppm	UF: 300	Rozen et al. 1984
	Intermediate	**0.007 ppm** (0.02 mg/m^3)	Delayed splenic lymphocyte reaction to foreign antigens	$LOAEL_{HEC}$	1.98 ppm	UF: 300	Rosenthal and Snyder 1987
	Chronic	**0.002 ppm** ($6x10^{-3}$ mg/m^3)	Decreased number of peripheral lymphocytes	$LOAEL_{ADJ}$	0.16 ppm	UF: 100	Lan et al. 2004a
Oral	Acute	**$9x10^{-4}$ mg/kg/day**	Decreased peripheral WBC, lymphocyte, monocyte, and neutrophil counts	$NOAEL_{ADJ}$	0.09 mg/kg/day	UF: 100	Li et al. 2018
	Intermediate	**$9x10^{-4}$ mg/kg/day**	Decreased peripheral WBC, lymphocyte, monocyte, and neutrophil counts	$NOAEL_{ADJ}$	0.09 mg/kg/day	UF: 100	Li et al. 2018
	Chronic	**$3x10^{-4}$ mg/kg/day**	Decreased peripheral WBC, lymphocyte, monocyte, and neutrophil counts	$LOAEL_{ADJ}$	$9.1x10^{-4}$ mg/kg/day[b]	MF: 3[c]	Lan et al. 2004a

[a]See Appendix A for additional information.
[b]Route-to-route extrapolation from the provisional chronic-duration inhalation MRL to equivalent oral exposure.
[c]An uncertainty factor for human variability was not applied in deriving the provisional chronic-duration oral MRL because an uncertainty factor of 10 for human variability was included in deriving the provisional chronic-duration inhalation MRL, which is the basis for the provisional chronic-duration oral MRL.

ADJ = adjusted for intermittent exposure; HEC = human equivalent concentration; LOAEL = lowest observed adverse effect level; MF = modifying factor; NOAEL = no-observed-adverse-effect level; POD = point of departure; UF = uncertainty factor; WBC = white blood cell