CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

ATSDR's *Toxicological Profile for Isophorone* was released in 1989. In order to update the literature in this profile, ATSDR conducted a literature search focused on health effects information as described in Appendix B. Chapters 2 and 3 were revised to reflect the most current health effects data; Chapter 7 was updated to reflect the most current regulations and guidelines for isophorone. In some cases, other sections of the profile were updated as needed or for consistency with the updated health effects data. However, the focus of the update to this profile is on health effects information.

Isophorone (CAS Number 78-59-1) is a clear liquid with a peppermint-like odor. It is a solvent for a large number of natural and synthetic polymers, resins, waxes, fats, and oils. Specifically, it is used as a solvent for concentrated vinyl chloride/acetate-based coating systems for metal cans, other metal paints, nitrocellulose finishes, printing inks for plastics, some herbicide and pesticide formulations, adhesives with food contract, and adhesives for plastics, poly(viny1) chloride, and polystyrene materials (Papa and Sherman 1981). Isophorone is released to the air mainly in urban centers, as a result of evaporation of solvents containing this chemical. The most likely exposure of the general population is to contaminated air.

1.2 SUMMARY OF HEALTH EFFECTS

Little information is available on the effects of isophorone in humans. Acute exposure studies conducted in human subjects show that exposure to isophrone in air is irritating to the eyes and respiratory tract (Hazleton Labs 1965b; Silverman et al. 1946). No information regarding effects of oral exposure of humans to isophorone was identified.

In laboratory animals, several studies have evaluated the acute lethality and irritant effects of inhalation, oral, or dermal exposure to isophorone. By all routes, acute exposure produces irritation and tissue damage at the point of contact (e.g., portal of entry). However, available acute inhalation, oral, and dermal exposure studies did not evaluate comprehensive endpoints. Inhalation studies have evaluated effects of intermediate and chronic exposure to isophorone, although comprehensive toxicological endpoints were not examined and studies evaluated only single exposure concentrations. Therefore, it is not possible to determine the most sensitive effects of intermediate and chronic inhalation exposures. The

oral exposure database includes intermediate- and chronic-duration studies that evalauted comprehensive toxicological endpoints, including cancer.

Effects of inhaled and oral isophorone are depicted in Figures 1-1 and 1-2, respectively. Inhalation studies identify the respiratory tract, eyes, and skin as the most sensitive targets for exposure to isophorone in air. Other observed effects include neurological, hematological, developmental, and hepatic. Oral exposure studies identified several effects including those to the neurological, gastrointestinal, hepatic, and renal systems.

Irritation. Exposure to isophorone produces irritation and damage at the site of contact. Respiratory tract and ocular irritation has been observed in human subjects and laboratory animals exposed to isophorone in air. In animals, dermal and ocular irritation and damage occurred following direct contact exposure. Hyperkeratosis of the forestomach of male mice was observed following chronic gavage exposure to isophorone (NTP 1986).

Neurological Effects. Neurological effects have been observed in laboratory animals following inhalation and oral exposure. Effects observed in acute inhalation studies include central nervous system (CNS) depression, neurobehavioral changes, and coma (DeCeaurriz et al. 1981b, 1984; Hazelton Labs 1965a). The lowest exposure associated with neurological effects is a 4-hour exposure to 89 ppm in mice for neurobehavioral changes (DeCeaurriz et al. 1984). Neurological effects also have been observed in oral exposure studies in animals. Effects include CNS depression in male rats following exposure to a single dose of 1,450 mg/kg (Hazelton Labs 1964), stagger in mice exposed to 1,000 mg/kg/day for 16 days (NTP 1986), and lethargy in rats exposed to 1,000 mg/kg/day for 13 weeks (NTP 1986). However, neurological effects were not observed in rats or mice at oral doses up to 500 mg//kg/day in chornic exposure studies (NTP 1986).

Hepatic Effects. Chronic inhalation and oral exposure studies provided evidence of isophorone-induced hepatic toxicity. Microvacuolization of the liver was observed in mice and rabbits exposed to inhaled isophorone for 18 months at a concentration of 250 ppm (Dutertre-Catella 1976). In the NTP (1986) oral study, necrosis of the liver was observed in mice exposed to 250 mg/kg/day for 103 weeks; however, no hepatic damage was observed in rats at doses up to 500 mg/kg/day (NTP 1986).

Renal Effects. The NTP (1986) chronic study reported renal inflammation in mice exposed to 500 mg/kg/day. In this same study in male rats, renal effects consistent with alpha 2μ-globulin-induced

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

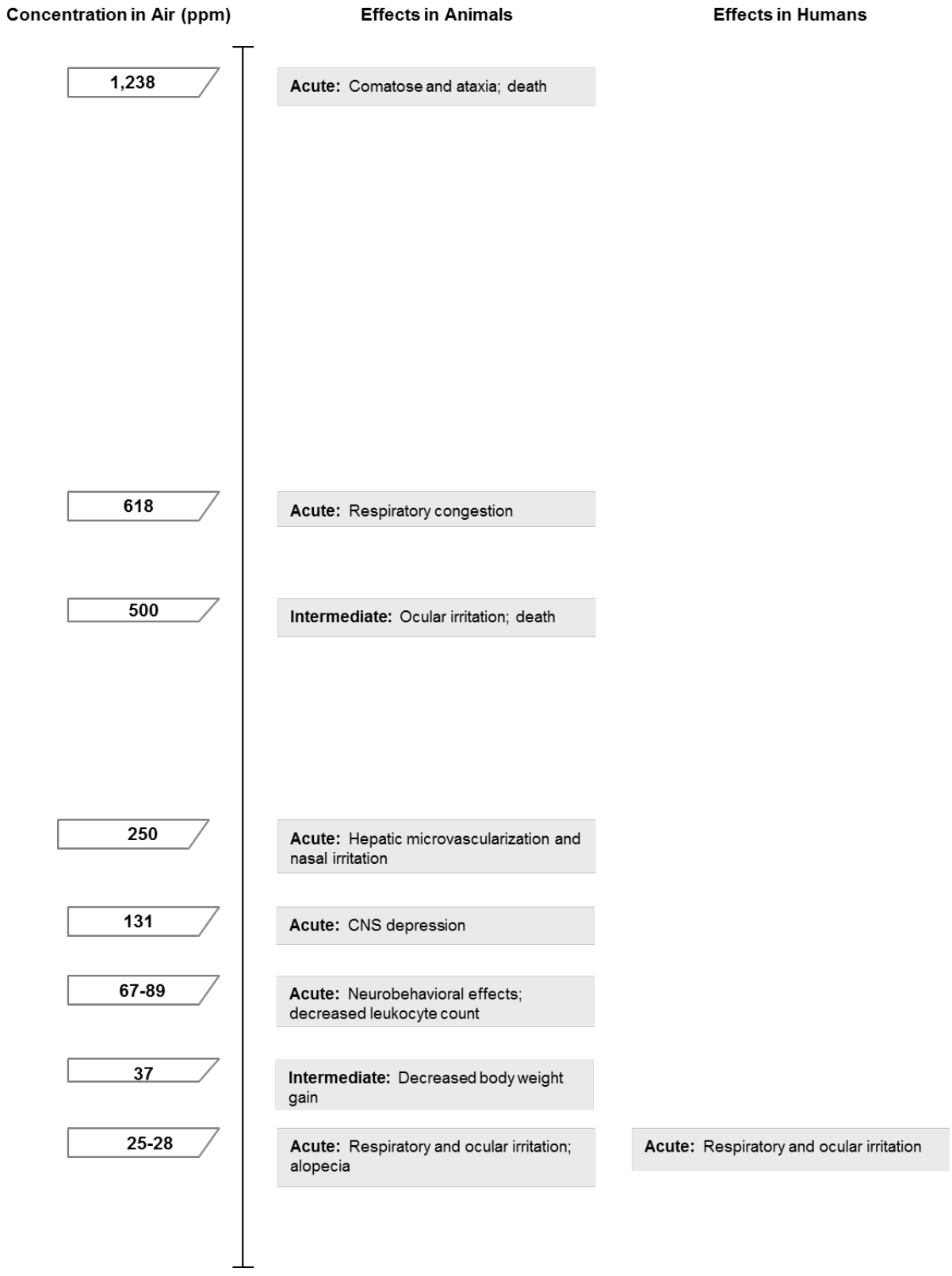
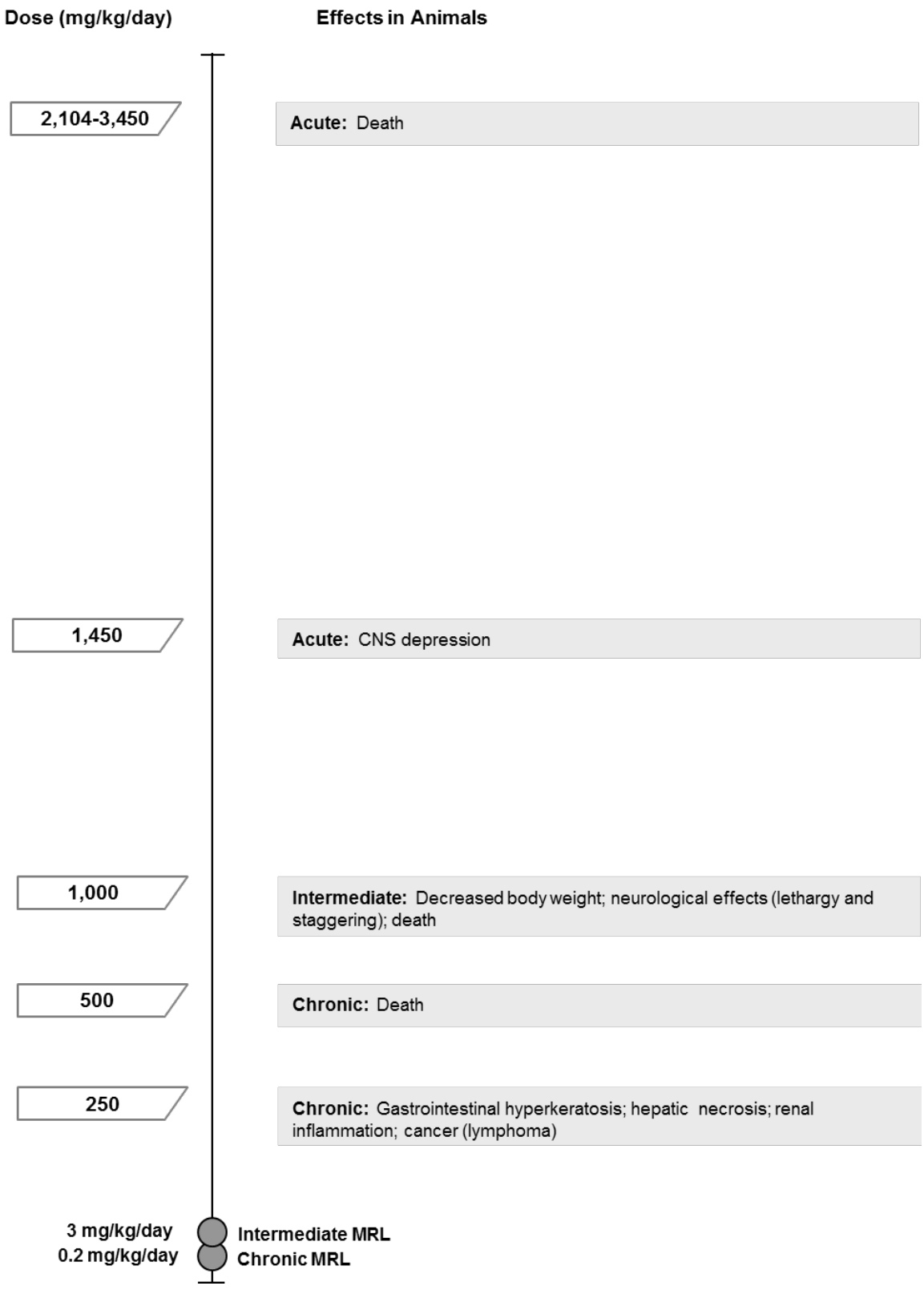


Figure 1-2. Health Effects Found in Animals Following Oral Exposure to Isophorone



damage to renal proximal tubules was observed at doses 250 and 500 mg/kg/day. This effect is unique to male rats and is not toxicologically relevant to human health (EPA 1991; Swenberg 1993).

Cancer Effects. Cancer has been observed in rats and mice exposed to oral isophorone for 103 weeks (NTP 1986). The lowest cancer effect level (CEL) of 250 mg/kg/day was observed for lymphoma in mice. At 500 mg/kg/day, liver and skin tumors were observed in mice. In rats, preputial gland tumors were observed in male at a dose of 500 mg/kg/day; although it has been proposed that these tumors may be attributed to alpha 2μ-globulin (WHO 1995). Kidney tumors also were observed in male rats exposed to 250 and 500 mg/kg/day; however, these tumors were due to renal damage induced by accumulation of alpha 2μ-globulin and, therefore, are not relevant to human health (EPA 1991; Swenberg 1993).

The U.S. Department of Health and Human Services (NTP 2016) and the International Agency for Research on Cancer (IARC 2017) have not categorized the carcinogenicity of isophorone. EPA categorized it as a possible human carcinogen (Group C) based on no data in humans and limited evidence of carcinogenicity in animals (IRIS 2003).

1.3 MINIMAL RISK LEVELS (MRLs)

The inhalation database was not considered adequate for deriving inhalation MRLs. As presented in Figure 1-3, available information on acute exposure in humans to isophorone in air identifies respiratory and ocular irritation as the most sensitive effects. The acute exposure duration in human subjects was very short (≤15 minutes) and, therefore, not suitable for the basis of the acute-duration inhalation MRL. Acute exposure studies in animals did not examine comprehensive toxicological endpoints. Intermediate- and chronic-duration inhalation studies in animals used only a single exposure level and did not examine comprehensive toxicological endpoints. Therefore, available studies do not provide sufficient information to derive inhalation MRLs.

The oral database was considered adequate for derivation of intermediate- and chronic-duration oral MRLs; these values are summarized in Table 1-1 and discussed in greater detail in Appendix A. The most sensitive effects of oral exposure to isophorone in laboratory animals are shown in Figure 1-4. The available acute oral exposure studies were designed to assess lethality and did not examine comprehensive toxicological endpoints. Thus, data are inadquate to derive an acute-duration oral MRL.

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

Body weight is the most sensitive target of isophorone inhalation exposure.
Numbers in triangles and circles are the lowest LOAELs (ppm) among health effects in humans and animals, respectively

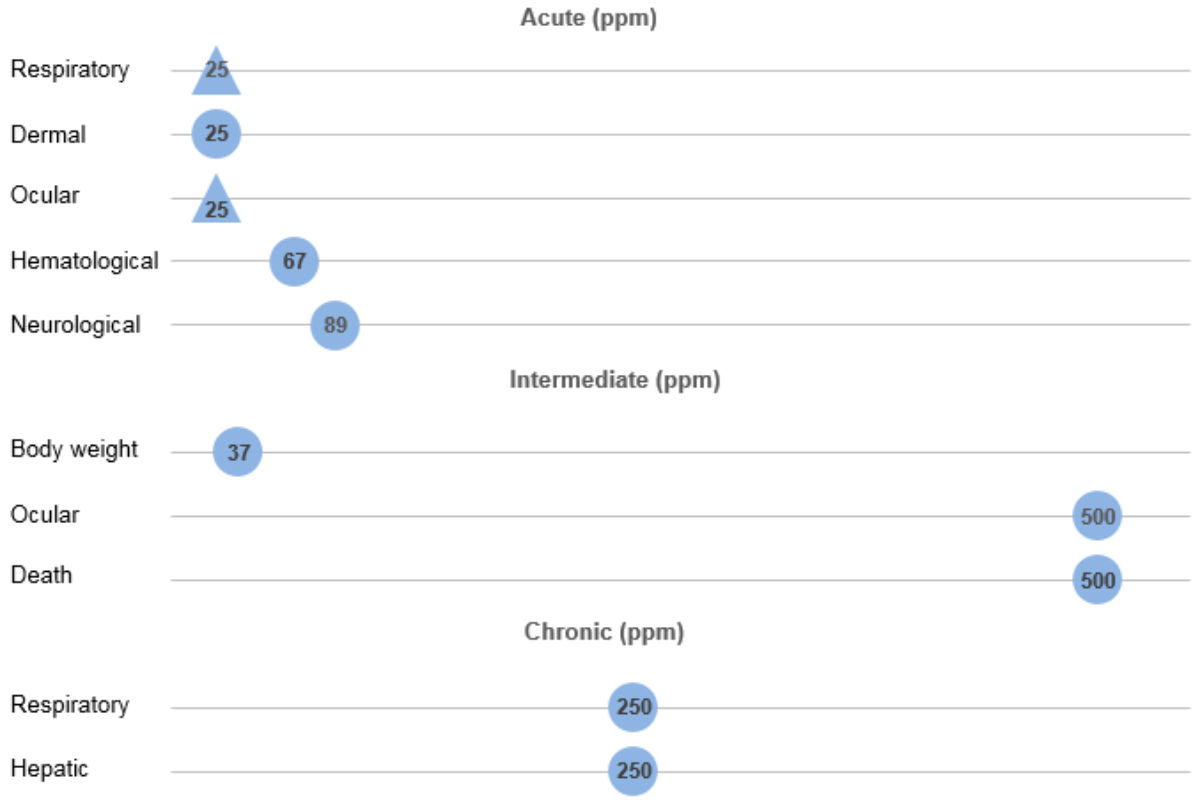


Figure 1-4. Summary of Sensitive Targets of Isophorone – Oral

Gastrointestinal, hepatic and renal are the most sensitive target of isophorone oral exposure.
Numbers in circles are the lowest LOAELs for all health effects in animals; no human data were identified.

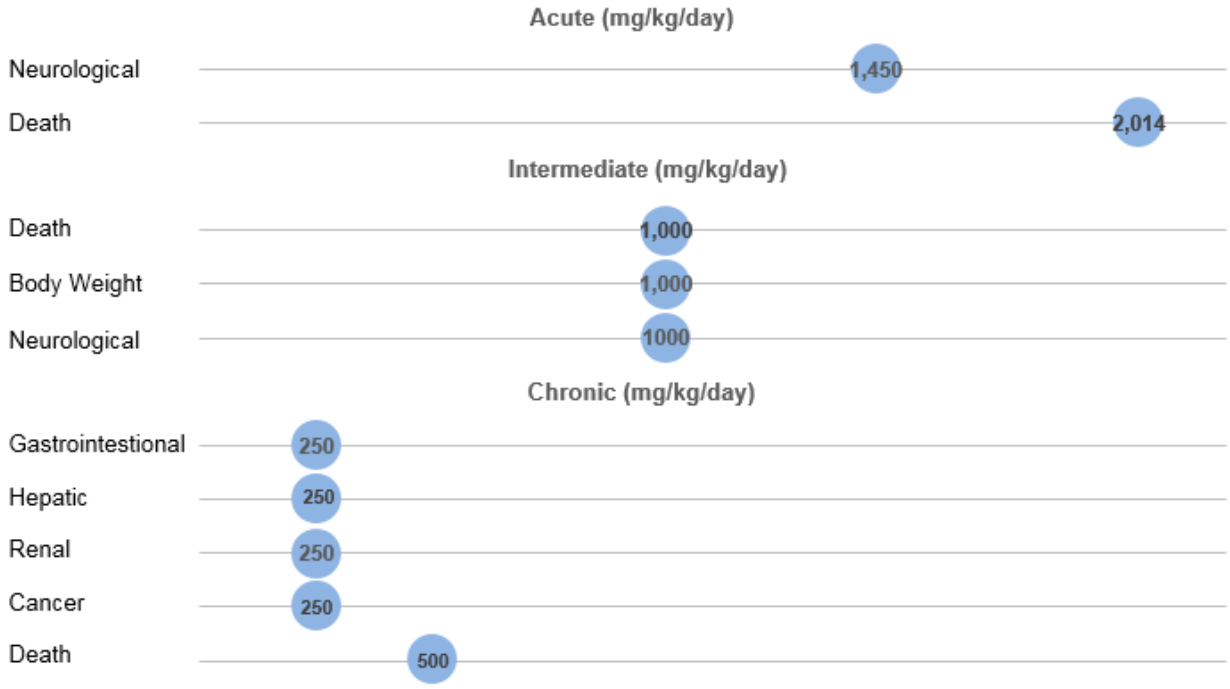


Table 1-1. Minimal Risk Levels (MRLs) for Isophorone[a]

Exposure duration	MRL	Critical effect	Point of departure	Uncertainty factor	Reference
Inhalation exposure (ppm)					
Acute	Insufficient data for MRL derivation				
Intermediate	Insufficient data for MRL derivation				
Chronic	Insufficient data for MRL derivation				
Oral exposure (mg/kg/day)					
Acute	Insufficient data for MRL derivation				
Intermediate	3 mg/kg/day	No adverse effects	311.8 (NOAEL)	100	AME Inc. 1972a
Chronic	0.2 mg/kg/day	Renal, hepatic, stomach lesions	179[b] (LOAEL)	1,000	NTP 1986

[a]See Appendix A for additional information.
[b]Adjusted for daily exposure (exposure was to 250 mg/kg/day 5 day/week).

LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level