CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

Acrolein is a reactive aldehyde primarily used as an intermediate in chemical manufacturing and as a biocide. It is used in the synthesis of many organic chemicals, such as acrylic, as a biocide in agricultural and industrial water supply systems, in the manufacture of methionine (an animal feed supplement), as a component of chemical weapons, and historically as a warning agent (due to its pungent odor) in methyl chloride refrigerant, which is no longer manufactured or used. Acrolein can be formed in burning tobacco, wood, plastics, gasoline and diesel fuel, paraffin wax, and in the heating of animal and vegetable fats and oils at high temperatures. It is also found naturally in the body in very small amounts as a product of lipid oxidation and the metabolism of α-hydroxyamino acids.

Although the general population is endogenously exposed to small amounts of acrolein, the general population is not likely to receive high level exposures of acrolein. Acrolein is expected to volatilize rapidly from surface water and soil. Degradation in water, soil, and air occur quickly. Thus, environmental persistence is not expected. When applied to surface water as an herbicide, the half-life of acrolein was reported to be <1–3 days. It has not been found as a contaminant in drinking water; however, more comprehensive monitoring needs to be done. Acrolein has been detected in very low levels in rainwater in Los Angeles, California, a high-smog area. Average outdoor air acrolein concentrations measured at various monitoring stations ranged from 0.062 to 0.591 ppbv (parts acrolein per billion parts of air by volume). The concentrations of acrolein in indoor air range from <0.02 to 18 ppbv in residential homes. Acrolein concentrations are found to be typically higher in indoor air when comparing paired indoor/outdoor samples taken at a site. A burned cigarette has been measured to generate 3–220 μg of acrolein, which may result in the smoker or bystander inhaling higher amounts of acrolein not only from the cigarette, but also from the exhaled smoke from the smoker compared to persons without exposure to cigarette smoke.

Acrolein has been identified in at least 33 of the 1,868 hazardous waste sites in United States that have been proposed for inclusion on the U.S. Environmental Protection Agency (EPA) National Priorities List. However, the number of sites in which acrolein has been evaluated is not known. The main route of acrolein exposure for the general population stems from indoor air: smoking (cigarettes, e-cigarettes, marijuana), smoking-related exposures, cooking with oils and fats, and building materials. Ingestion of some foods and beverages and consumption of contaminated drinking water can also be routes of

exposure. Children and adults are expected to be exposed to acrolein by the same routes of exposure. Like adults, children may be exposed to unknown levels of acrolein from inhaling smoking or breathing in exhaled smoke from a smoker. Since acrolein is volatile, ineffectively transported in soil, and nonpersistent in the environment, children's dermal exposure from soil contact or ingestion is not likely to differ from adults.

1.2 SUMMARY OF HEALTH EFFECTS

Information on the toxicity of acrolein comes primarily from animal studies; however, a limited number of case reports, human controlled exposure studies, and observational epidemiology studies contribute to the identification of primary toxicity targets. Most of the animal studies evaluated inhalation exposure, with a smaller number studying oral and dermal exposure. Respiratory effects were the most common endpoint evaluated in both humans and animals.

As shown in Figures 1-1 and 1-2, the most sensitive effects in laboratory animals and humans following exposure to acrolein include respiratory effects (inhalation), immunological effects (inhalation), and gastrointestinal effects (oral). A systematic review of these noncancer endpoints resulted in the following hazard identification conclusions:

- Respiratory effects are a presumed health effect for humans following inhalation of acrolein.
- Immunological effects are a suspected health effect for humans following inhalation of acrolein.
- Gastrointestinal effects are a suspected health effect for humans following ingestion of acrolein.

Respiratory Effects. Several human studies and numerous inhalation studies in animals support the identification of the respiratory tract as a presumed target for humans. The most sensitive respiratory effects appear to be nasal irritation in humans and nasal lesions in animals, with subsequent decreased breathing rate and throat irritation in humans. Rapid onset of nose and throat irritation and a reduction in breathing rate (believed to be a protective measure triggered by nose irritation) was reported by volunteers acutely exposed to low levels (0.3 ppm) (Weber-Tschopp et al. 1977). In animals, nasal and pulmonary lesions, decreased respiratory rate, and increased lung weights were seen in acute-, intermediate-, and chronic-duration animal studies (see Tables 2-1 through 2-3). Acute-duration exposure to 0.3–3 ppm resulted in nasal and lung lesions (Arumugam et al. 1999a; Buckley et al. 1984; Cassee et al. 1996a) and decreased respiratory rates in mice and rats, likely due to respiratory irritation (Hazari et al. 2008; Kurhanewicz et al. 2017; Murphy et al. 1963; Perez et al. 2015). Observed effects following intermediate- and chronic-duration exposures to acrolein (1–3 ppm) include histological alterations and

inflammation in the respiratory tract of rats, monkeys, guinea pigs, dogs, rabbits, and hamsters (Dorman et al. 2008; Feron et al. 1978; Leach et al. 1987; Lyon et al. 1970; Matsumoto et al. 2021). Respiratory effects were similar in type of effect and severity across species and exposure duration.

Figure 1-1. Health Effects Found in Humans and Animals Following Inhalation Exposure to Acrolein

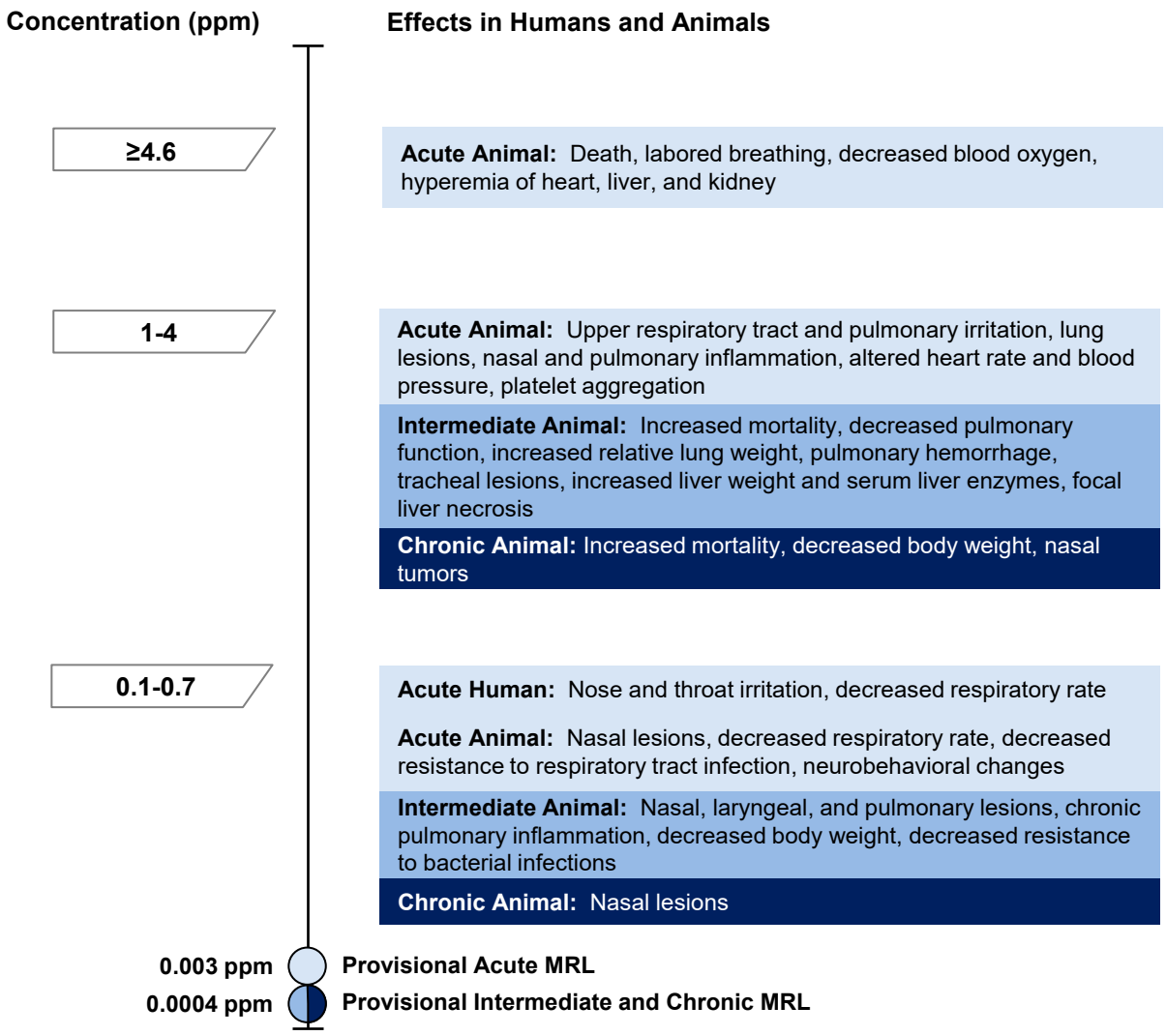
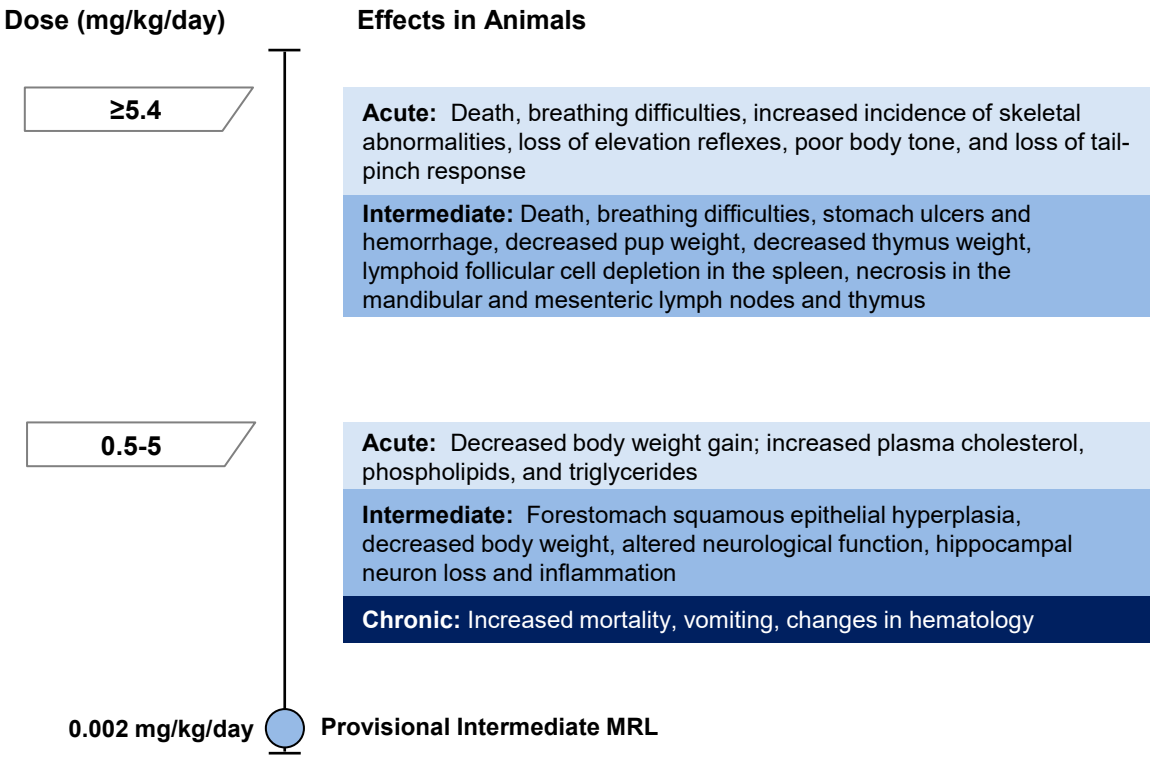


Figure 1-2. Health Effects Found in Animals Following Oral Exposure to Acrolein



Immunological Effects. Immune studies in humans are limited to one controlled exposure study. No effects on inflammatory markers in the serum (IL-6) and sputum (IL-6 and IL-8) were seen in volunteers who inhaled 0.11 ppm of acrolein for 2 hours (Dwivedi et al. 2015). In animal studies, inhalation of acrolein alone did not affect the histology of immune organs after acute- (Kasahara et al. 2008; Skog 1950), intermediate- (Feron et al. 1978; Leach et al. 1987; Sherwood et al. 1986; Conklin et al. 2017b), or chronic-duration exposure (Feron and Kruysse 1977; Matsumoto et al. 2021). Oral administration of acrolein for 14 weeks resulted in atrophy and necrosis in the thymus and depletion of lymphoid follicles in the spleen of rats and mice (Auerbach et al. 2008; NTP 2006a). However, other oral studies reported no effects on immune organs after acute- (Sakata et al. 1989), intermediate- (Parent et al. 1992c), or chronic-duration exposure (Parent et al. 1991a, 1992a, 1992b). Several studies reported that acrolein exposure alters immune function. Following inhalation of acrolein, animals exhibited decreased bactericidal activity, decreased alveolar macrophages, or increased mortality from pulmonary bacterial infection (Aranyi et al. 1986; Astry and Jakab 1983; Bouley et al. 1975; Sherwood et al. 1986). Inhalation exposure to acrolein also suppressed pulmonary inflammatory responses in rodents following allergen challenge (Kim et al. 2019; O'Brien et al. 2016; Spiess et al. 2013).

Ocular Effects. Acrolein vapor or liquid causes adverse ocular effects through irritation at the point of contact. At low airborne levels (0.3 ppm), ocular irritation is perceived in humans as rapid-onset, mild-to-moderate stinging of the eyes accompanied by increased blinking (Weber-Tschopp et al. 1977). Lacrimation occurs at higher levels (0.81 ppm), with an increase in the severity of irritation (Sim and Pattle 1957). At low levels of vapor exposure, humans appear to adapt to ocular irritation, as volunteers exposed to a constant level of acrolein vapors for 60 minutes reported increasing irritation of the eyes up to 40 minutes but reported no further increase in discomfort thereafter (Weber-Tschopp et al. 1977). Dogs and monkeys appear to be more sensitive than rodents to acrolein, as evidenced by lacrimation and blinking or closing of the eyes during intermediate-duration inhalation exposure to 3.7 ppm; however, no observable ocular changes were reported in guinea pigs or rats exposed for the same duration (Lyon et al. 1970). Direct liquid or vapor application of 30 µL into the eyes of rabbits caused severe eyelid swelling and inflammation, corneal opacity, excessive tear secretion, and corneal edema (Gupta et al. 2020). Exposure to vapors generated after 10 µL of acrolein was applied to a filter paper disc and then placed in a glass goggle resulted in corneal erosions in rabbit eyes (Dachir et al. 2015).

Gastrointestinal Effects. The irritation of gastrointestinal mucosa appears to be the primary effect of oral exposure to acrolein. Human data for oral exposures are not available. The gastrointestinal effects in rats and mice gavaged with acrolein were dose-related following intermediate-duration exposures, but chronic-duration studies in dogs suggest possible adaptation to the irritating effects. Forestomach squamous epithelial hyperplasia was observed at doses ≥2.5 mg/kg/day in 14-week rat and mouse studies (Auerbach et al. 2008; NTP 2006a). Conversely, chronic-duration dosing levels of 2–4.5 mg/kg/day produced no significant gross or histopathological effects in the esophagus, stomach, or intestines of rats, mice, or dogs (Parent et al. 1991a, 1992a, 1992b). Intermediate-duration exposure to doses from 4 to 25 mg/kg/day in mice, rats, and rabbits produced severe mucosal inflammation, ulceration, focal hemorrhage, and edema (Parent et al. 1992c; Sakata et al. 1989). Dogs chronically given acrolein doses by capsule as low as 0.5 mg/kg/day vomited significantly through the first 4 weeks of exposure but appeared to adapt, as vomiting incidence was reduced thereafter (Parent et al. 1992b). Data were not available to determine if an adaptive effect for chronic-duration oral exposures would be observed at higher dose levels.

Cancer. No adequate studies were available evaluating the carcinogenic potential of acrolein in humans. Information from animal studies is conflicting and limited. An inhalation study reported increased incidence of nasal tumors in female rats (rhabdomyomas, 8%) and female mice (adenomas, 32%) exposed to 2 and 1.6 ppm acrolein, respectively, for 2 years, although similar results were not observed in male

rats or mice (Matsumoto et al.2021). One oral study reported increased incidence of neoplasms of the adrenal cortex in high-dose female rats (5/20 adenomas, 2/20 hyperplastic nodules) after drinking water containing acrolein (up to 36 mg/kg/day for 104–124 weeks) (Lijinsky and Reuber 1987); however, re-evaluation of this study by an independent pathology working group concluded that the incidence of cortical tumors was within limits of historical controls (Goodman 1990). No carcinogenic effects were seen in rats exposed to 2.5 mg/kg/day for 102 weeks (Parent et al. 1992a), mice exposed to 4.5 mg/kg/day or dogs exposed to 2 mg/kg/day (Parent et al. 1992b) for 12–18 months.

The International Agency for Research on Cancer (IARC) IARC has classified acrolein as "probably carcinogenic to humans" (Group 2A) based on "sufficient" evidence of carcinogenicity in experimental animals and "strong" mechanistic evidence (IARC 2021). The U.S. Environmental Protection Agency (EPA) concluded that the potential carcinogenicity of acrolein cannot be determined because the existing "data are inadequate for an assessment of human carcinogenic potential for either the oral or inhalation route of exposure" (IRIS 2003). The Department of Health and Human Services (HHS) has not classified acrolein as to its carcinogenicity (NTP 2004).

1.3 MINIMAL RISK LEVELS (MRLs)

As illustrated in Figure 1-3, available inhalation data for acrolein suggest that the respiratory and immunological systems are the most sensitive targets for toxicity. The inhalation database was considered adequate for derivation of acute-, intermediate-, and chronic-duration provisional MRLs.

The oral database was considered adequate for derivation of an intermediate-duration provisional MRLs for acrolein. The acute- and chronic-duration data were insufficient for deriving MRLs. As illustrated in Figure 1-4, gastrointestinal and hematological effects appear to be the most sensitive targets of acrolein toxicity 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 Acrolein – Inhalation

Available data indicate that the respiratory tract and immune system are the most sensitive targets of acrolein inhalation exposure.

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

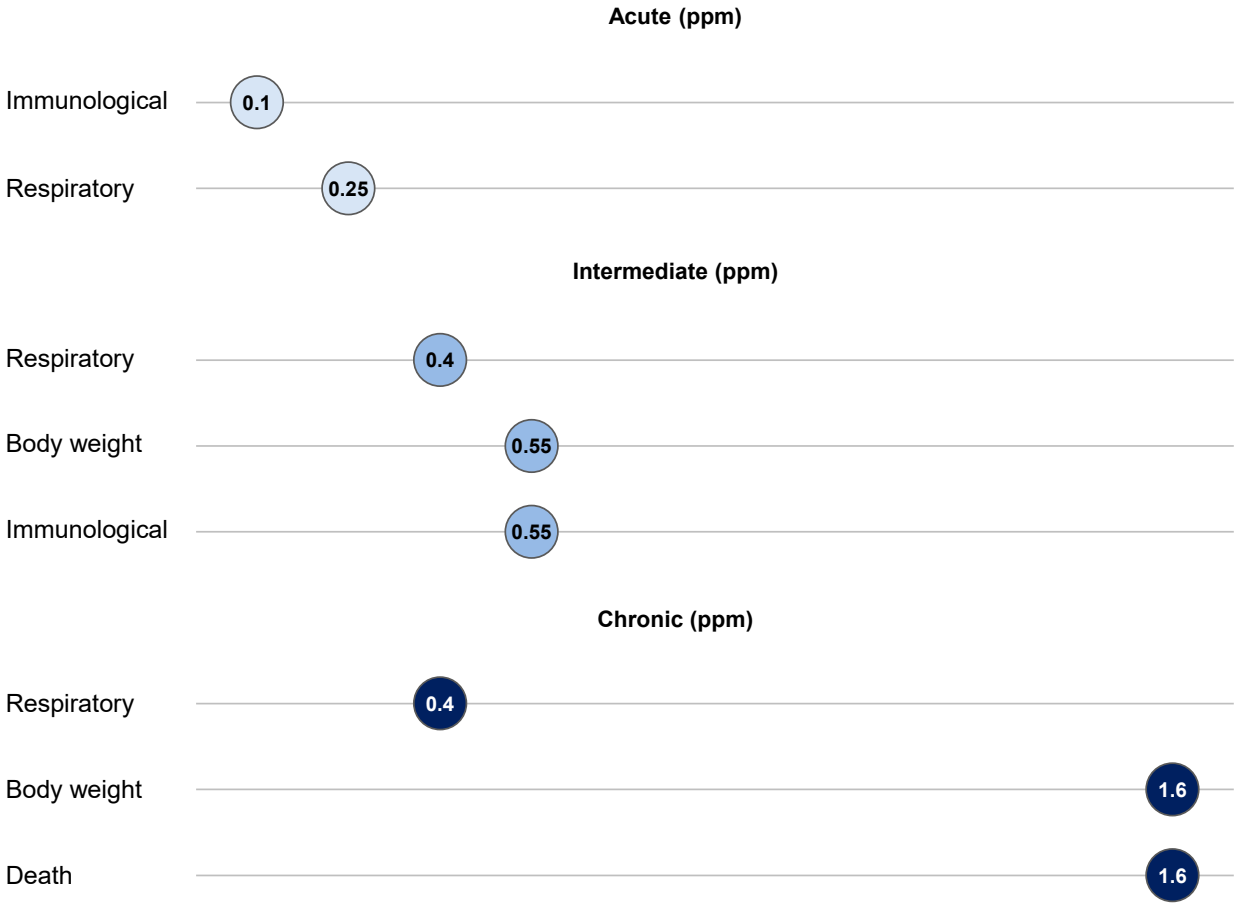


Figure 1-4. Summary of Sensitive Targets of Acrolein – Oral

Available data indicate that gastrointestinal and hematological effects are the most sensitive targets of acrolein oral exposure.

Numbers in circles are the lowest LOAELs for all health effects in animals.
No reliable dose response data were available for humans.

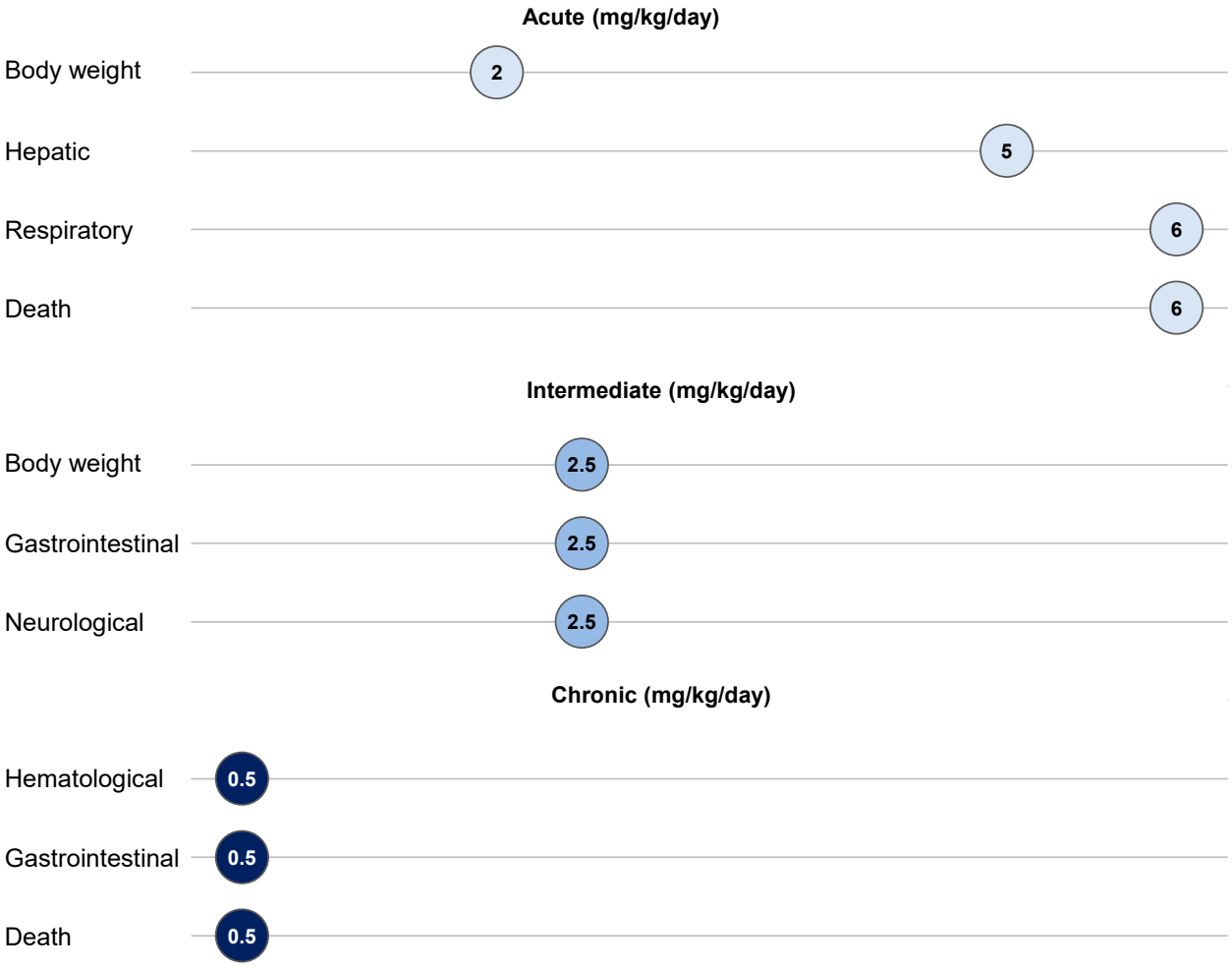


Table 1-1. Minimal Risk Levels (MRLs) for Acrolein[a]

Exposure route	Exposure duration	Provisional MRL	Critical effect	POD type	POD value	Uncertainty/ modifying factor	Reference
Inhalation	Acute	**0.003 ppm** (0.007 mg/m^3)	Nose and throat irritation and deceased respiratory rate in human subjects	LOAEL	0.3 ppm	UF: 100	Weber-Tschopp et al. 1977
	Intermediate	**4x10^{-4} ppm**[b] (9x10^{-4} mg/m^3)	Nasal respiratory gland metaplasia in rats	$BMCL_{HEC}$	0.012 ppm	UF: 30	Matsumoto et al. 2021
	Chronic	**4x10^{-4} ppm** (9x10^{-4} mg/m^3)	Nasal respiratory gland metaplasia in rats	$BMCL_{HEC}$	0.012 ppm	UF: 30	Matsumoto et al. 2021
Oral	Acute	None	–	–	–	–	–
	Intermediate	**0.002 mg/kg/day**	Forestomach squamous epithelial hyperplasia in male mice	$BMDL_{10}$	0.22 mg/kg/day	UF: 100	Auerbach et al. 2008; NTP 2006a
	Chronic	None	–	–	–	–	–

[a]See Appendix A for additional information.
[b]The chronic-duration inhalation MRL was adopted for the intermediate-duration inhalation MRL.

BMCL = benchmark concentration lower confidence limit; $BMDL_{10}$ = benchmark dose lower confidence limit (subscript denotes benchmark response: i.e., 10 = dose associated with 10% extra risk); HEC = human equivalent concentration; LOAEL = lowest observed adverse effect level; POD = point of departure; UF = uncertainty factor