CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

- Acrylonitrile is a volatile substance used in the manufacture of acrylic fibers, plastics, and other chemicals.
- The general public can be exposed to very low levels of acrylonitrile through contact with consumer products such as acrylic carpeting or by ingestion of food stored in acrylic plastic containers as well as from inhalation of smoke from tobacco, marijuana, or other acrylonitrile-containing burning biomass.
- Workers involved in the production of acrylic fibers, resins, and chemical intermediates may be exposed to higher levels of acrylonitrile.
- Acrylonitrile and its metabolites can be measured in blood and urine.

1.2 SUMMARY OF HEALTH EFFECTS

Information on the toxicity of acrylonitrile primarily comes from inhalation and oral exposure studies in laboratory animals. These studies have evaluated a wide range of potential endpoints following acute, intermediate, or chronic-duration exposure. More limited information comes from a small number of human studies, most of which are case reports/case series involving inhalation exposure.

As illustrated in Figures 1-1 and 1-2, the most sensitive effects appear to be nasal lesions following inhalation exposure, non-glandular stomach (i.e., forestomach) damage following oral exposure, neurological effects, developmental effects, and cancer. A systematic review of the noncancer endpoints resulted in the following hazard identification conclusions:

- Respiratory effects following inhalation exposure are a presumed health effect for humans
- Gastrointestinal effects following oral exposure are a presumed health effect for humans
- Neurological effects are a presumed health effect for humans
- Developmental effects are a presumed health effect for humans

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

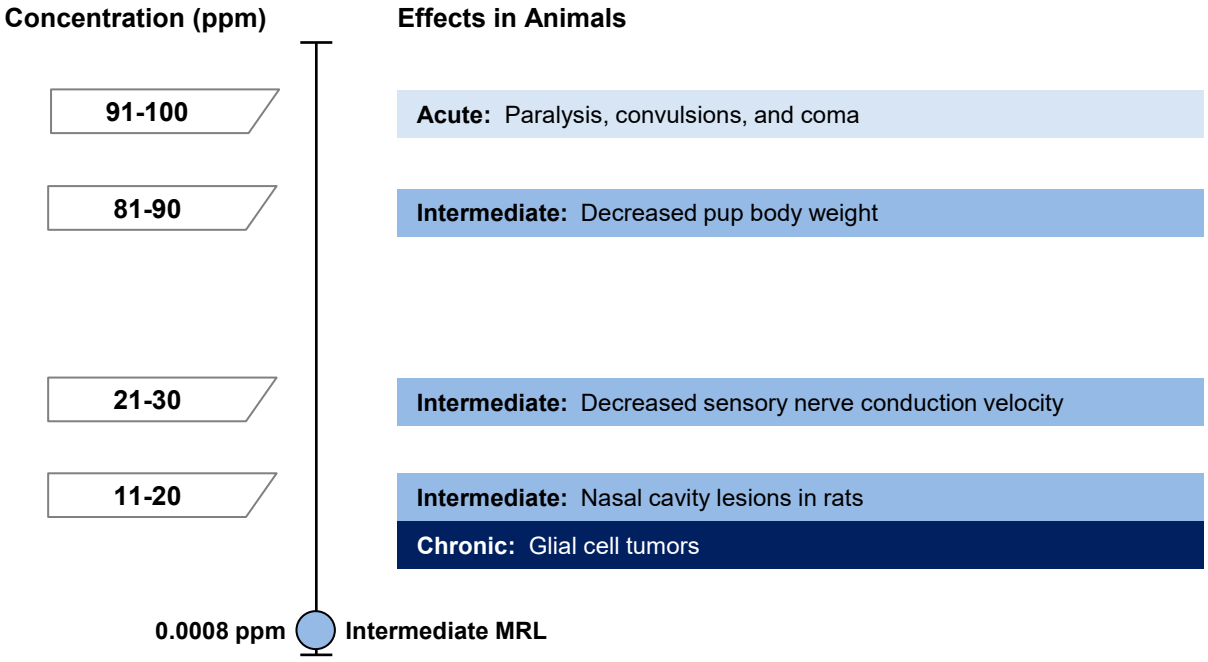
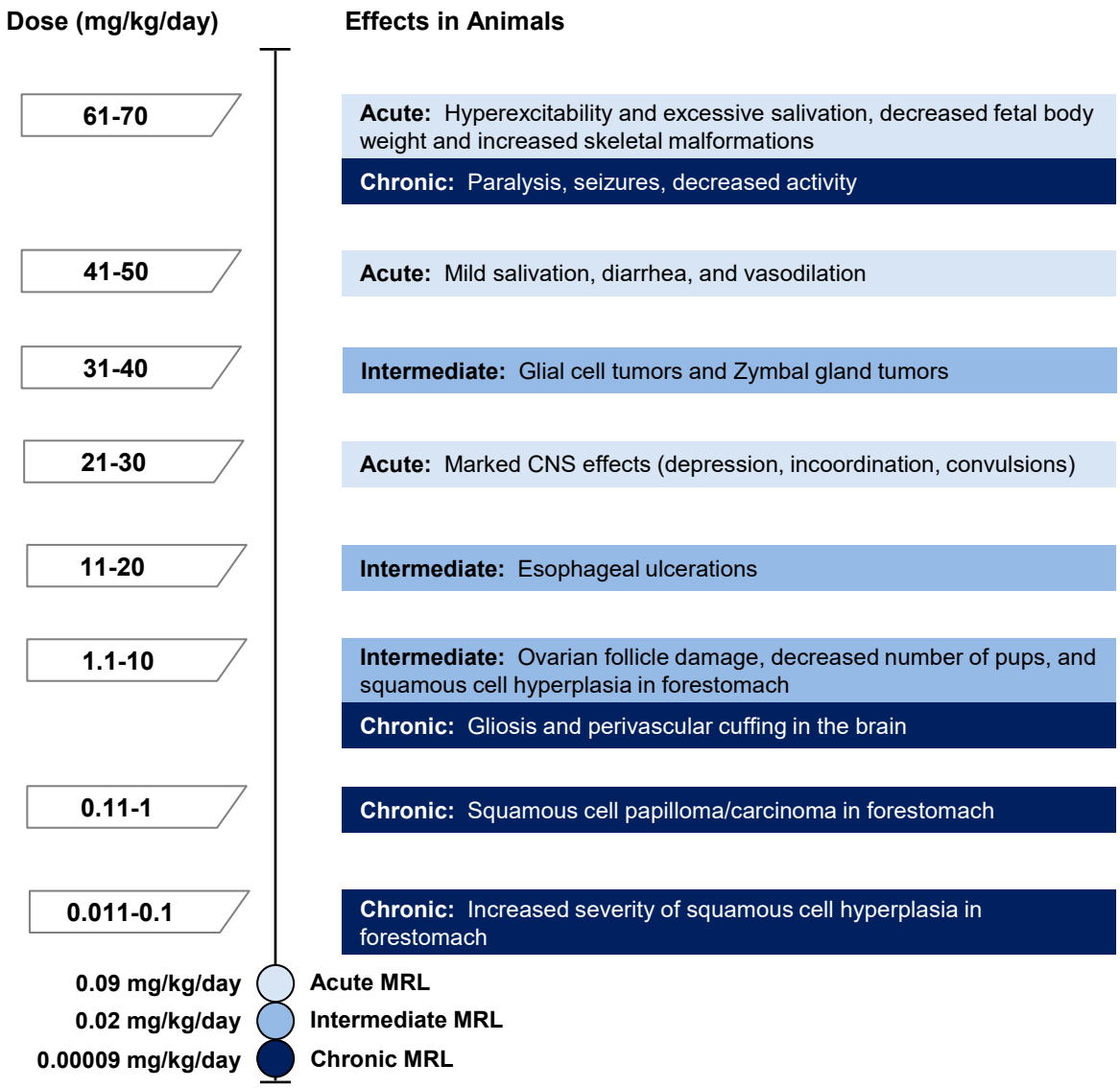


Figure 1-2. Health Effects Found in Animals Following Oral Exposure to Acrylonitrile



Respiratory Effects. Respiratory tract irritation has been reported in humans acutely exposed to acrylonitrile vapors (Simons et al. 2016; Wilson 1944; Wilson et al. 1948); a longer-term study of workers found an increased risk of deaths from pneumonitis (Koutros et al. 2019). Respiratory irritation was also reported in several animal species following inhalation exposure (Dudley and Neal 1942). Longer term inhalation exposure resulted in hyperplasia of nasal cavity respiratory/transitional zone epithelium, squamous metaplasia, and subacute inflammation in rats (Nemec et al. 2008) and nasal turbinate irritation in rats (Quast et al. 1980a, 1983).

Gastrointestinal Effects. Histological alterations have been observed in the non-glandular stomach (i.e., forestomach) of rats and mice following acute-, intermediate-, and chronic-duration oral exposure. The alterations include squamous cell hyperplasia, hyperkeratosis, and squamous metaplasia (Ghanayem et al. 1997; Johannsen and Levinskas 2002a, 2002b; NTP 2001; Quast 2002; Szabo et al. 1984). In dogs, intermediate-duration oral exposure resulted in esophageal ulcerations (Quast et al. 1975).

Neurological Effects. Humans acutely exposed to acrylonitrile display clinical signs similar to those associated with cyanide poisoning, including labored and irregular breathing, dizziness, cyanosis, limb weakness, and convulsions (Baxter 1979). Some animal species also display cyanide poisoning symptoms including mice (Ahmed and Patel 1981), whereas rats display cholinergic effects including excessive salivation, miosis, and polyuria (Ahmed and Farooqui 1982; Ahmed and Patel 1981; Dudley and Neal 1942; Ghanayem et al. 1991; Murray et al. 1978). Long-term exposure to higher doses of acrylonitrile have resulted in hindlimb weakness, decreased activity, paralysis, and seizures in rats (Bigner et al. 1986; Gagnaire et al. 1998). Other neurological effects include decreased sensory nerve conduction velocity (Gagnaire et al. 1998) and glial cell tumors and perivascular cuffing in the brain (Quast 2002; Quast et al. 1980a).

Developmental Effects. Developmental effects have been observed in the offspring of rats following inhalation and oral exposure. The observed effects included decreases in fetal or pup body weight and skeletal malformations (Friedman and Beliles 2002; Murray et al. 1978; Saillenfait and Sabate 2000). Maternal toxicity, particularly decreased body weight gain, was typically observed at the same doses as the developmental effects. The results of *in vitro* studies (Saillenfait and Sabate 2000; Saillenfait et al. 1992, 1993) suggest that developmental effects (decreased embryonic growth and increased morphological alterations) can occur in the absence of maternal effects.

Cancer Effects. A large number of epidemiological studies have evaluated possible associations between occupational exposure to acrylonitrile and cancer. In general, these studies have not reported increased risk of cancer associated with acrylonitrile occupational exposure. In contrast, a number of animal studies have consistently found increases in the incidence of several cancer types including glial cell tumors in the brain and spinal cord of rats (the study investigators categorized these tumors as astrocytomas; see Section 2.19 for additional details), Zymbal gland carcinomas in rats, and forestomach tumors in rats and mice.

The Department of Health and Human Services (HHS) has categorized acrylonitrile as "reasonably anticipated to be a human carcinogen" (NTP 2021). The U.S. Environmental Protection Agency (EPA) has categorized it as a probable human carcinogen (IRIS 2002). The International Agency for Research on Cancer (IARC) concluded that acrylonitrile is "carcinogenic to humans" (Group 1) (Stayner et al. 2024).

1.3 MINIMAL RISK LEVELS (MRLs)

The inhalation database was considered adequate for deriving an intermediate-duration inhalation MRL (see Table 1-1). The respiratory tract and nervous system were the most sensitive targets following inhalation exposure; cancer has also been observed at low concentrations. The lowest LOAELs for these endpoints are presented in Figure 1-3. The oral database was considered adequate for derivation of acute-, intermediate-, and chronic-duration oral MRLs for acrylonitrile (see Table 1-1). As presented in Figure 1-4, the forestomach, nervous system, and cancer effects were the most sensitive outcomes.

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

Available data indicate that the respiratory tract and nervous system are the most sensitive targets of acrylonitrile inhalation exposure.
Numbers in circles are the lowest LOAELs for all health effects in animals; no human data were identified.

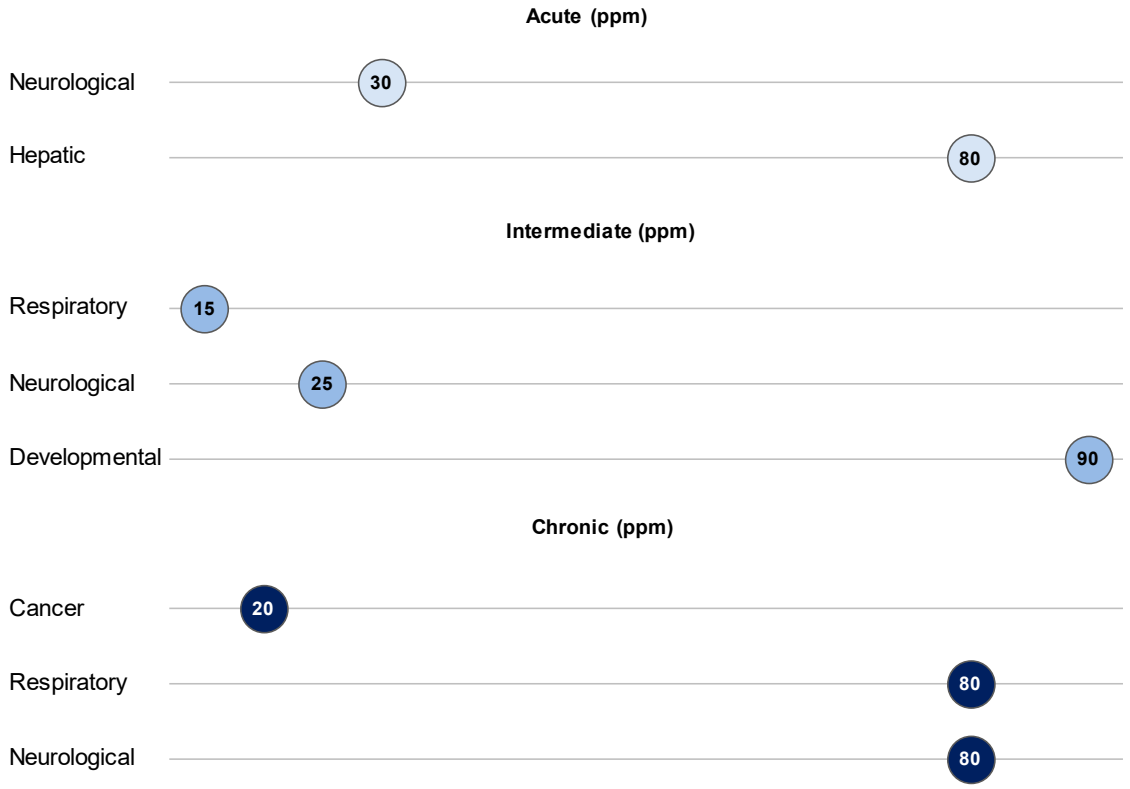


Figure 1-4. Summary of Sensitive Targets of Acrylonitrile – Oral

Available data indicate that the forestomach, nervous system, and cancer are the most sensitive targets of acrylonitrile oral exposure.

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

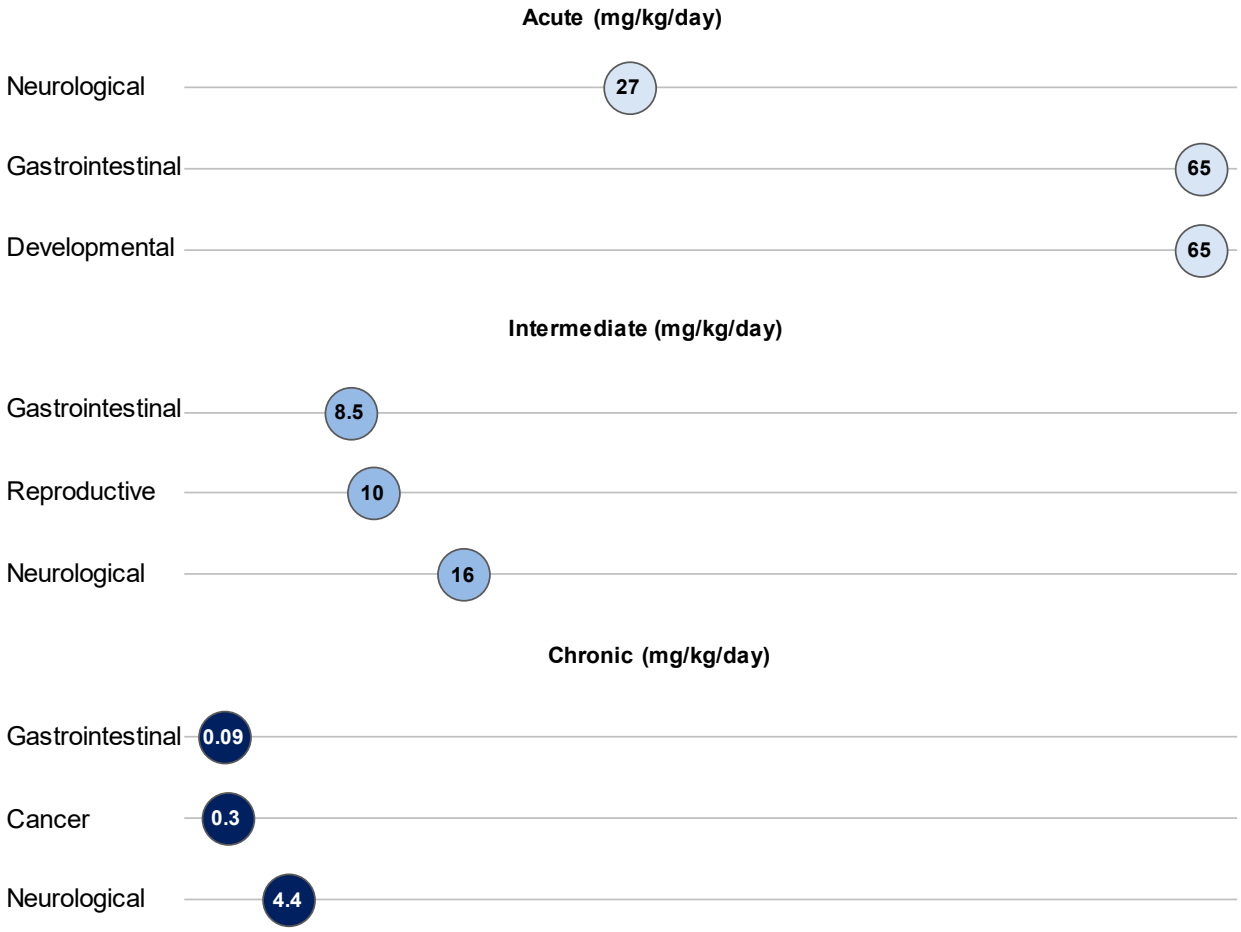


Table 1-1. Minimal Risk Levels (MRLs) for Acrylonitrile[a]

Exposure route	Exposure duration	MRL	Critical effect	POD type	POD value	Uncertainty/ modifying factor	Reference
Inhalation	Acute	None	–	–	–	–	–
	Intermediate	**$8x10^{-4}$ ppm**	Hyperplasia of nasal respiratory/ transitional zone epithelium	$BMCL_{HEC\text{-}model\ average}$	0.073 ppm	UF: 30	Nemec et al. 2008
	Chronic	None	–	–	–	–	–
Oral	Acute	**0.09 mg/kg/day**	Fetal malformations	$BMDL_{05\text{-}model\ average}$	9.27 mg/kg/day	UF: 100	Murray et al. 1978
	Intermediate	**0.02 mg/kg/day**	Nonglandular stomach hyperplasia	$BMDL_{10}$	2.48 mg/kg/day	UF: 100	Quast 2002
	Chronic	**$9x10^{-5}$ mg/kg/day**	Increased severity of forestomach hyperplasia	LOAEL	0.09 mg/kg/day	UF: 1,000	Johannsen and Levinskas 2002b

[a]See Appendix A for additional information.

BMCL = benchmark concentration lower confidence limit; $BMDL_{05}$ = benchmark dose lower confidence limit 5%; $BMDL_{10}$ = benchmark dose lower confidence limit 10%; HEC = human equivalent concentration; LOAEL = lowest-observed-adverse-effect level; POD = point of departure; UF = uncertainty factor