Toxicological Profile for Acrylonitrile

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U.S. Department of Health and Human Services
Agency for Toxic Substances and Disease Registry

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DISCLAIMER

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FOREWORD

This toxicological profile is prepared in accordance with guidelines developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for these toxic substances described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a relevance to public health discussion which would allow a public health professional to make a real-time determination of whether the presence of a particular substance in the environment poses a potential threat to human health. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to the protection of public health are identified by ATSDR.

Each profile includes the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a toxic substance to ascertain the levels of significant human exposure for the substance due to associated acute-, intermediate-, and chronic-duration exposures;

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health due to acute-, intermediate-, and chronic-duration exposures; and

(C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staffs of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

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VERSION HISTORY

Date	Description
April 2025	Final toxicological profile released
August 2023	Draft for public comment toxicological profile released
December 1990	Final toxicological profile released

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ATSDR scientists review peer reviewers' comments and determine whether changes will be made to the profile based on comments. The peer reviewers' comments and responses to these comments are part of the administrative record for this compound.

The listing of peer reviewers should not be understood to imply their approval of the profile's final content. The responsibility for the content of this profile lies with ATSDR.

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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

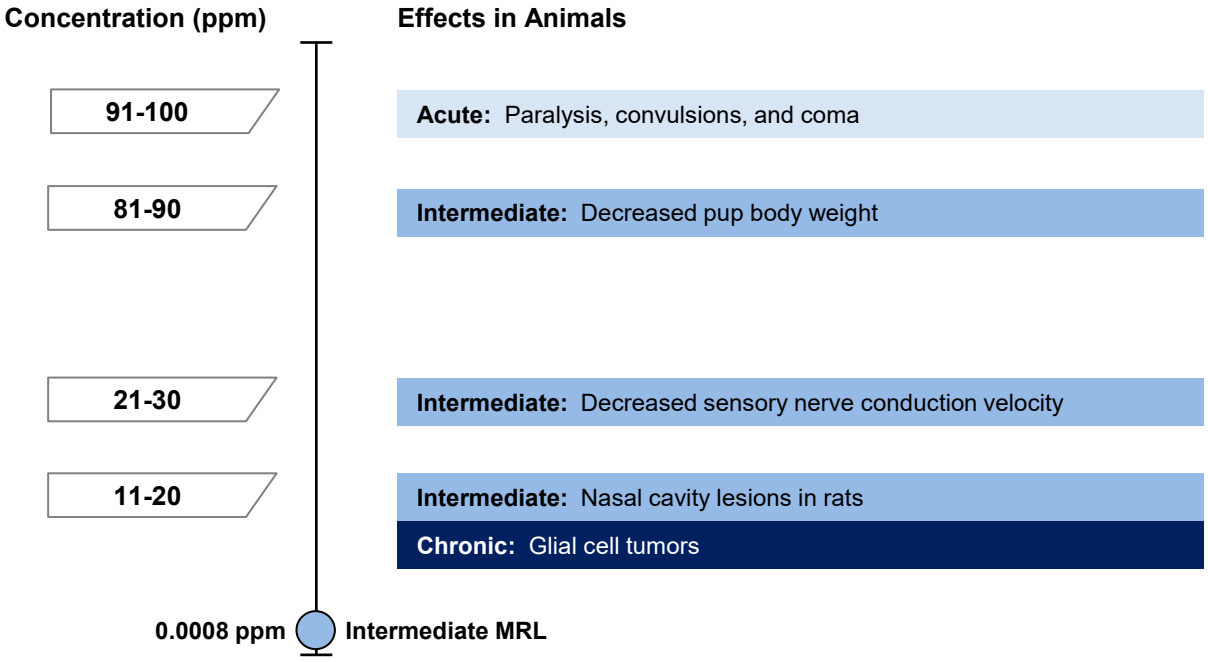
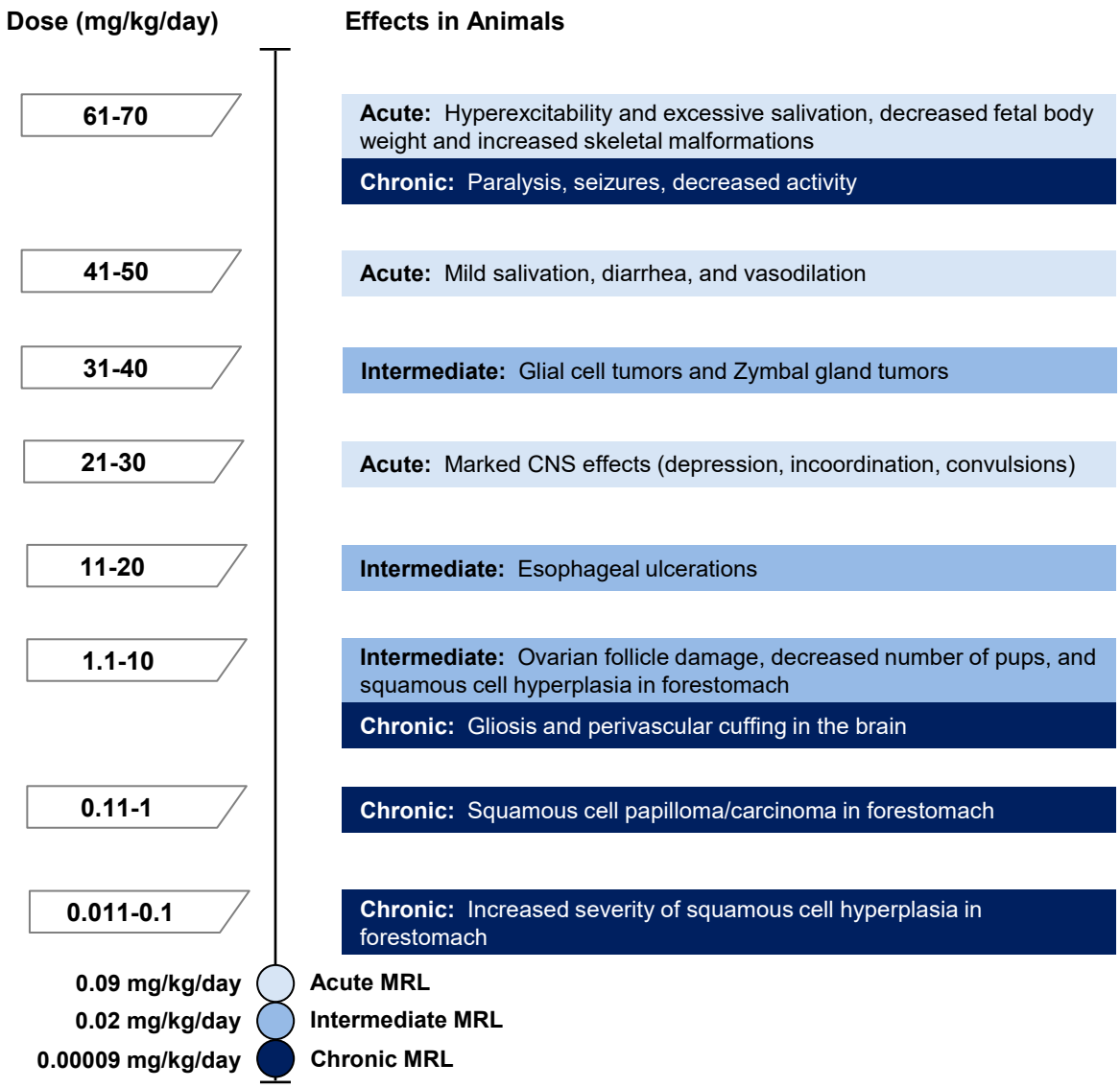


Figure 1-2. Health Effects Found in Animals Following Oral Exposure to Acrylonitrile



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.

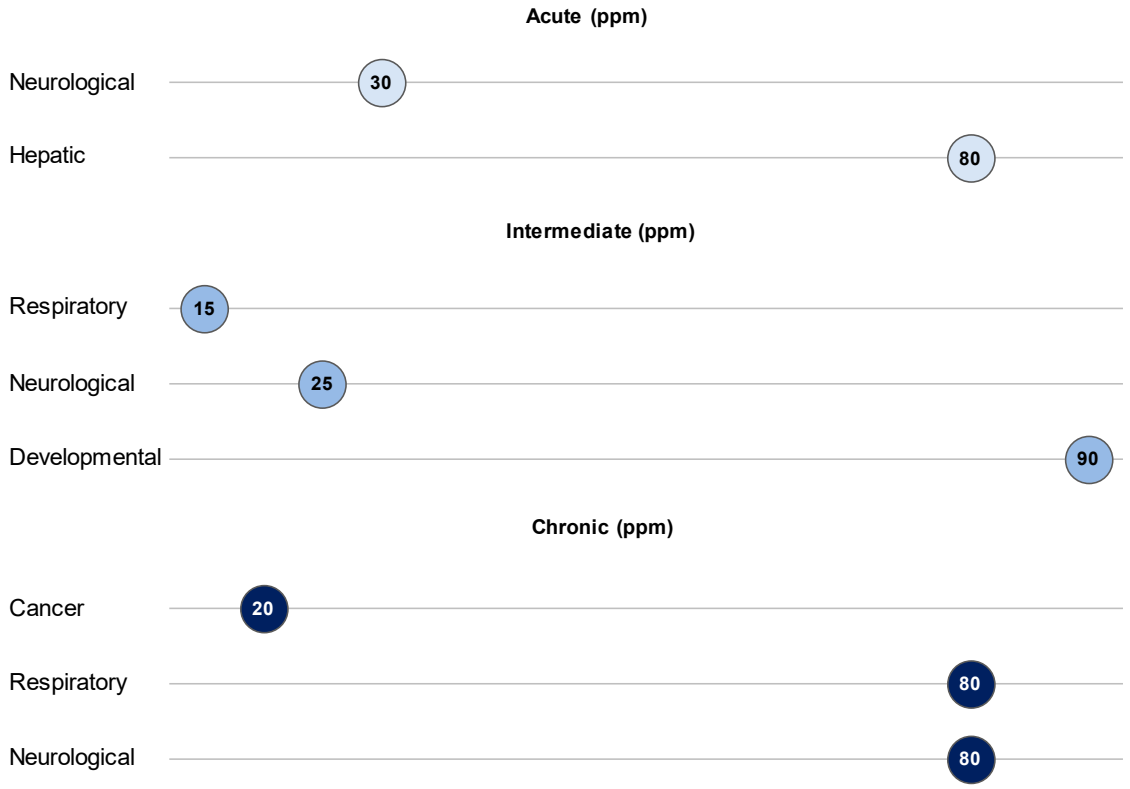


Figure 1-4. Summary of Sensitive Targets of Acrylonitrile – Oral

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.

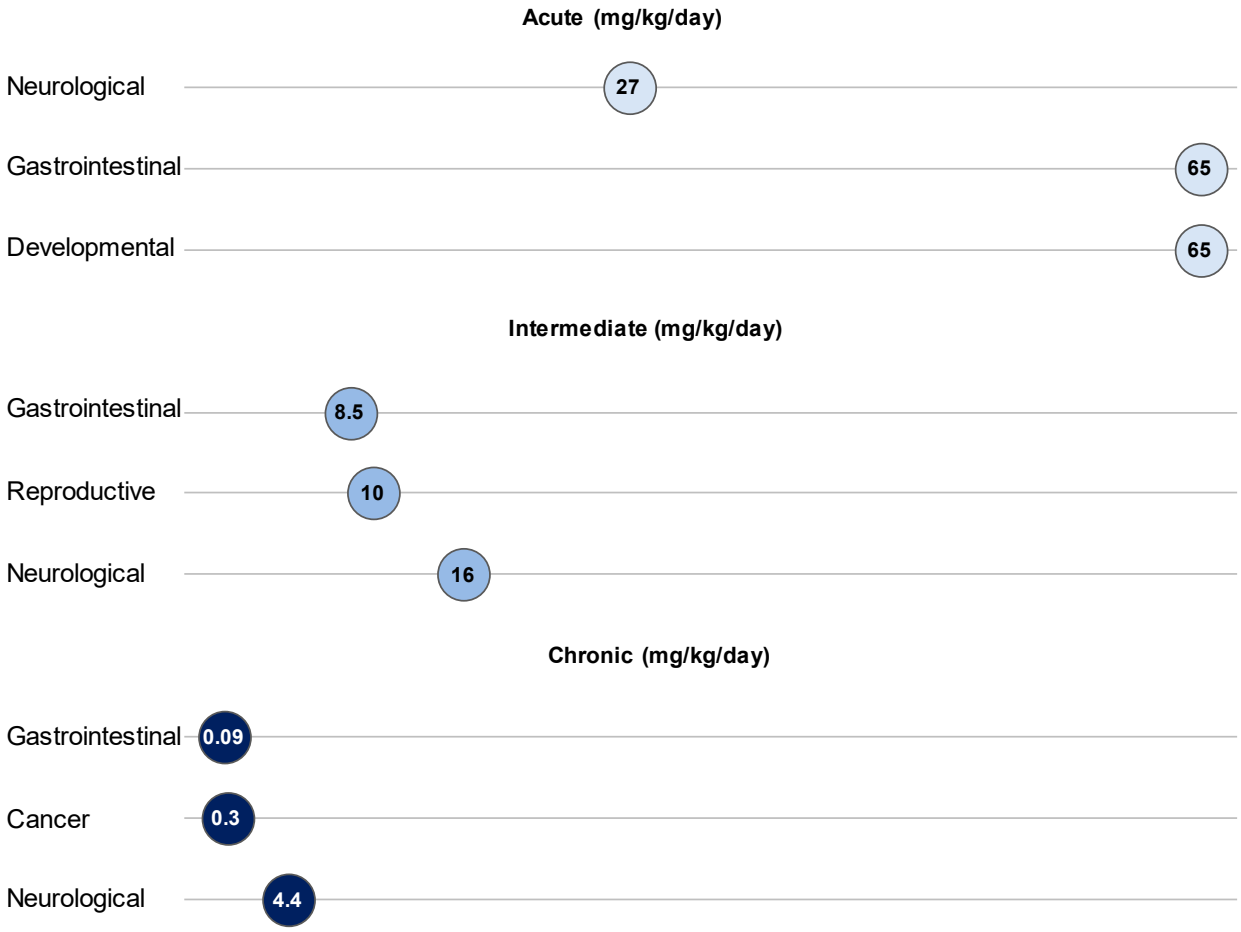


Table 1-1. Minimal Risk Levels (MRLs) for Acrylonitrile[a]

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

CHAPTER 2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of acrylonitrile. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health. When available, mechanisms of action are discussed along with the health effects data; toxicokinetic mechanistic data are discussed in Section 3.1.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized by health effect. These data are discussed in terms of route of exposure (inhalation, oral, and dermal) and three exposure periods: acute (≤14 days), intermediate (15–364 days), and chronic (≥365 days).

As discussed in Appendix B, a literature search was conducted to identify relevant studies examining health effect endpoints. Figure 2-1 provides an overview of the database of studies in humans or experimental animals included in this chapter of the profile. These studies evaluate the potential health effects associated with inhalation, oral, or dermal exposure to acrylonitrile, but may not be inclusive of the entire body of literature. A systematic review of the scientific evidence of the health effects associated with exposure to acrylonitrile was also conducted; the results of this review are presented in Appendix C.

Human and animal inhalation studies are presented in Table 2-1 and Figure 2-2; animal oral studies are presented in Table 2-2 and Figure 2-3; and dermal data are presented in Table 2-3.

Levels of significant exposure (LSEs) for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. Effects have been classified into “less serious LOAELs” or “serious LOAELs (SLOAELs).” “Serious” effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). “Less serious” effects are those that are not expected to cause

significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an endpoint should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these endpoints. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health. Levels of exposure associated with cancer (cancer effect levels, CELs) of acrylonitrile are indicated in Tables 2-1 and 2-2 and Figures 2-2 and 2-3.

A User's Guide has been provided at the end of this profile (see Appendix D). This guide should aid in the interpretation of the tables and figures for LSEs and MRLs.

The health effects of acrylonitrile have been evaluated in epidemiological and laboratory animal studies. As illustrated in Figure 2-1, most of the health effects data come from inhalation and oral studies in laboratory animals. Animal data are available for all health effects and exposure duration categories. The most examined endpoints were neurological, body weight, respiratory, and gastrointestinal.

The human and animal studies suggest several sensitive targets of acrylonitrile toxicity (see Appendix C for details on the systematic review):

- **Respiratory Endpoints:** Respiratory effects following inhalation exposure are a presumed health effect for humans based on low evidence in human acute-duration exposure studies and a high level of evidence of nasal irritation in rats.
- **Gastrointestinal Endpoints:** Gastrointestinal effects following oral exposure are a presumed health effect for humans based on a high level of evidence of increased incidence or severity of forestomach hyperplasia in rats and mice.
- **Neurological Endpoints:** Neurological effects are a presumed health effect for humans based on a moderate level of evidence in humans and a high level of evidence in several animal species. The neurological effects include overt signs of neurotoxicity similar to cyanide poisoning,

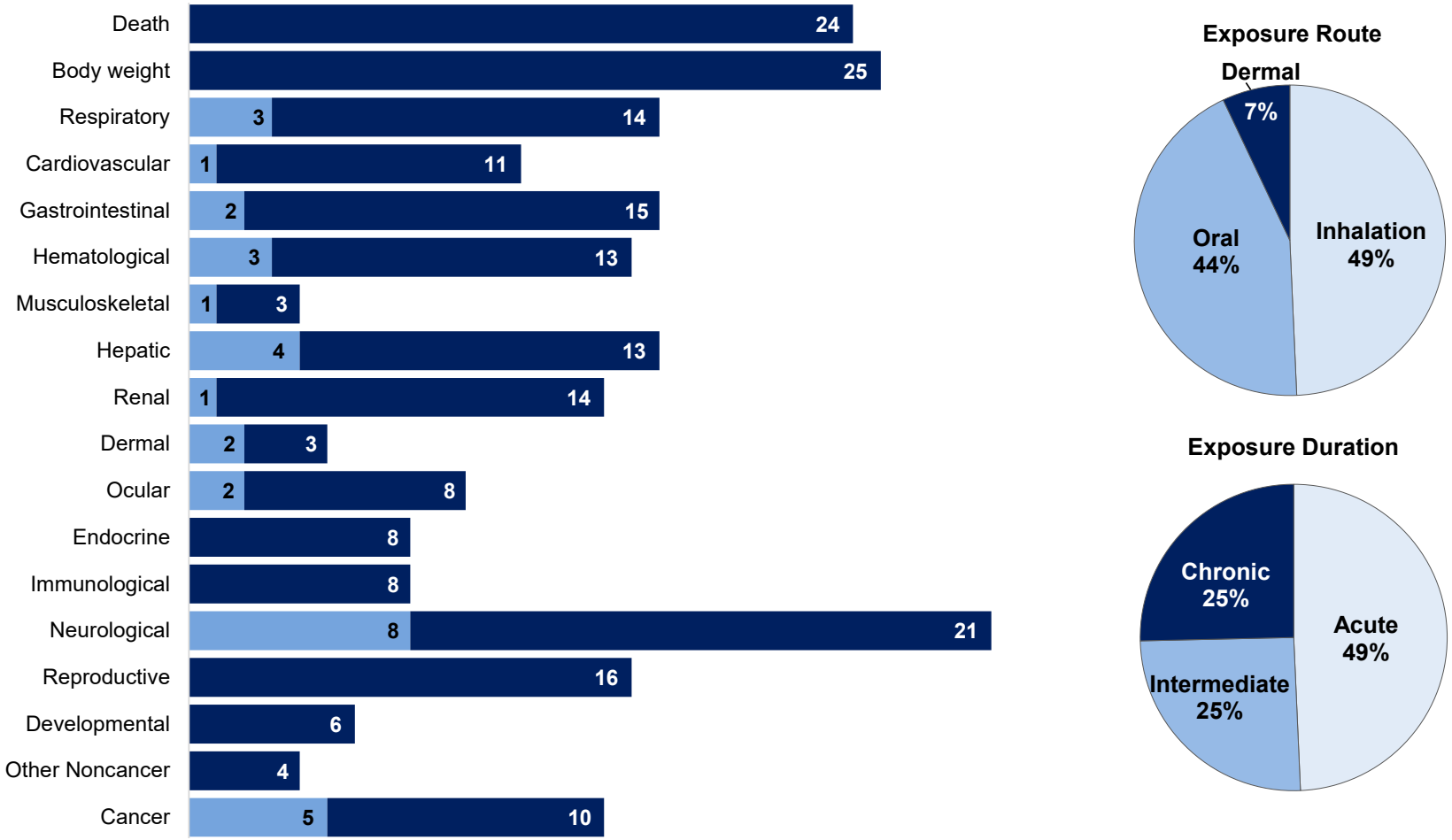
cholinergic symptoms, decreased activity, paralysis, and convulsions. Other neurological effects including decreased sensory nerve conduction velocity, and glial lesions.

- **Developmental Endpoints:** Developmental effects are a presumed health effect for humans based on a high level of evidence in animals. Developmental effects such as decreased body weight and skeletal malformations have been reported following inhalation and oral exposures. These developmental effects were often reported at maternally toxic doses.

Figure 2-1. Overview of the Number of Studies Examining Acrylonitrile Health Effects*

Most studies examined neurological, body weight, respiratory, and gastrointestinal effects of acrylonitrile

Fewer studies evaluated health effects in humans than animals (counts represent studies examining endpoint)



*Includes studies discussed in Chapter 2. A total of 80 studies (including those finding no effect) have examined toxicity; most studies examined multiple endpoints.

Table 2-1. Levels of Significant Exposure to Acrylonitrile – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
ACUTE EXPOSURE									
Jakubowski et al. 1987									
1	Human 5–6 M	8 hours	2.3, 4.6	CS	Neuro	4.6			
Wilson et al. 1948									
2	Human NR	20-45 minutes (Occupational)	16-100	CS	Dermal		16		Skin irritation
					Neuro		16		Irritability
Dudley and Neal 1942									
3	Monkey (NS) 2–5 M, F	4 hours	65, 90	CS	Neuro	65	90		Weakness in 1/2 monkeys
Dudley and Neal 1942									
4	Rat (NS) 16 NS	4 hours	100, 130, 315, 635	CS	Death			315	31% mortality
					Dermal		100		Skin redness
Gut et al. 1984									
5	Rat (Wistar) 8 M	5 days 8 hours/day	0, 129	OW, HP, OF, BC	Bd wt		129		16% decrease in body weight
					Resp	129			
					Hepatic	129			
					Renal	129			
Gut et al. 1984									
6	Rat (NS) 8 M	12 hours	0, 26, 58, 125	BC	Other noncancer		26		Increased blood glucose
Kiplinger 2005									
7	Rat (Sprague Dawley) 5 M, 5 F	4 hours	0, 539, 775, 871, 1,006, 1,181	LE, CS, BW, GN	Death			946 M 920 F	LC_{50}
					Neuro		775	871	LOAEL: tremors SLOAEL: ataxia

Table 2-1. Levels of Significant Exposure to Acrylonitrile – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Murray et al. 1978									
8	Rat (Sprague-Dawley) 35–37 F	GDs 6–15 6 hours/day	0, 40, 80	BW, DX	Bd wt			40	25% decreased maternal weight gain
					Develop	40	80		Increase in total number of malformations
Rouisse et al. 1986									
9	Rat (NS) 7 M	4 hours	0, 100, 200	BC, UR	Renal	100	200		Glycosuria, proteinuria
Wang et al. 1995									
10	Mouse (Kunming) 12 M	7 or 14 days 2 hours/day 6 days/week	0, 55	RX	Repro	55			
Dudley and Neal 1942									
11	Dog (NS) 2–3 M, F	4 hours	30, 65, 100, 110, 165	CS	Death			65	1/2 died at 65 ppm
					Neuro		30	100	LOAEL: salivation SLOAEL: paralysis, convulsions, and coma
Dudley and Neal 1942									
12	Rabbit (NS) 2–3 NS	4 hours	100, 135, 260, 580	CS	Death			260	100% mortality
					Dermal		100		Skin redness
Dudley and Neal 1942									
13	Guinea pig (NS) 8–16 NS	4 hours	100, 265, 575, 1,160	GN, CS	Death			575	63% mortality
					Ocular	100	575		Eye irritation

Table 2-1. Levels of Significant Exposure to Acrylonitrile – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Dudley and Neal 1942									
14	Cat (NS) 2–4 NS	4 hours	100, 275, 600	CS	Death			600	2/2 cats died
					Neuro		100	275	LOAEL: salivation SLOAEL: pain
INTERMEDIATE EXPOSURE									
Gagnaire et al. 1998									
15	Rat (Sprague-Dawley) 12 M	24 weeks 6 hours/day 5 days/week	0, 25, 50, 100	BW, NX	Bd wt	50	100		11% decrease body weight gain
					Neuro		25		Decreased sensory nerve conduction velocity
Nemec et al. 2008									
16	Rat (Sprague-Dawley) 25 M, 25 F	2 generations 18 weeks 6 hours/day 7 days/week	0, 5, 15, 45, 90	BW, FI, BC, DX, OW, HP	Bd wt	45		90	11.8% decrease body weight gain in F0 males, >20% in F1 adult males, and 12% in F1 females
					Resp	5	15[b]		Nasal cavity lesions in F1 rats included hyperplasia of respiratory/transitional zone epithelium, squamous metaplasia, and subacute inflammation at ≥15 ppm and degeneration of the olfactory epithelium at 45 ppm. ($BMCL_{10\text{-model average}}$ of 0.73 ppm
					Repro	90			
					Develop	45	90		Decreased F1 pup body weight on PND 14 and 21 (5.8–12.2%)

Table 2-1. Levels of Significant Exposure to Acrylonitrile – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Quast et al. 1983									
17	Rat (Sprague-Dawley) 7 M, 7 F	6 months 6 hours/day 5 days/week	0, 20, 80	CS, BW, WI, HE, BC, UR, OW, GN, HP	Bd wt	80			
					Resp	20	80		Slight irritation of nasal turbinates
					Cardio	80			
					Gastro	80			
					Hemato	80			
					Hepatic	80			
					Renal	80			Decreases in urine specific gravity in females at ≥20 ppm and males at 80 ppm; no histological damage
					Ocular	80			
					Endocr	80			
					Immuno	80			
					Repro	80			
Quast et al. 1983									
18	Rat (Sprague-Dawley) 13 M, 13 F	12 months 6 hours/day 5 days/week	0, 20, 80	CS, BW, WI, HE, BC, UR, OW, GN, HP	Bd wt	20 F	80 F		12% decrease in body weight gain in females
					Resp	20	80		Slight irritation of nasal turbinates
					Cardio	80			
					Gastro	20	80		Gastric irritation
					Hemato	80			
					Hepatic	80			
					Renal	80			
					Ocular	80			
					Endocr	80			

Table 2-1. Levels of Significant Exposure to Acrylonitrile – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Immuno	80			
					Repro	80			
Wang et al. 1995									
19	Mouse (Kunming) 12 M	28 days 2 hours/day 6 days/week	0, 28, 41, 55	RX	Repro		28		Increased sperm aberrations
CHRONIC EXPOSURE									
Maltoni et al. 1977									
20	Rat (NS) 30 M, 30 F	52 weeks 5 days/week 4 hours/day	0, 5, 10, 20, 40	BW, CS	Bd wt	40			
					Cancer			5	CEL: multiple tumors
Maltoni et al. 1988									
21	Rat (NS) 114–127 M, F	104 weeks 5 days/week 7 hours/day	0, 60	HP	Cancer			60	CEL: multiple tumors
Quast et al. 1980a									
22	Rat (Sprague-Dawley) 100 M, 100 F	2 years 5 days/week 6 hours/day	0, 20, 80	CS, BW, WI, HE, BC, UR, OW, GN, HP	Death			20	Early deaths
					Bd wt	20	80		Decreased body weight (~10%)
					Resp	20	80		Irritation of the nasal mucosa
					Cardio	80			
					Gastro	80			
					Hemato	80 M			
					Hepatic	80			
					Renal	80			
					Neuro			80	Focal gliosis
					Cancer			20 F	

Table 2-1. Levels of Significant Exposure to Acrylonitrile – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
								80 M	CEL: glial cell tumors[c] in females at ≥20 ppm and males at 80 ppm. At 80 ppm: Zymbal gland carcinoma, squamous epithelial papilloma or carcinoma of the tongue (males only), adenocarcinoma in the small intestine (males only), mammary gland adenocarcinoma (females only)

[a]The number corresponds to entries in Figure 2-2.
[b]Used to derive an intermediate-duration inhalation minimal risk level (MRL) of 0.0008 ppm ($8x10^{-4}$ ppm) for acrylonitrile based on a $BMCL_{10\text{-,model average}}$ of 0.73 ppm, adjusted to continuous duration exposure and converted to a human equivalent concentration ($BMCL_{HEC}$) of 0.024 ppm, and divided by a total uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustments and 10 for human variability); see Appendix A for more detailed information regarding the MRL.
[c]The study investigators diagnosed these tumors as astrocytomas.

BC = blood chemistry; Bd wt or BW = body weight; $BMCL_{10}$ = benchmark concentration lower confidence limit 10%; Cardio = cardiovascular; CEL = Cancer Effect Level; CS = clinical signs; Develop = developmental; DX = developmental toxicity; Endocr = endocrine; F = female(s); FI = food intake; Gastro = gastrointestinal; GD = gestation day; GN = gross necropsy; HE = hematology; Hemato = hematological; HP = histopathology; LC_{50} = median lethal concentration; LOAEL = lowest-observed-adverse-effect level; M = males(s); Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; NX = neurotoxicity; OW = organ weight; PND = postnatal day; Repro = reproductive; Resp = respiratory; SLOAEL = serious lowest-observed-adverse-effect level; UR = urinalysis; WI = water intake

Figure 2-2. Levels of Significant Exposure to Acrylonitrile – Inhalation
Acute (≤14 days)

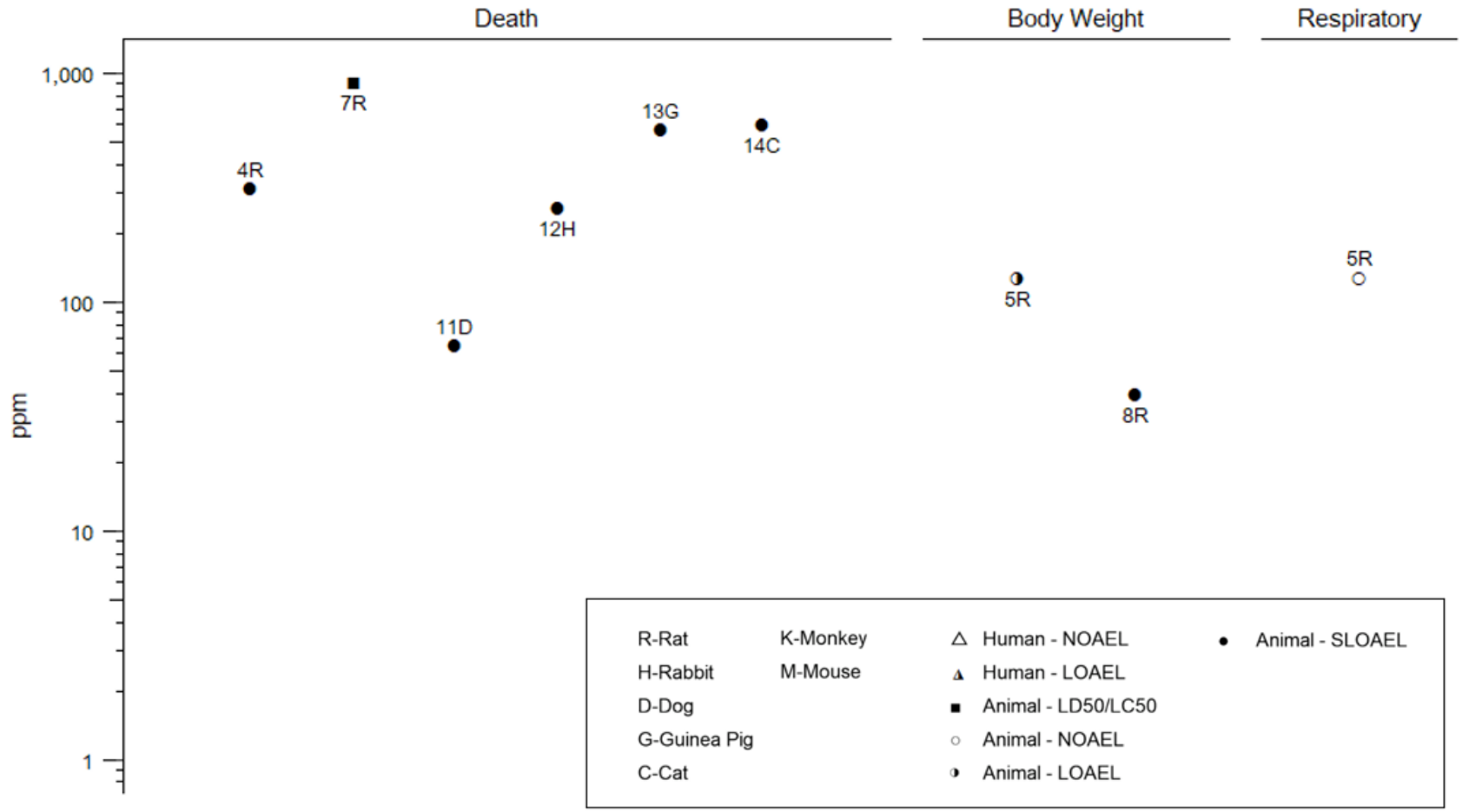


Figure 2-2. Levels of Significant Exposure to Acrylonitrile – Inhalation
Acute (≤14 days)

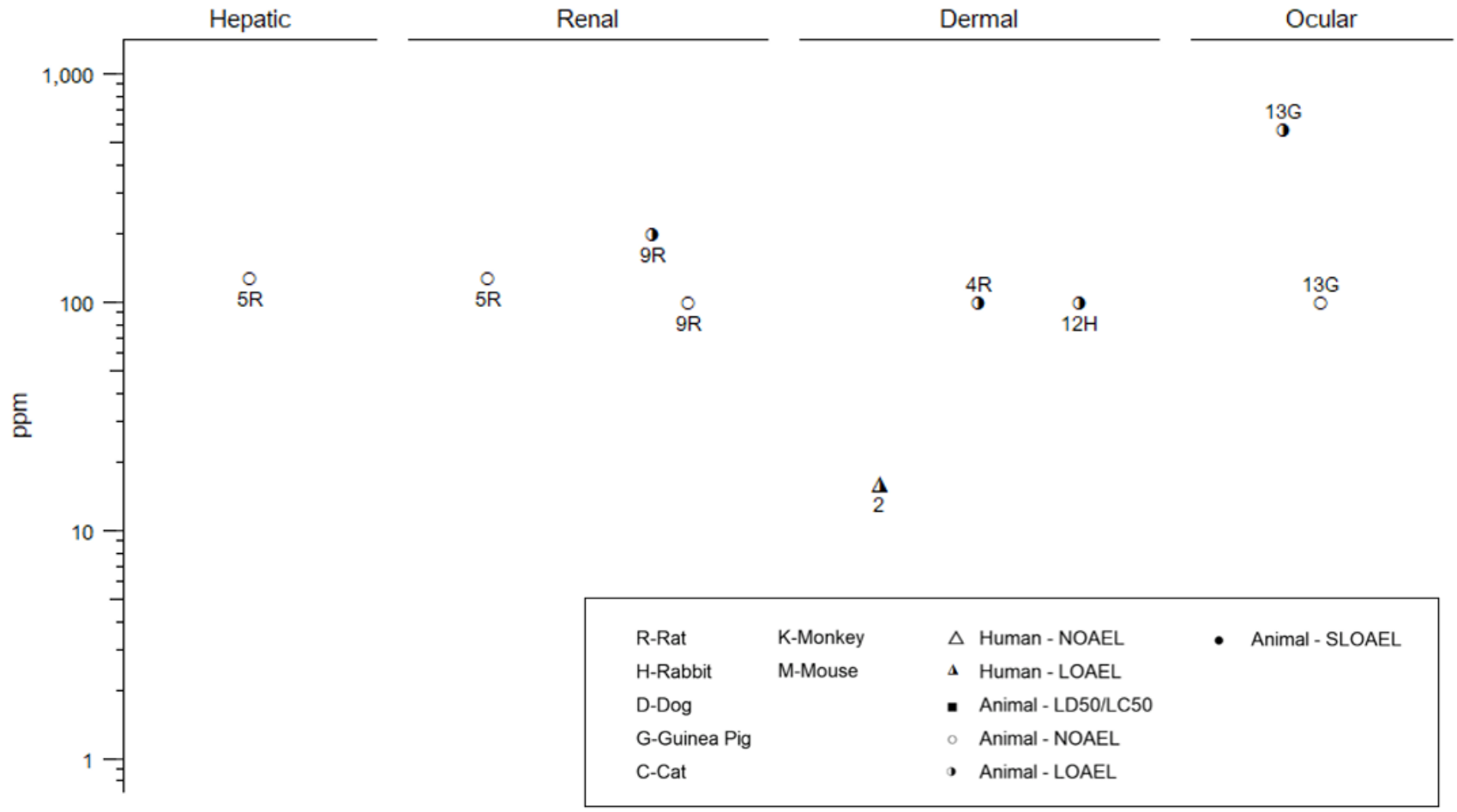


Figure 2-2. Levels of Significant Exposure to Acrylonitrile – Inhalation
Acute (≤14 days)

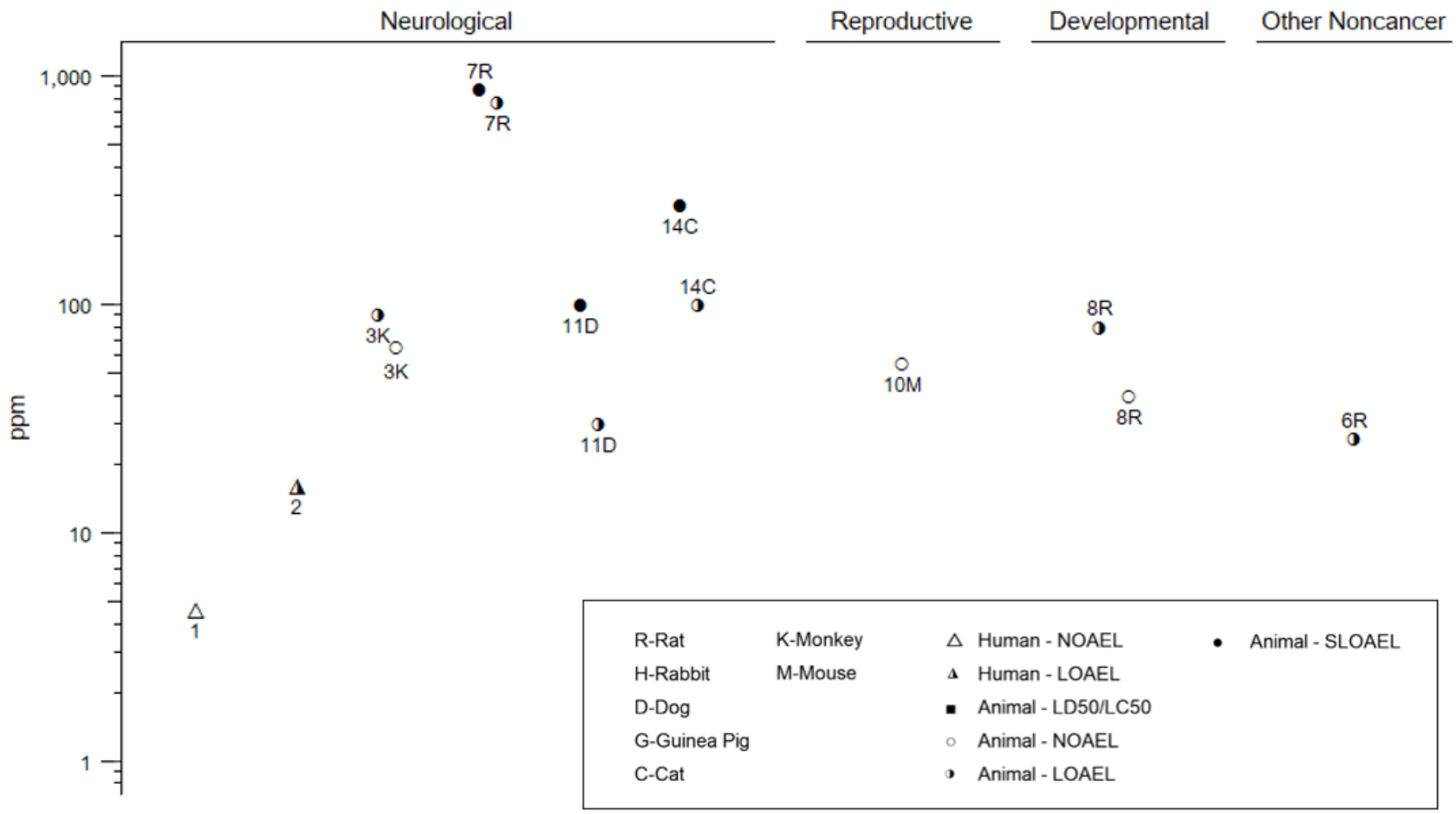


Figure 2-2. Levels of Significant Exposure to Acrylonitrile – Inhalation
Intermediate (15–364 days)

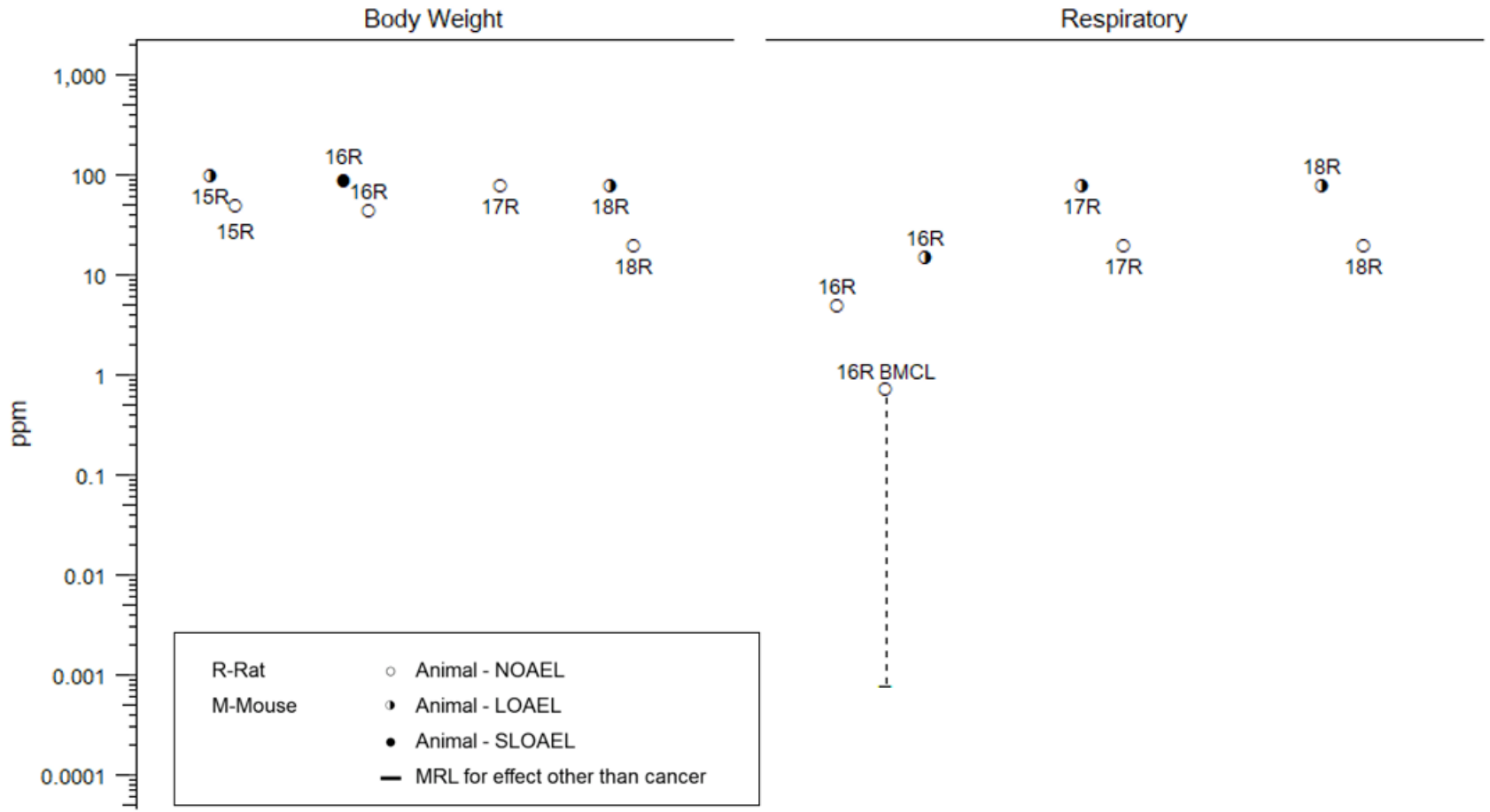


Figure 2-2. Levels of Significant Exposure to Acrylonitrile – Inhalation
Intermediate (15–364 days)

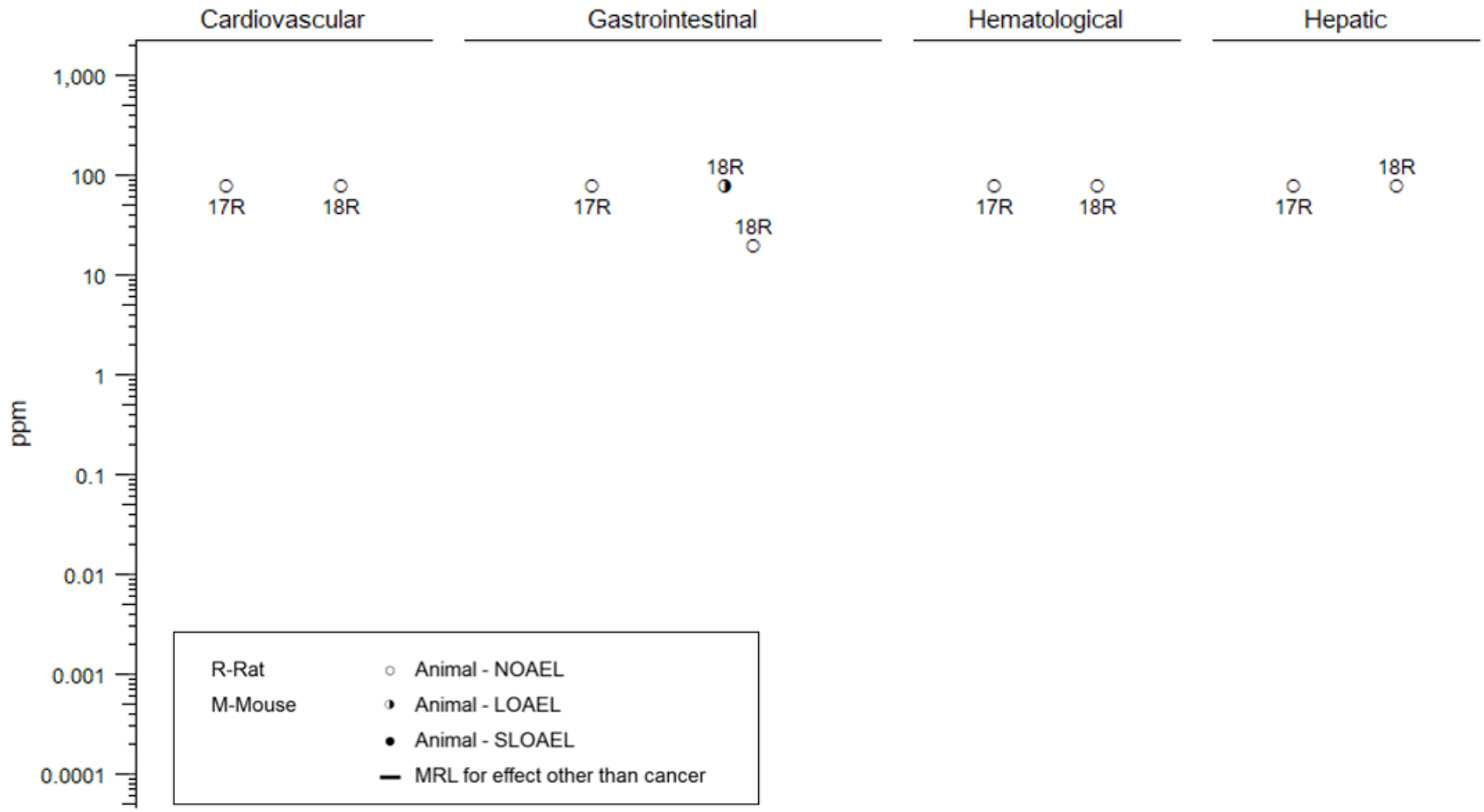


Figure 2-2. Levels of Significant Exposure to Acrylonitrile – Inhalation
Intermediate (15–364 days)

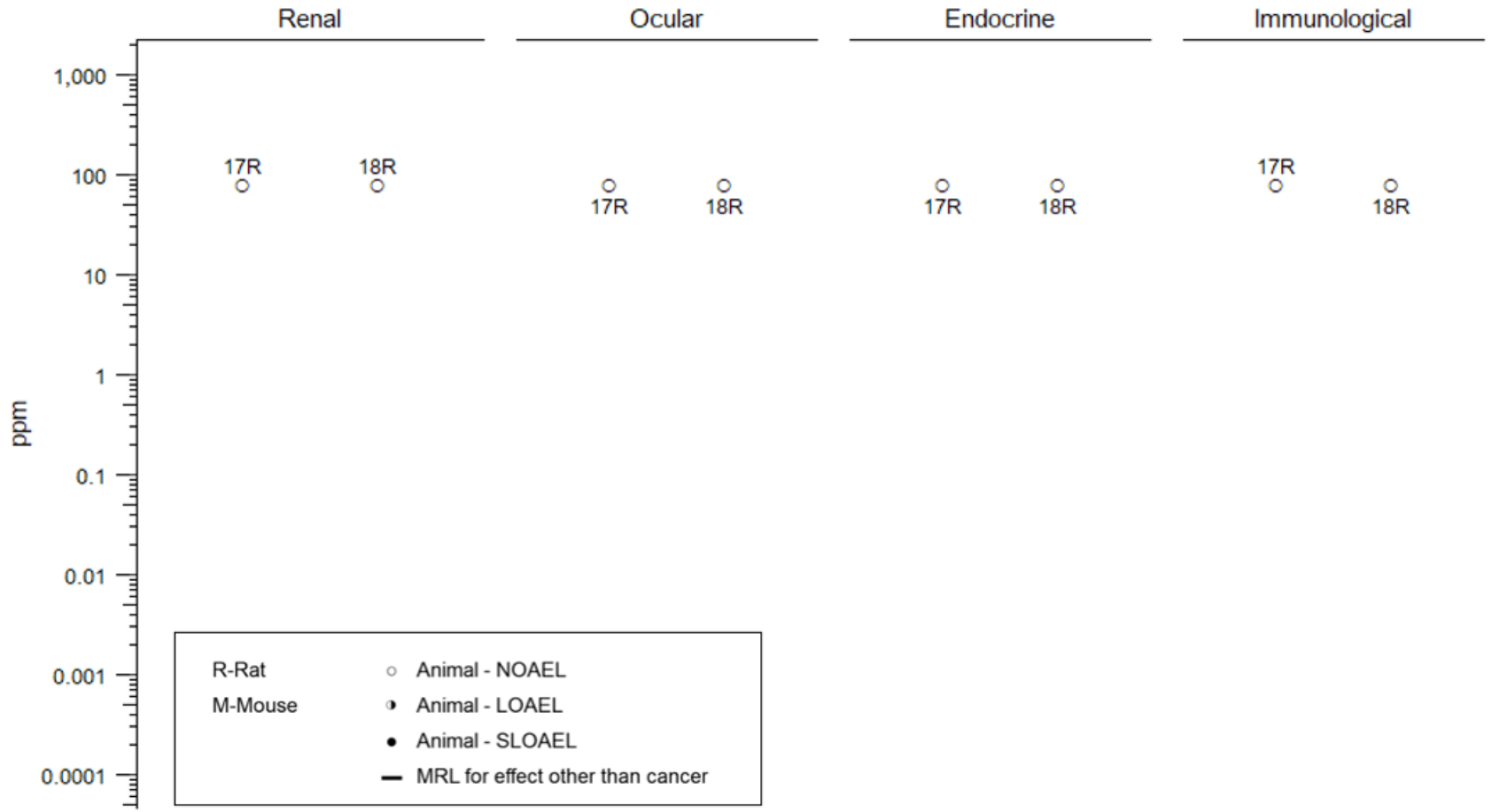


Figure 2-2. Levels of Significant Exposure to Acrylonitrile – Inhalation
Intermediate (15–364 days)

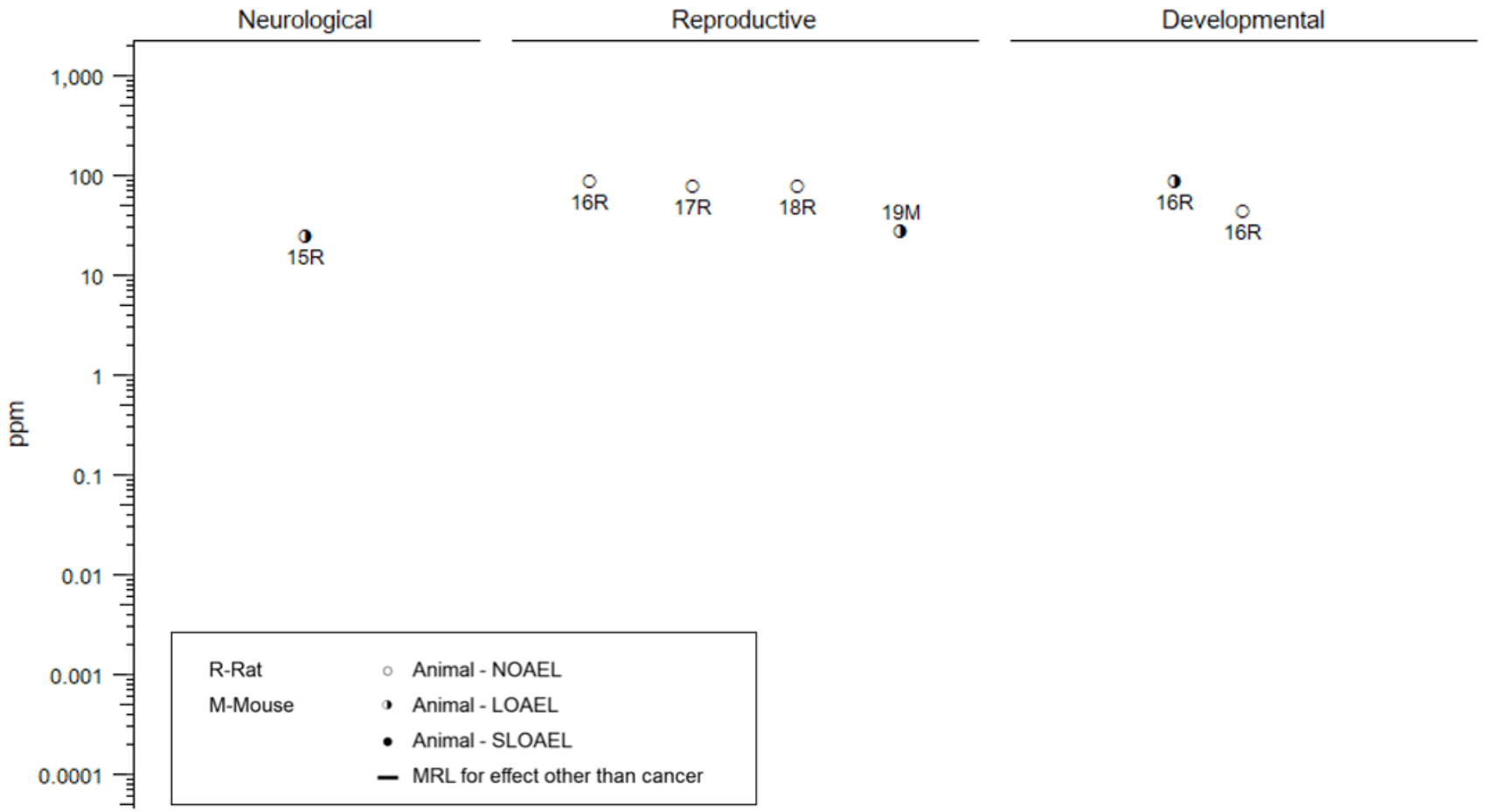


Figure 2-2. Levels of Significant Exposure to Acrylonitrile – Inhalation
Chronic (≥365 days)

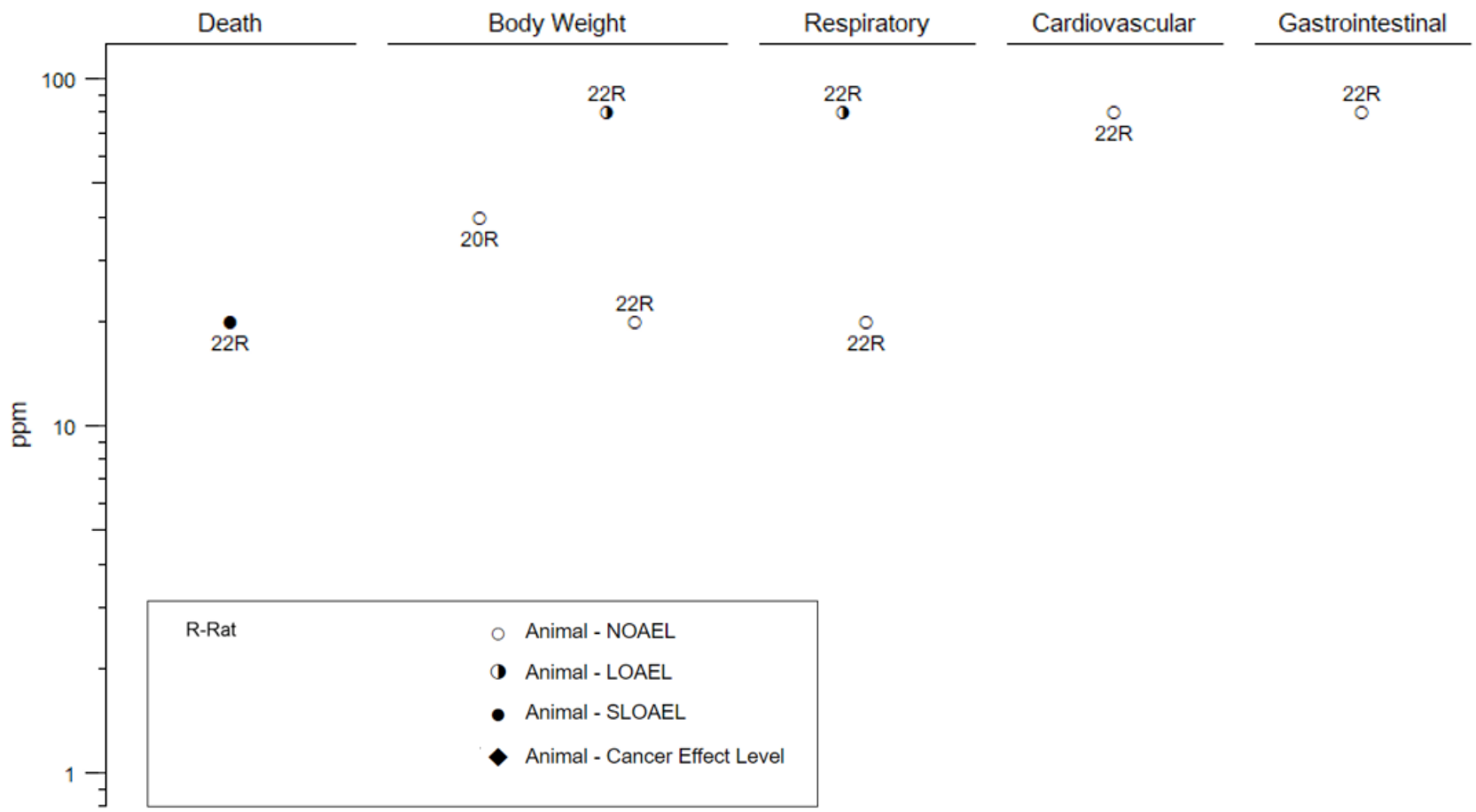


Figure 2-2. Levels of Significant Exposure to Acrylonitrile – Inhalation
Chronic (≥365 days)

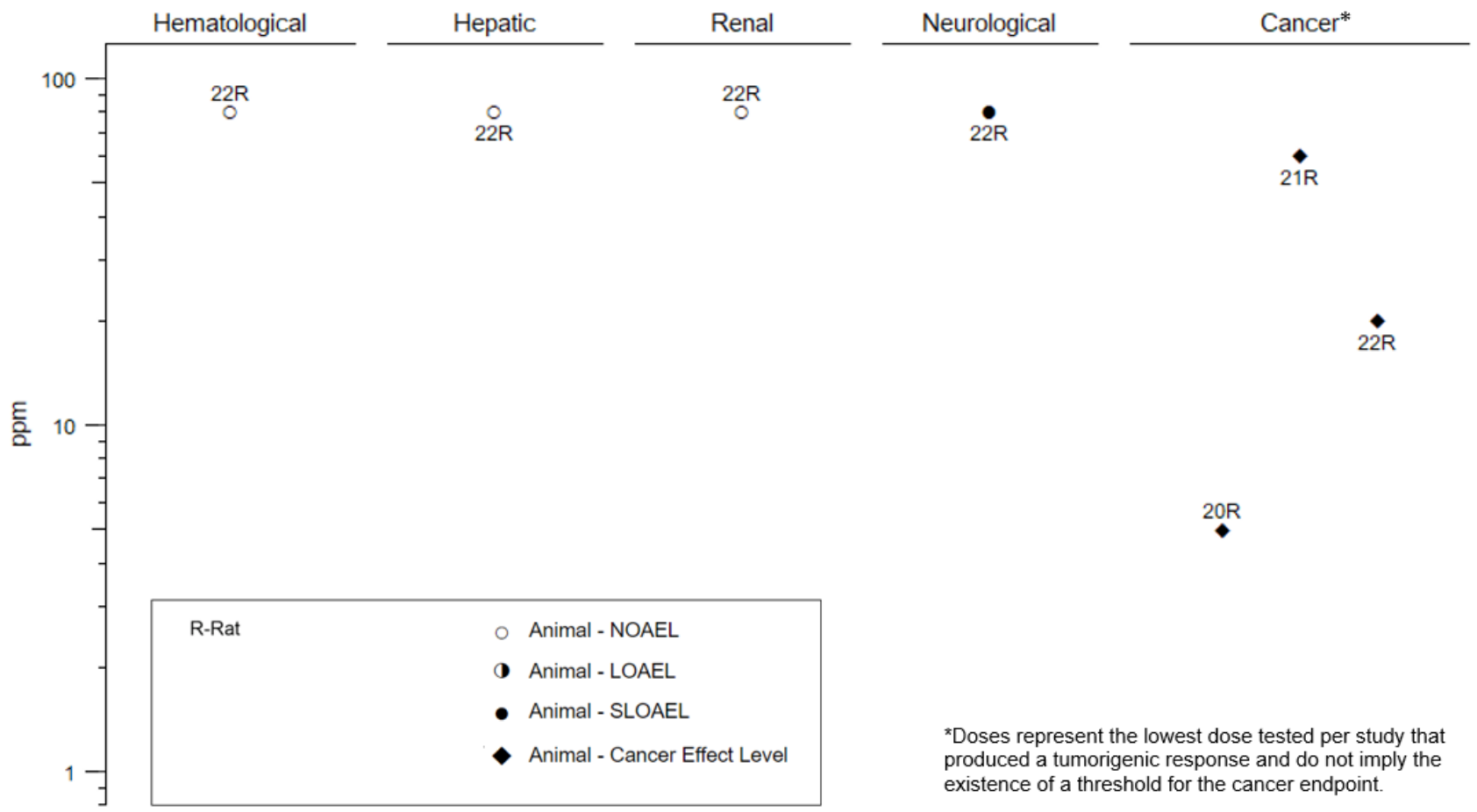


Table 2-2. Levels of Significant Exposure to Acrylonitrile – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
ACUTE EXPOSURE									
DOT 1972									
1	Rat	ND		LE	Death			93	LD_{50}
Farooqui and Ahmed 1983									
2	Rat (Sprague-Dawley) 3–4 M	Once (GW)	0, 80	HE, BC	Hemato		80		Decreased hematocrit, mean cell hemoglobin, and platelet counts
Murray et al. 1978									
3	Rat (Sprague-Dawley) 20–38 F	GDs 6–15 (G)	0, 10, 25, 65	BW, GN, FI, OW, WI, DX	Bd wt	25		65	Decreased maternal weight gain (27–88%)
					Gastro	25	65		Thickening of the non-glandular stomach
					Neuro	25	65		Hyperexcitability and excessive salivation in dams
					Develop	25[b]	65		Decreased fetal body weight (7%) and crown-rump length and increases in the incidence of short tail, short trunk, and missing vertebrae malformations and total malformations ($BMDL_{05\text{-model average}}$ of 9.27 mg/kg/day)
Saillenfait and Sabate 2000									
4	Rat (Sprague-Dawley) 4 F	GD 10 (GW)	0, 100	DX	Bd wt			100	Maternal weight loss (magnitude not reported)
					Develop			100	Abnormal or poor development, misdirected allantois, trunk, and caudal extremities

Table 2-2. Levels of Significant Exposure to Acrylonitrile – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
NTP 2001									
5	Mouse (B6C3F1) 10 M, 10 F	2 days (GW)	0, 5, 10, 20, 40, 60	CS, BW, HE, OW, HP	Death			40	8/10 males and 3/10 females died on study day 1; 100% mortality in males and females at 60 mg/kg
INTERMEDIATE EXPOSURE									
Dang et al. 2017									
6	Rat (Sprague Dawley), 10 M	12 weeks 6 days/week (GO)	0, 20	BW, OW, HP, RX	Repro		20		Decreased sperm motility and sperm concentration
Friedman and Beliles 2002 (Data also reported in Beliles et al. 1980)									
7	Rat (CD BR) 10–15 , 20–30 F	24 (M) or 48 (F) weeks (3-generation study) (W)	M: 0, 11, 37; F: 0, 20, 40	CS, DX, FX, HP, GN	Bd wt	20 F	40 F		Decreased body weight (~15%) after 10 weeks with decreased food and water consumption
						11 M	37 M		
					Neuro	40 F			No overt signs of neurotoxicity
						37 M			
					Repro	40 F			
						37 M			
					Develop			20	Decreased pup viability at ≥20 mg/kg/day in F1b generation and at 40 mg/kg/day in other generations
					Cancer			40 F	CEL: glial cell tumors[c] and Zymbal gland tumors in F0 and F1 females

Table 2-2. Levels of Significant Exposure to Acrylonitrile – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Gagnaire et al. 1998									
8	Rat (Sprague-Dawley) 12 M	12 weeks 5 days/week (GO)	0, 12.5, 25, or 50	BW, OF	Bd wt	25	50		17% decrease in body weight gain
					Neuro	25		50	Decreased sensory motor conduction velocity; weakness in the hindlimbs and inability to rear
Ghanayem et al. 1997									
9	Rat (Fischer-344) 12 M	6 weeks (GW)	0, 12, 23	BW, HP	Bd wt	23			
					Gastro	12	23		Mild squamous hyperplasia in forestomach
					Hepatic	23			
Humiston et al. 1975									
10	Rat (Sprague-Dawley) 27 M, 23 F	90 days (W)	M: 0, 4, 8, 17, 38; F: 0, 5, 10, 22, 42	BW, HP	Bd wt	10	22		Decreased weight gain
					Cardio	42 F			
						38 M			
					Gastro	42 F			
						38 M			
					Hepatic	42 F			
						38 M			
					Renal	42 F			
						38 M			
					Neuro	42 F			
						38 M			
					Repro	42 F			
						38 M			

Table 2-2. Levels of Significant Exposure to Acrylonitrile – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Johannsen and Levinskas 2002a (results also reported in Bio/Dynamics 1980b)									
11	Rat (Fischer-344) 100 M, 100 F	6–12 months (W)	M: 0.1, 0.3, 0.8, 2.5, 8.4; F: 0.1, 0.4, 1.3, 3.7, 10.9	BW, FI, HP, OW, UR, WI	Bd wt	10.9 F 8.4 M			
					Hemato	3.7 F 8.4 M	10.9 F		Decreased hemoglobin and increased reticulocyte levels in females
Quast 2002 (results also reported in Quast et al. 1980b)									
12	Rat (Sprague-Dawley) 48 M, 48 F	1 year (W)	M: 0, 3.4, 8.5, 21.3; F; 0, 4.4, 10.8, 25.0	BC, BW, FI, WI	Death			25 F	29% mortality in females
					Bd wt	10.8 F 3.4 M	25 F 8.5 M		Decreased weight gain with concomitant decreases in food and water consumption; 11% in males at 8.5 mg/kg/day and 18% in females at 25 mg/kg/day
					Resp	25 F 21.3 M			
					Cardio	25 F 21.3 M			
					Gastro	4.4 F 3.4 M	10.8 F 8.5 M[d]		Squamous cell metaplasia of the forestomach ($BMDL_{10}$ of 2.48 mg/kg/day)
					Hemato	25 F 21.3 M			
					Hepatic	25 F 21.3 M			
					Renal	25 F 21.3 M			
					Immuno	25 F 21.3 M			

Table 2-2. Levels of Significant Exposure to Acrylonitrile – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Shi et al. 2021									
13	Rat (Sprague-Dawley) 12 M	28 days 6 days/week (GO)	0, 46	CS, BW, OW, HP, RX	Repro		46		Increased sperm head and tail morphological alterations
Szabo et al. 1984									
14	Rat (Sprague-Dawley) 6–10 F	3 weeks (W)	0, 14, 70, 280	OW, HP, CS	Endocr	14		70	Adrenal atrophy
Luo et al. 2022									
15	Mouse (Kunming) 50 F	28 days (GW)	0, 5, 10, 20	BW, OW, HP, RX, DX	Bd wt	10		20	Decreased terminal body weight (29%)
					Repro		5		Follicular development effects: increased atretic follicles, decreased preovulatory follicles, increased ratio of follicles with apoptotic granulosa cells, increased inflammation in follicles, and decreased oocyte development
					Develop			5	Decreased number of pups/live births
NTP 2001									
16	Mouse (B6C3F1) 10 M, 10 F	14 weeks 5 days/week (GW)	0, 5, 10, 20, 40, 60	CS, BW, HE, OW, HP	Death			40	8/10 males and 3/10 females died on study day 1; 100% mortality in males and females at 60 mg/kg
					Bd wt	40 F 20 M			

Table 2-2. Levels of Significant Exposure to Acrylonitrile – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Resp	40 F			
						20 M			
					Cardio	40 F			
						20 M			
					Gastro	20 F 20 M	40 F		Forestomach inflammation and hyperplasia in females at 40 mg/kg
					Hemato	10 M	5 F 20 M		Decreased hemoglobin levels in females at ≥5 mg/kg; decreased total leukocytes and lymphocytes in males at 20 mg/kg and females at 40 mg/kg
					Musc/skel	40 F			
						20 M			
					Hepatic	40 F			
						20 M			
					Renal	40 F			
						20 M			
					Endocr	40 F			
						20 M			
					Immuno	40 F			
						20 M			
					Repro	40 F			
						20 M			

Table 2-2. Levels of Significant Exposure to Acrylonitrile – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Tandon et al. 1988									
17	Mouse (CD-1) 12 M	60 days (G)	0, 1, 10	BI, BW, OW, HP, RX	Bd wt	10			
					Repro	1		10	Decreased sperm count, degeneration of seminiferous tubules
Quast et al. 1975									
18	Dog (NS) 4 M, F	6 months (W)	M: 0, 10, 16, 17; F: 8, 17, 18	CS, HE, HP	Death	10		16	5/8 deaths
					Bd wt	10		16	Weight loss
					Gastro	10		16	Esophageal ulcerations
					Hemato	10	16		Decreased RBC
					Renal	18			
					Neuro	10		16	Depression, lethargy
CHRONIC EXPOSURE									
Bigner et al. 1986									
19	Rat (Fischer-344) 50–198 M, 50–202 F 18 months (W)		M: 0, 13, 65; F: 0, 14, 72	BW, CS	Death			14 F	Increased mortality
								13 M	
					Bd wt		14 F	72 F	LOAEL: Decreases in weight gain SLOAEL: Weight loss
							13 M	65 M	
					Neuro	14 F		72 F	Neurological signs of toxicity including paralysis, seizures, and decreased activity
						13 M		65 M	
					Cancer			72 F	CEL: brain tumor
								65 M	

Table 2-2. Levels of Significant Exposure to Acrylonitrile – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Gallagher et al. 1988									
20	Rat (Sprague-Dawley) 20 M	2 years (W)	0, 1.5. 7.1, 28	FI, WI, BW, HP	Cancer			28	CEL: Zymbal's gland squamous carcinoma
Johannsen and Levinskas 2002b (results also reported in Bio/Dynamics 1980a)									
21	Rat (Sprague-Dawley) 100 M, 100 F	M: 22 months F: 19 months (W)	M: 0, 0.09, 8.0 F: 0, 0.15, 10.7	CS, FI, WI, BW, HE, BC, UR, OW, HP	Death			10.7 F 8 M	Early deaths
					Bd wt	10.7 F 0.09 M	8 M		10% decreased body weight
					Resp	10.7 F 8 M			
					Cardio	10.7 F 8 M			
					Gastro	0.15 F	10.7 F 0.09 M[e]		Increased severity of squamous cell hyperplasia in forestomach
					Hemato	10.7 F 0.09 M	8 M		Decreased hemoglobin, increased reticulocytes
					Hepatic	10.7 F 8 M			
					Renal	0.15 F 8 M	10.7 F		Transitional hyperplasia
					Dermal	10.7 F 8 M			
					Ocular	10.7 F 8 M			

Table 2-2. Levels of Significant Exposure to Acrylonitrile – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Endocr	10.7 F 8 M			
					Immuno	10.7 F 8 M			
					Neuro	10.7 F 8 M			
					Repro	10.7 F 8 M			
					Other noncancer	10.7 F 8 M			
					Cancer			10.7 F 8 M	CEL: brain and spinal glial cell tumors[c], Zymbal's gland carcinoma, forestomach papilloma
Johannsen and Levinskas 2002b (results also reported in Bio/Dynamics 1980c)									
22	Rat (Sprague-Dawley) 100 M, 100 F	20 months 7 days/week (GW)	0, 0.1, 10	CS, FI, WI, BW, HE, BC, UR, OW, HP	Death			10	Early deaths
					Bd wt	10 F 0.1 M	10 M		14% decreased body weight
					Resp	10			
					Cardio	10			
					Gastro	0.1	10		Increased severity of forestomach squamous hyperplasia
					Hemato	10 F 0.1 M	10 M		Decreased hemoglobin, hematocrit, and erythrocyte levels
					Hepatic	10			
					Renal	0.1	10		Transitional cell hyperplasia
					Dermal	0.1	10		Epidermal inclusion cysts

Table 2-2. Levels of Significant Exposure to Acrylonitrile – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Ocular	10			
					Endocr	10			
					Neuro	10			
					Repro	10			
					Other noncancer	10			
					Cancer			10	CEL: brain glial cell tumors[c], Zymbal's gland carcinoma, forestomach carcinoma, intestinal adenocarcinoma, mammary gland carcinoma
Johannsen and Levinskas 2002a (results also reported in Bio/Dynamics 1980b)									
23	Rat (Fischer-344) 100 M, 100 F	M: 26 months F: 23 months (W)	M: 0.1, 0.3, 0.8, 2.5, 8.4; F: 0.1, 0.4, 1.3, 3.7, 10.9	BW, FI, HP, OW, UR, WI	Death			1.3 F 8.4 M	Early deaths
					Bd wt	3.7 F 2.5 M	10.9 F 8.4 M		Decreased body weight (~12%)
					Resp	10.9 F 8.4 M			
					Cardio	10.9 F 8.4 M			
					Gastro	0.1 F 0.1 M	0.4 F 0.3 M		Hyperplasia and/or hyperkeratosis in forestomach
					Hemato	3.7 F 8.4 M	10.9 F		Decreased hemoglobin and increased reticulocytes in females
					Hepatic	10.9 F 8.4 M			

Table 2-2. Levels of Significant Exposure to Acrylonitrile – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Renal	10.9 F			
						8.4 M			
					Dermal	10.9 F	8.4 M		Epidermal inclusion cysts in males
						2.5 M			
					Endocr	10.9 F			
						8.4 M			
					Immuno	10.9 F			
						8.4 M			
					Neuro	10.9 F			
						8.4 M			
					Repro	10.9 F			
						8.4 M			
					Cancer			0.3 M	CEL: squamous cell papilloma/carcinoma in forestomach at ≥0.3 mg/kg/day neoplastic tumors in Zymbal gland, brain, spinal cord, and mammary gland
Maltoni et al. 1977									
24	Rat (NS) 30 M, 30 F	52 weeks 3 times/week 1 times/day (G)	0, 5	BW, CS	Other noncancer	5			
					Cancer			5	CEL: multiple tumors
Quast 2002 (results also reported in Quast et al. 1980b)									
25	Rat (Sprague-Dawley) 48 M, 48 F	2 years (W)	M: 0, 3.4, 8.5, 21; F: 0, 4.4, 10.8, 25	BC, BW, FI, WI, HP	Death			4.4 F 21.3 M	Early deaths, 45.8% mortality by study days 481–510 in males and 41.7% in females by study days 541–570

Table 2-2. Levels of Significant Exposure to Acrylonitrile – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Bd wt		3.4		Decreased weight gain with concomitant decreases in water intake and food intake
					Resp	25 F 21.3 M			
					Cardio	25 F 21.3 M			
					Gastro	3.5 M	4.4 F 8.5 M		Hyperplasia/hyperkeratosis of forestomach at 8.5 mg/kg/day in males and ≥4.4 mg/kg/day
					Hemato	25 F 21.3 M			
					Musc/skel	25 F 21.3 M			
					Hepatic	25 F 21.3 M			
					Renal	25 F 21.3 M			
					Ocular	25 F 21.3 M			
					Immuno	25 F 21.3 M			
					Neuro	21.3 M		4.4 F	Gliosis and perivascular cuffing in the brain
					Cancer			4.4 F 3.4 M	CEL: brain glial cell tumors[c] at 3.4/4.4 mg/kg/day; Zymbal gland carcinoma forestomach

Table 2-2. Levels of Significant Exposure to Acrylonitrile – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
NTP 2001 (results of this study were also published by Ghanayem et al. 2002)									
26	Mouse (B6C3F1) 50 M, 50 F	104 weeks 5 days/week (GW)	0, 2.5, 10, 20	CS, BW, HP	Death			20	Decreased survival
					Bd wt	20			
					Resp	20			
					Cardio	20			
					Gastro	10 F	20 F		
						2.5 M	10 M		Focal epithelial hyperplasia in the forestomach in males at ≥10 mg/kg and females at 20 mg/kg; hyperkeratosis in males at 20 mg/kg
					Hemato	20			No histological alterations in bone marrow
					Musc/skel	20			
					Hepatic	20			
					Renal	20			
					Ocular	20			
					Endocr	20			
					Immuno	20			
					Neuro	20			
					Repro		2.5		Increase ovarian cysts at ≥2.5 mg/kg; ovarian atrophy at ≥10 mg/kg

Table 2-2. Levels of Significant Exposure to Acrylonitrile – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Cancer			10	CEL: forestomach and Harderian gland tumors in males and females and ovarian and lung tumors in females

[a]The number corresponds to entries in Figure 2-3.
[b]Used to derive an acute-duration oral MRL of 0.09 mg/kg/day for acrylonitrile based on a $BMDL_{05\text{-model average}}$ of 9.27 mg/kg/day and divided by a total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability); see Appendix A for more detailed information regarding the MRL.
[c]Study investigators diagnoses these tumors as astrocytomas.
[d]Used to derive an intermediate-duration oral MRL of 0.02 mg/kg/day for acrylonitrile based on a $BMDL_{10}$ of 2.48 mg/kg/day and divided by a total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability); see Appendix A for more detailed information regarding the MRL.
[e]Used to derive a chronic-duration oral MRL of 0.00009 mg/kg/day ($9x10^{-5}$ mg/kg/day) for acrylonitrile based on a LOAEL of 0.09 mg/kg/day and divided by a total uncertainty factor of 1,000 (10 for the use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability); see Appendix A for more detailed information regarding the MRL.

BC = blood chemistry; Bd wt or BW = body weight; BI = biochemical changes; $BMDL_{05}$ = benchmark dose lower confidence limit 10%; $BMDL_{10}$ = benchmark dose lower confidence limit 10%; Cardio = cardiovascular; CEL = Cancer Effect Level; CNS = central nervous system; CS = clinical signs; Develop = developmental; DX = developmental toxicity; Endocr = endocrine; F = female(s); FI = food intake; FX = fetal toxicity; (G) = gavage; (GW) = gavage in water; Gastro = gastrointestinal; GD = gestation day; GN = gross necropsy; GSH = glutathione; HE = hematology; Hemato = hematological; HP = histopathology; LD_{50} = median lethal dose; LOAEL = lowest-observed-adverse-effect level; M = males(s); MRL = Minimal Risk Level; Musc/skel = musculoskeletal; ND = no data; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; OW = organ weight; RBC = red blood cell; Repro = reproductive; Resp = respiratory; RX = reproductive toxicity; SLOAEL = serious lowest-observed-adverse-effect level; UR = urinalysis; (W) = drinking water; WI = water intake

Figure 2-3. Levels of Significant Exposure to Acrylonitrile – Oral
Acute (≤14 days)

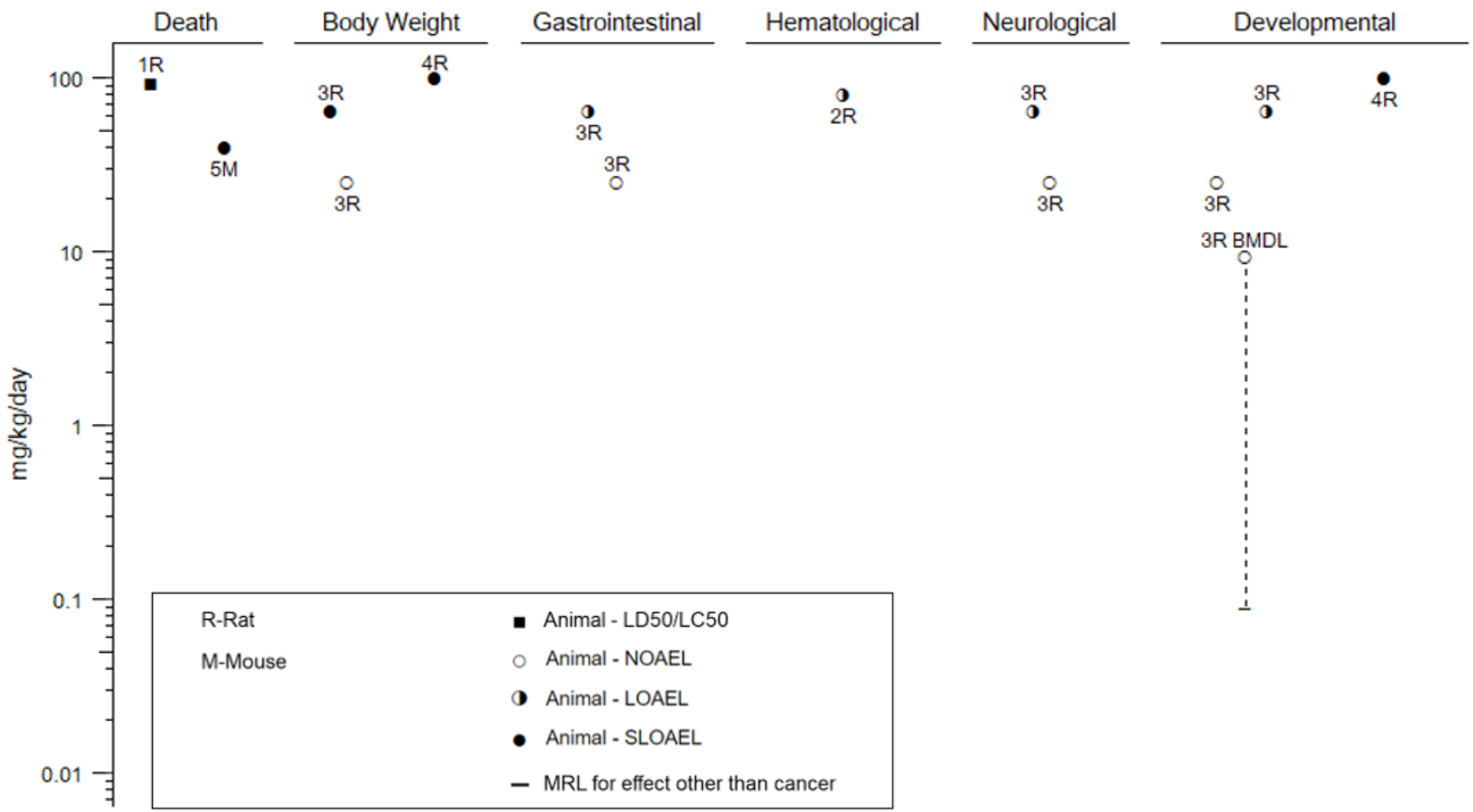


Figure 2-3. Levels of Significant Exposure to Acrylonitrile – Oral
Intermediate (15–364 days)

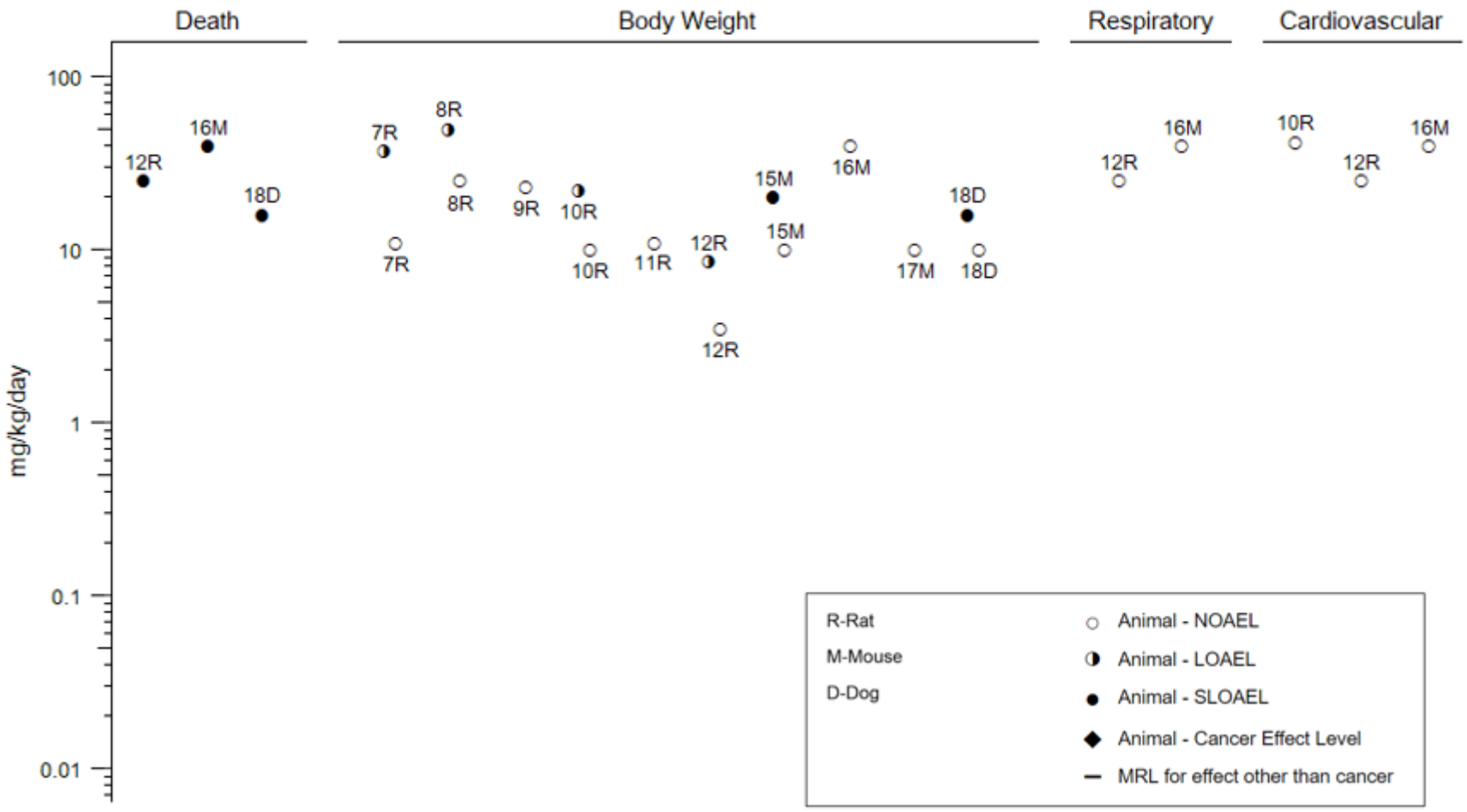


Figure 2-3. Levels of Significant Exposure to Acrylonitrile – Oral
Intermediate (15–364 days)

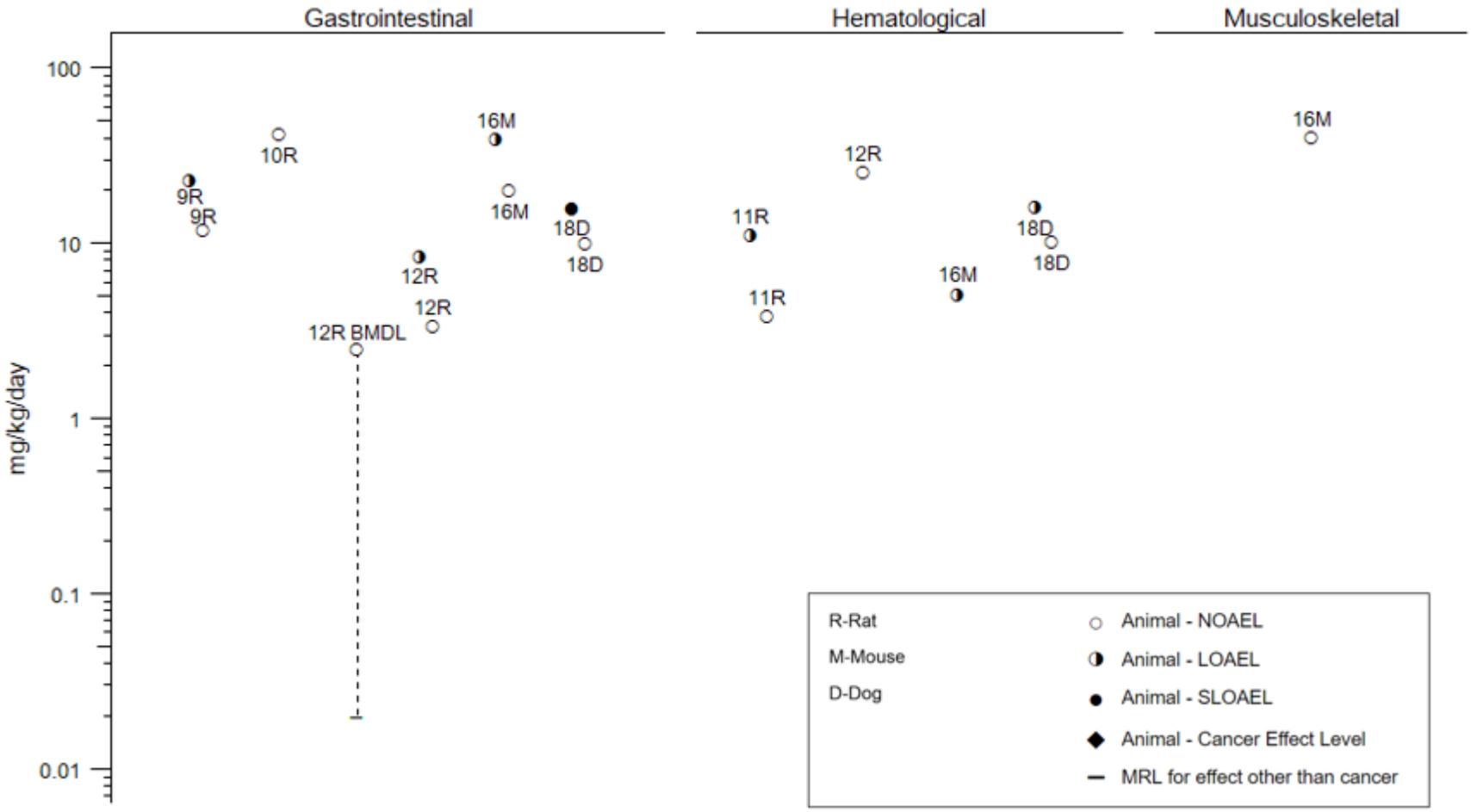


Figure 2-3. Levels of Significant Exposure to Acrylonitrile – Oral
Intermediate (15–364 days)

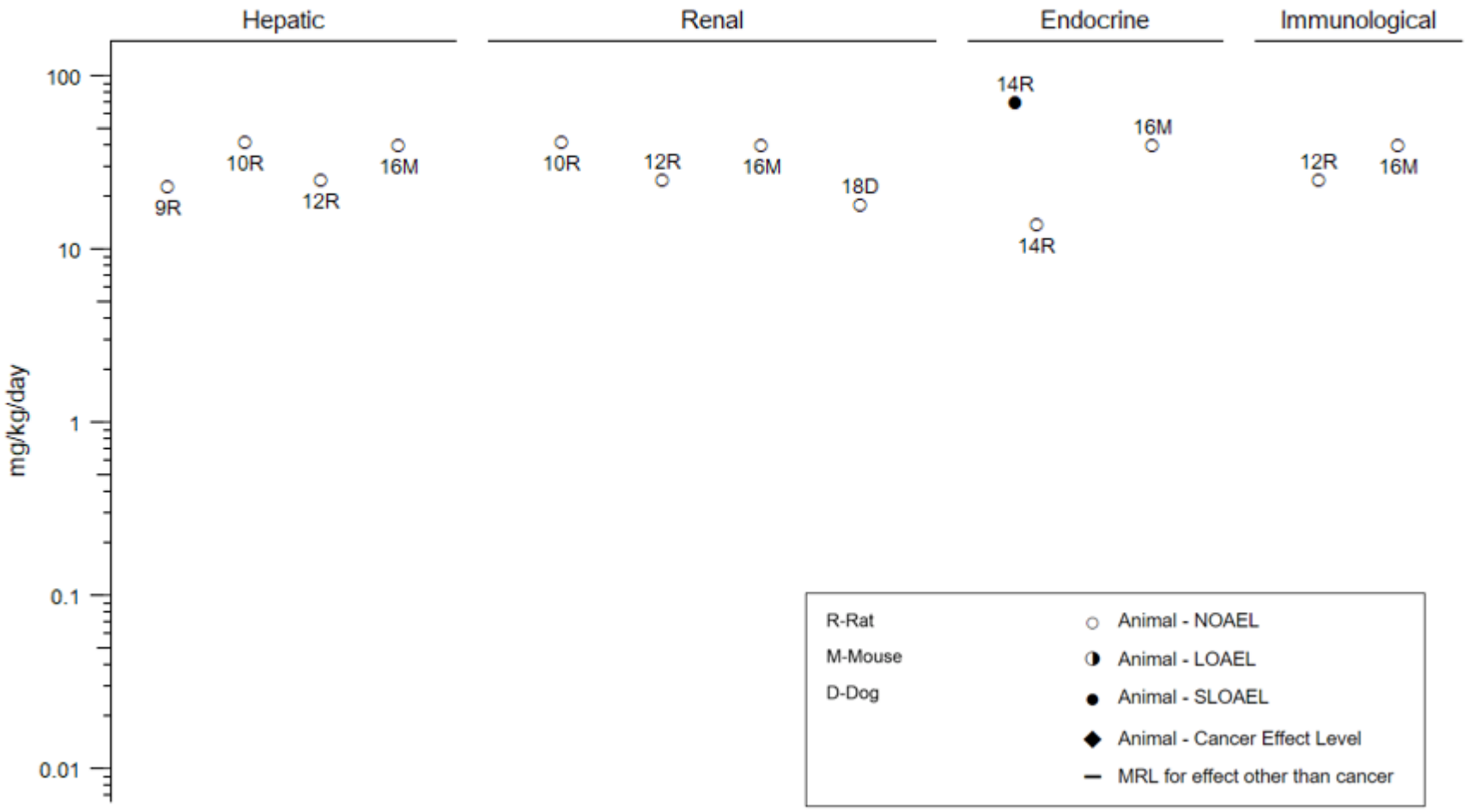


Figure 2-3. Levels of Significant Exposure to Acrylonitrile – Oral
Intermediate (15–364 days)

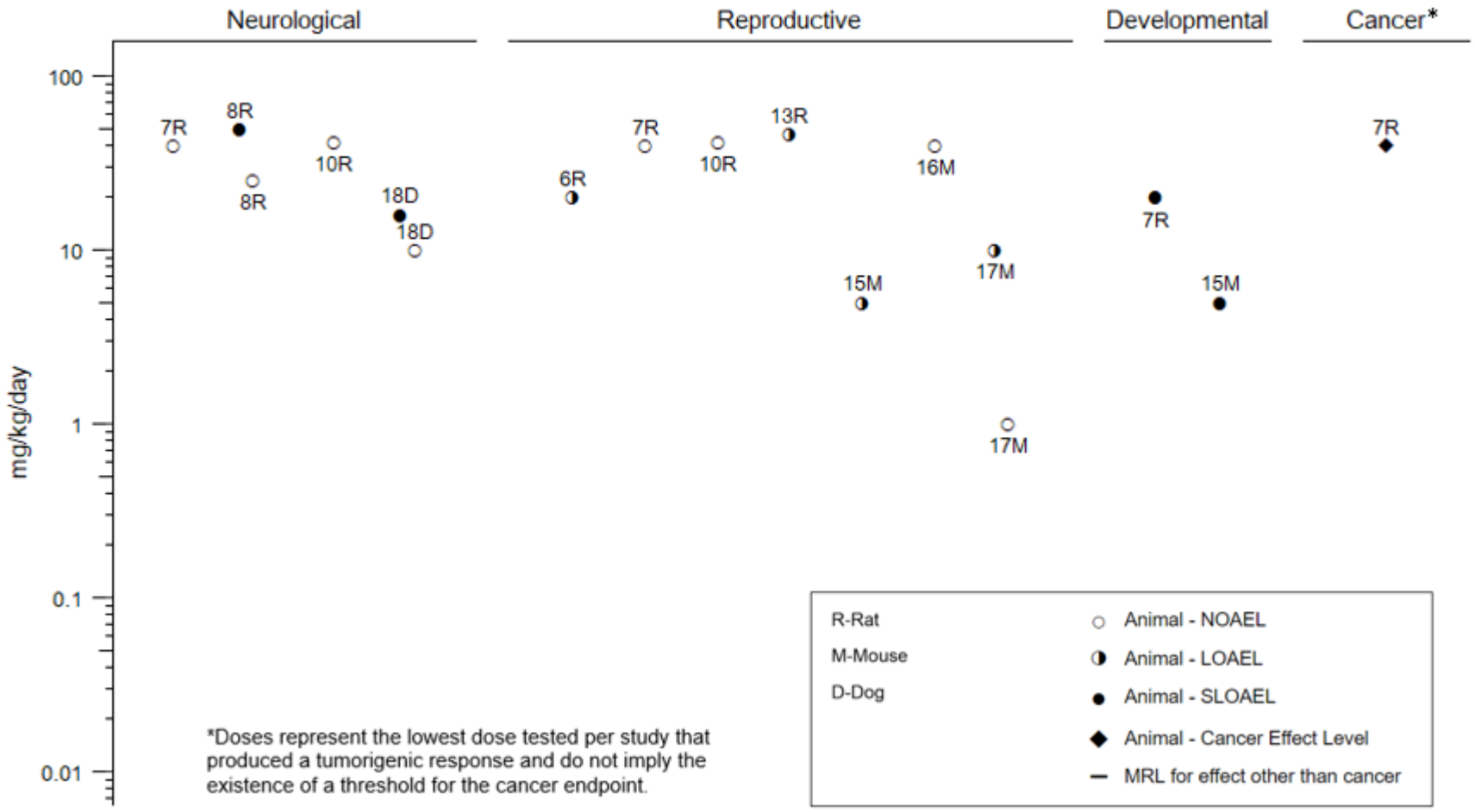


Figure 2-3. Levels of Significant Exposure to Acrylonitrile – Oral
Chronic (≥365 days)

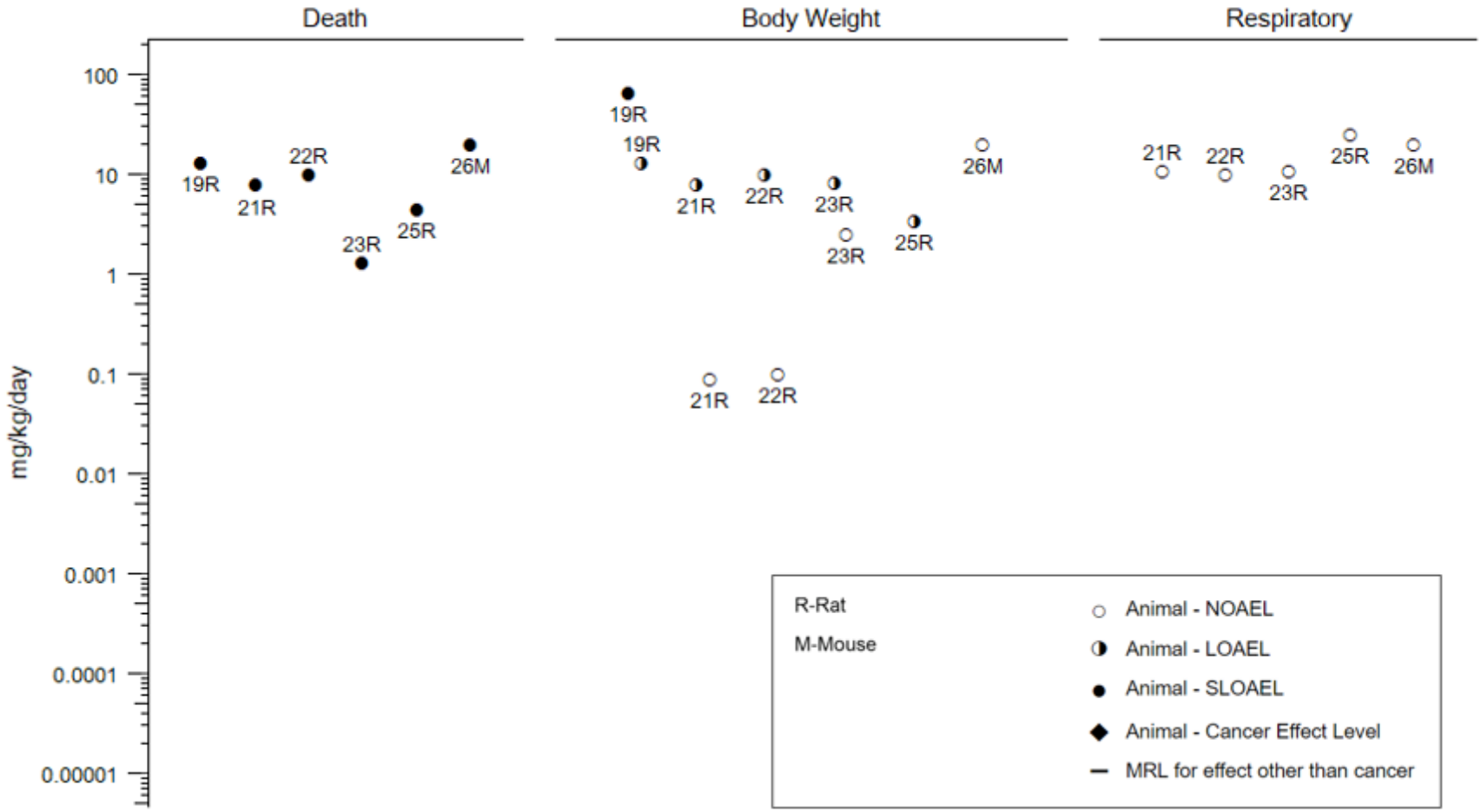


Figure 2-3. Levels of Significant Exposure to Acrylonitrile – Oral
Chronic (≥365 days)

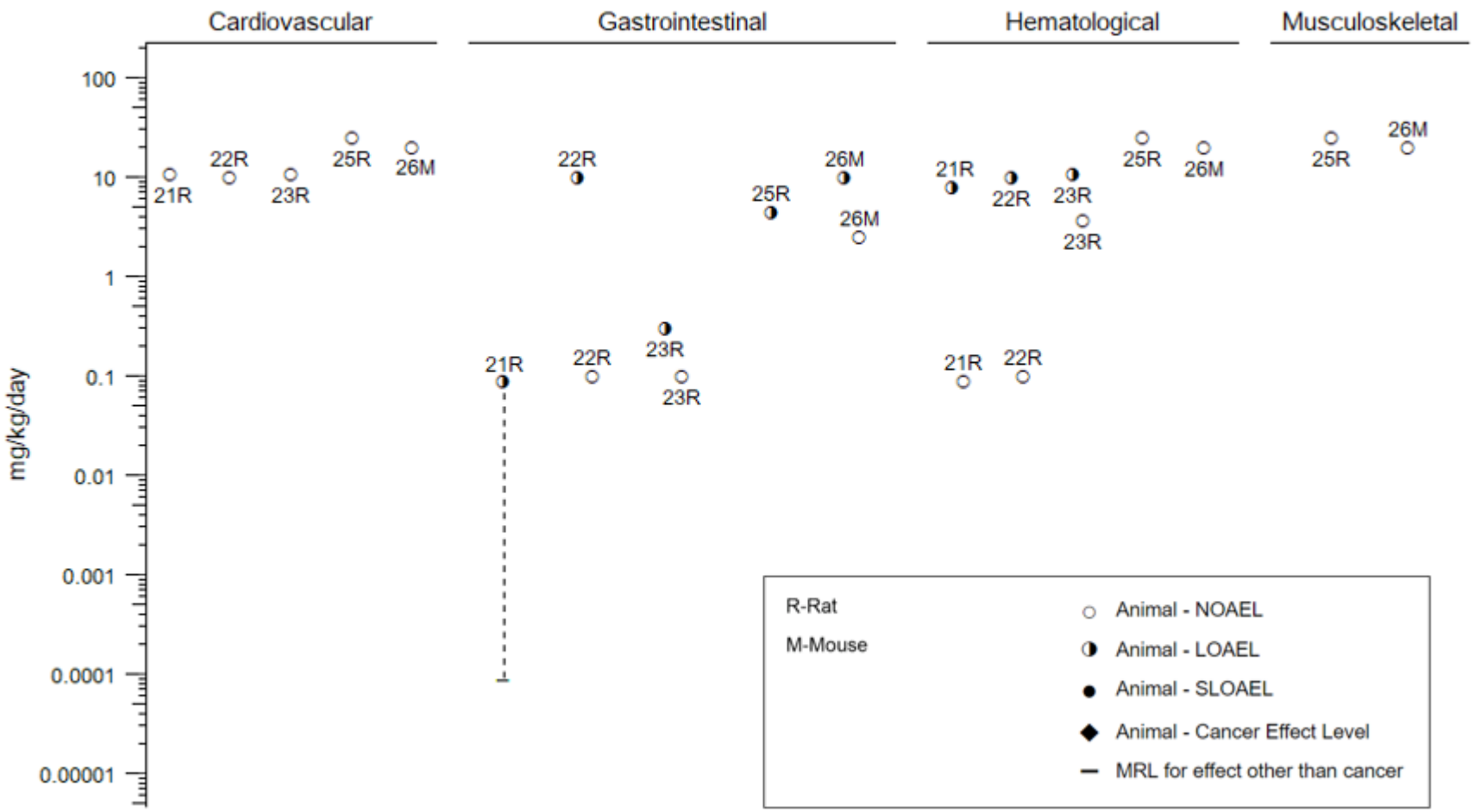


Figure 2-3. Levels of Significant Exposure to Acrylonitrile – Oral
Chronic (≥365 days)

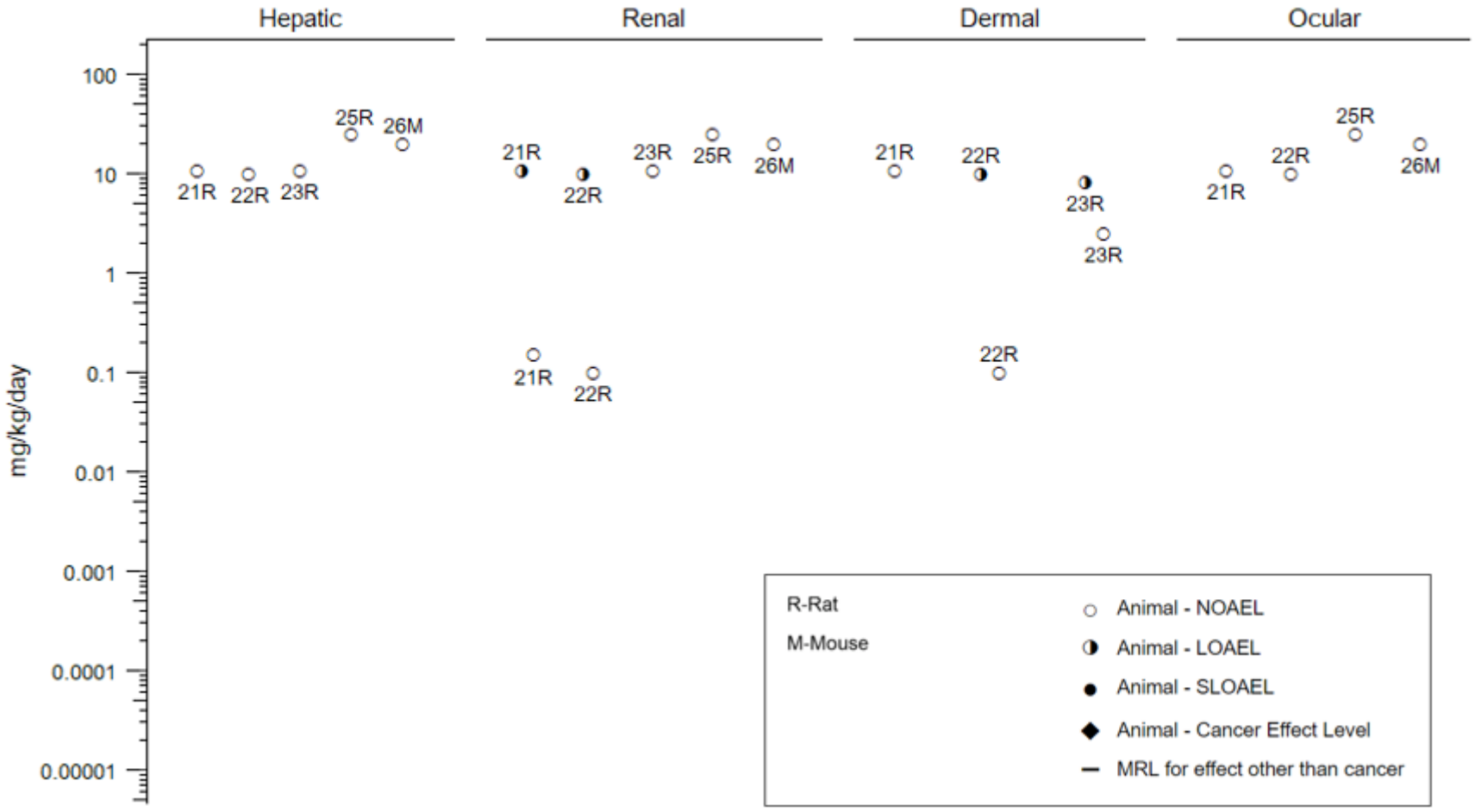


Figure 2-3. Levels of Significant Exposure to Acrylonitrile – Oral
Chronic (≥365 days)

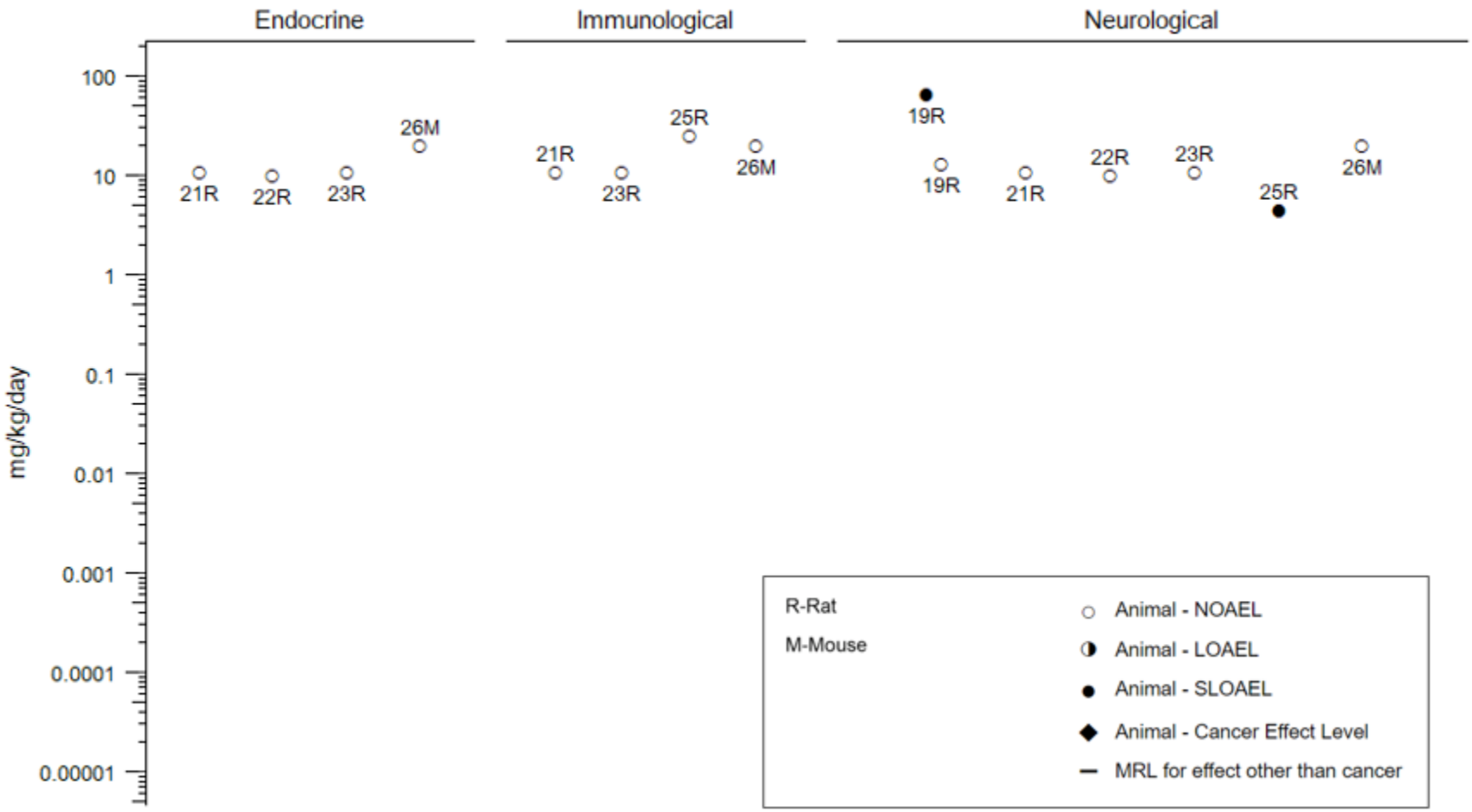


Figure 2-3. Levels of Significant Exposure to Acrylonitrile – Oral
Chronic (≥365 days)

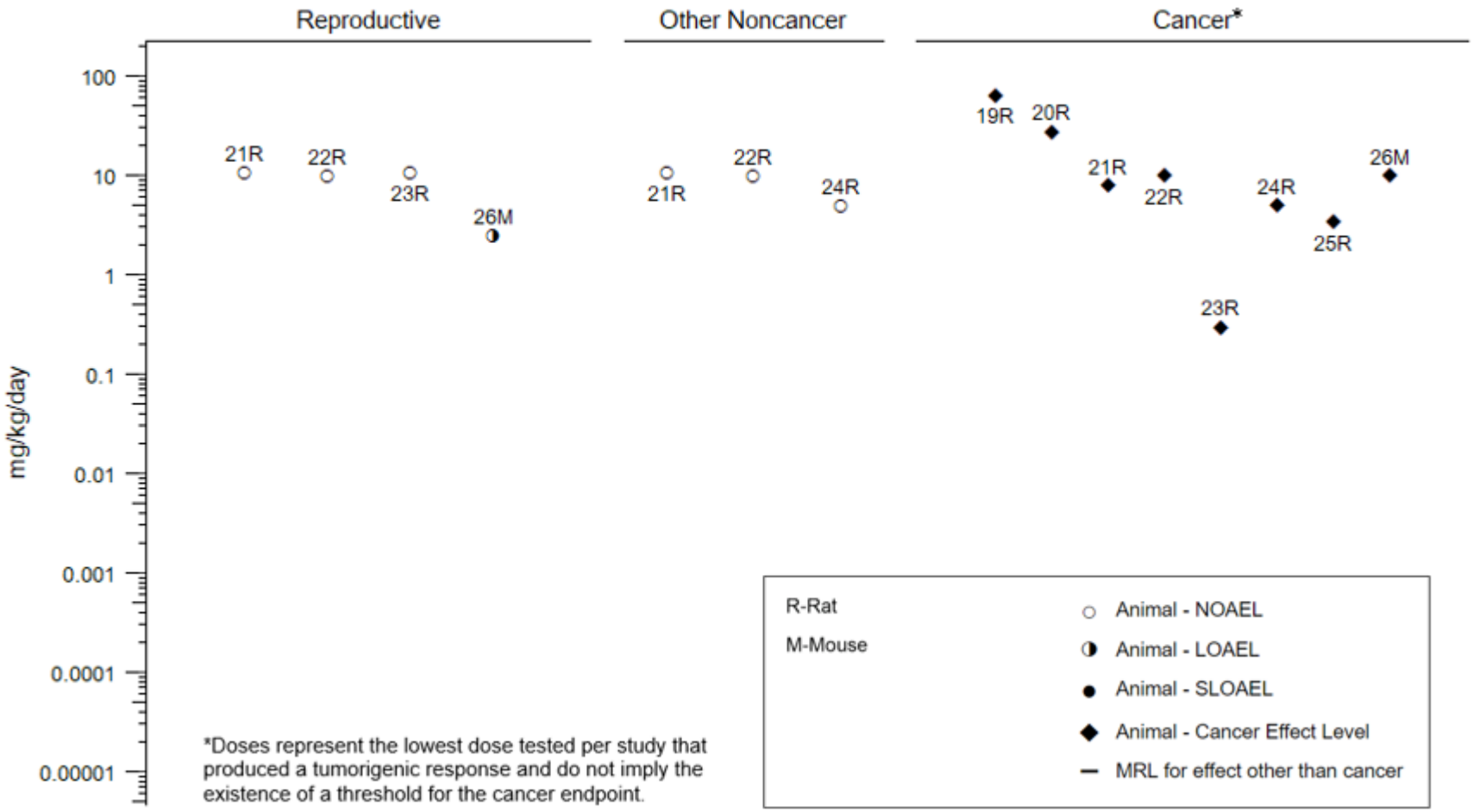


Table 2-3. Levels of Significant Exposure to Acrylonitrile – Dermal

Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
ACUTE EXPOSURE								
DOT 1972								
Rabbit	ND			Death			250	LD_{50}
Roudabush et al. 1965								
Rabbit (NS) 4 M, 4 F	ND	ND		Death			226	LD_{50}
Roudabush et al. 1965								
Guinea pig (NS) 4 M	ND	ND		Death			370	LD_{50}

F= female(s); LD_{50} = median lethal dose; LOAEL = lowest-observed-adverse-effect level; M = males(s); ND = no data; NOAEL = no-observed-adverse-effect level; NS = not specified

2.2 DEATH

A small number of deaths in humans have been reported in the literature. The death of a child (age 3 years) who was exposed by sleeping in a room that had been fumigated with acrylonitrile has been described by Grunske (1949). Respiratory malfunction, lip cyanosis, and tachycardia were among the symptoms described prior to death. Five adults who spent the night in the same room complained only of eye irritation or showed no signs of acrylonitrile poisoning. The concentrations of acrylonitrile in the air were not reported. Several other instances of death in children with only mild irritation in adults were reported by Grunske (1949), but not described in detail. Lorz (1950) reported the case of a 10-year-old girl who died following dermal exposure to acrylonitrile. An acrylonitrile preparation had been applied to the scalp of the child as a treatment for head lice. The child experienced nausea, headache, and dizziness. Death occurred 4 hours after application. The concentration was not specified in this case report.

Kiplinger (2005) estimated median lethal concentration (LC_{50}) values of 946 and 920 ppm in male and female rats, respectively, exposed to acrylonitrile for 4 hours. An acute-duration inhalation study by Dudley and Neal (1942) compared the lethality of acrylonitrile in several animal species exposed for 4 hours. The data presented indicate that species differences exist with respect to acute-duration lethal effects. Dogs appear to be the most susceptible species, but this is based on studies involving only a few animals. Deaths of at least a third of the animals in the group were observed at 65 ppm in dogs, 260 ppm in rabbits, 315 ppm in rats, 575 ppm in guinea pigs, and 600 ppm in cats; no deaths were observed in monkeys at the highest concentration tested (90 ppm). The cause of death varied among test species. In guinea pigs, death resulted from pulmonary irritation while in the other species convulsions and coma occurred (Dudley and Neal 1942). An oral LD_{50} of 347 mg/kg was calculated in mice (Tanii and Hashimoto 1984). In contrast to this finding, two studies reported deaths in mice shortly after exposure. Death was reported within 15–20 minutes of exposure to 54 mg/kg (Ahmed and Patel 1981) and with the first day of exposure to 40 mg/kg (NTP 2001). Roudabush et al. (1965) reported dermal LD_{50} values of 226 and 370 mg/kg in rabbits and guinea pigs, respectively.

In intermediate-duration studies, early deaths were observed in dogs exposed to 16 mg/kg/day in drinking water for 6 months (Quast et al. 1975) and in female rats exposed to 25.0 mg/kg/day in drinking water for 1 year (Quast 2002). Chronic-duration inhalation exposure to acrylonitrile has been reported to result in early deaths in female rats exposed to 20 ppm for 2 years (Quast et al. 1980a). Chronic-duration studies in rats indicate that lifetime exposure to doses ≥1.3 mg/kg/day may result in premature death (Bigner et

al. 1986; Gallagher et al. 1988; Johannsen and Levinskas 2002a, 2002b; Quast 2002). In mice, deaths were observed at ≥20 mg/kg (NTP 2001).

2.3 BODY WEIGHT

No studies were located regarding body weight effects in humans following exposure to acrylonitrile.

Decreases in body weight have been observed in laboratory animals exposed to acrylonitrile via inhalation or oral exposure. Decreased body weight was observed in rats following acute-duration exposures to air concentrations of ≥40 ppm (Gut et al. 1984; Murray et al. 1978), intermediate-duration exposure to ≥80 ppm (Gagnaire et al. 1998; Nemec et al. 2008; Quast et al. 1983), and chronic-duration exposure to 80 ppm (Quast et al. 1980a). Oral exposures to ≥65, ≥20, or ≥3.4 mg/kg/day resulted in decreased body weight following acute- (Murray et al. 1978; Saillenfait and Sabate 2000), intermediate- (Friedman and Beliles 2002; Gagnaire et al. 1998; Ghanayem et al. 1997; Humiston et al. 1975; Luo et al. 2022; Quast 2002), and chronic-duration (Bigner et al. 1986; Johannsen and Levinskas 2002a; Quast 2002) exposures, respectively.

2.4 RESPIRATORY

There are limited data on the respiratory toxicity of acrylonitrile in humans. Wilson et al. (1948) reported irritation of the nose and throat and a feeling of fullness in the chest in workers exposed to acrylonitrile at concentrations of 16–100 ppm for periods of 20–45 minutes. The workers were involved in cleaning operations and likely had repeated exposure to acrylonitrile, as well as other chemicals. In another report by these investigators, workers exposed to an unknown concentration of acrylonitrile reported nasal irritation (Wilson 1944). A mortality study conducted by Koutros et al. (2019) found an increased risk of deaths from pneumonitis in workers with exposures higher than the median level (>3.12 ppm-years cumulative exposure and duration of exposure of >14.5 years). A study by Simons et al. (2016) examined residents living near a train derailment, which resulted in tank cars exploding and releasing acrylonitrile, hydrogen cyanide, and nitrogen oxides fumes and spilling acrylonitrile into the sewer system. Symptoms of irritation were reported by 48.5% of nonsmokers and 65.5% of smokers; the most prevalent respiratory irritation symptoms were nose, throat, and airway problems (in 31.6 and 52.7% of nonsmokers and smokers, respectively) and coughing (in 18.4 and 30.9% of nonsmokers and smokers, respectively). The investigators examined possible associations between self-reported symptoms of irritation and N-2-cyanoethylvaline adduct levels (biomarker of acrylonitrile exposure) and found a significant

association among nonsmokers, but not among smokers. Two studies of male workers at six to seven acrylic fiber manufacturers in Japan found increases in the prevalence of respiratory tract irritation (Kaneko and Omae 1992; Sakurai et al. 1978). The average acrylonitrile exposure levels at the facilities with the highest exposure was 14.1 ppm; however, the investigators suggested that the irritation was likely due to short-term exposure to elevated acrylonitrile levels.

Acute-duration exposure effects on the respiratory tract of animals demonstrate species differences. In guinea pigs exposed to 575 ppm for 4 hours, marked irritation of the respiratory tract was evidenced by coughing and nasal exudate, with delayed death from lung edema (Dudley and Neal 1942). In other species (rats, rabbits, dogs, and monkeys), death occurred at lower doses than in guinea pigs but was not related to respiratory effects. In these animals, mild irritation of the respiratory tract and effects resembling cyanide poisoning were noted. Respiration was initially stimulated but then followed by rapid shallow breathing (Dudley and Neal 1942). A 5-day repeated exposure study did not find histological alterations in the lung of rats exposed to 129 ppm (Gut et al. 1984).

Intermediate- and chronic-duration inhalation studies in rats and mice suggest the respiratory tract, in particular, the nasal cavity, is a sensitive target of acrylonitrile toxicity. In a 2-generation study involving 18 weeks of exposure, nasal cavity transitional zone epithelium hyperplasia, squamous metaplasia, and subacute inflammation were observed in the P and F1 generation rats exposed to 15 ppm (6 hours/day, 7 day/week) (Nemec et al. 2008); the NOAEL was 5 ppm. At 45 ppm, degeneration of the olfactory epithelium was observed. In 6- and 12-month studies, slight irritation of the nasal turbinates was observed in rats exposed to 80 ppm (6 hours/day, 5 days/week), but not at 20 ppm (Quast et al. 1983). Chronic-duration exposure also resulted in irritation of the nasal mucosa characterized as flattening of the respiratory epithelium and hyperplasia of mucous secreting cells in the nasal turbinates at 20 ppm (6 hours/day, 5 days/week) and squamous metaplasia and focal inflammation at 80 ppm (Quast et al. 1980a). Suppurative pneumonia was also observed in males at 80 ppm.

Only one oral study reported respiratory effects; hyperplasia of bronchiole Clara cells was observed in rats administered a single dose of 46.5 mg/kg acrylonitrile (Ahmed et al. 1992). Histopathological evaluation of lung tissues showed no lung injury at doses up to 25 mg/kg/day for 1 or 2 years in rats (Johannsen and Levinskas 2002a, 2002b; NTP 2001; Quast 2002) or 40 mg/kg for 14 weeks or 20 mg/kg for 2 years in mice (NTP 2001).

2.5 CARDIOVASCULAR

In humans, tachycardia was among the symptoms described in a 3-year-old child who was exposed by sleeping in a room that had been fumigated with acrylonitrile. The child died as a result of the exposure (Grunske 1949). No studies were located regarding cardiovascular effects in animals following inhalation exposure to acrylonitrile.

With the exception of increases in heart weight, intermediate- and chronic-duration inhalation and oral studies have not reported cardiovascular effects in laboratory animals. In the absence of other evidence of heart damage, the increases in weight were not considered adverse. No adverse cardiovascular effects were seen in rats exposed to inhalation concentrations of 80 ppm for 6, 12, or 24 months (Quast et al. 1980a, 1983), rats exposed to oral doses as high as 60 mg/kg/day for intermediate durations of ≥ 90 days (Humiston et al. 1975; Quast 2002), mice exposed to 20 mg/kg for 14 weeks (NTP 2001), rats exposed to doses as high as 10.9 mg/kg/day for approximately 2 years (Johannsen and Levinskas 2002a, 2002b; Quast 2002), or mice exposed to 20 mg/kg for 2 years (NTP 2001).

2.6 GASTROINTESTINAL

There is limited information on the gastrointestinal toxicity of acrylonitrile in humans. Wilson (1944) reported nausea, vomiting, and diarrhea among workers in the rubber industry exposed to acrylonitrile; no information on exposure level, duration, or potential exposure to other compounds was reported. Simons et al. (2016) reported nausea in residents living in the area of the derailment of a train carrying acrylonitrile (see Section 2.4 for more information on the study). The study found a significant association between N-2-cyanoethylvaline adduct levels and self-reported nausea among nonsmokers.

Non-neoplastic gastrointestinal effects have not been reported in rats exposed to up to 80 ppm acrylonitrile vapors (6 hours/day, 5 days/week) for 6 or 24 months (Quast et al. 1980a, 1983). Histological evidence of gastric irritation at the junction between the glandular and non-glandular stomach was observed in rats exposed to 80 ppm for 12 months (Quast et al. 1983); however, the investigators suggested that this may be due to decreased growth and presumed decreased food consumption rather than a direct effect of acrylonitrile. As discussed in Section 2.19, this study found increases in the incidence of tongue and small intestine neoplastic tumors.

Oral exposure studies in laboratory animals demonstrated that the gastrointestinal tract is a target of acrylonitrile toxicity. Focal erosions and ulcerations in the esophagus were observed in dogs exposed to 16 mg/kg/day acrylonitrile in drinking water for 6 months (Quast et al. 1975). Thickening of the non-glandular stomach (i.e., forestomach) was observed in rats dams administered 65 mg/kg/day acrylonitrile on gestation days (GDs) 6–15 (Murray et al. 1978). Suggestive evidence of gastrointestinal bleeding, as measured by increased heme content in the gastrointestinal tract, was observed in rats receiving a single gavage dose of 50 mg/kg (Ghanayem and Ahmed 1983). Intermediate- and chronic-duration gavage or drinking water exposure resulted in proliferative lesions in the non-glandular stomach including squamous hyperplasia, hyperplasia, hyperkeratosis, and/or squamous cell metaplasia in rats and mice (Ghanayem et al. 1997; Johannsen and Levinskas 2002a, 2002b; NTP 2001; Quast 2002; Szabo et al. 1984). The lowest LOAELs were 8.5 and 40 mg/kg/day in rats (Quast 2002) and mice (NTP 2001) following intermediate-duration exposure and 0.4 and 10 mg/kg/day in rats (Johannsen and Levinskas 2002a) and mice (NTP 2001) following chronic-duration exposure. It is also noted that an increase in the severity of squamous cell hyperplasia was observed in rats exposed to >0.09 mg/kg/day for 22 months, although the incidence of lesions did not differ from controls (Johannsen and Levinskas 2002b). Most studies have not reported effects in the glandular stomach with the exception of the Szabo et al. (1984) study, which reported hyperplasia in rats exposed to 14 or 70 mg/kg/day for 60 days. Chronic-duration oral exposure also resulted in increases in the incidence of squamous cell papillomas and/or carcinomas in rats and mice (Johannsen and Levinskas 2002a, 2002b; NTP 2001; Quast 2002).

2.7 HEMATOLOGICAL

A report of workers in the rubber industry exposed to an unspecified concentration of acrylonitrile and exhibiting jaundice also indicated that some workers had “low grade anemia” (Wilson 1944). No alterations in hemoglobin levels were detected in Japanese workers exposed to acrylonitrile for 10–13 years at exposure levels averaging 2.1–14.1 ppm (Sakurai et al. 1978). Another study of the Japanese workers at these seven acrylic fiber manufacturing facilities also found no alterations in hematological parameters; the time-weighted average (TWA) acrylonitrile concentration was 1.13 ppm in the high exposure group (Muto et al. 1992).

In a chronic-duration inhalation study in rats (Quast et al. 1980a), some changes in the blood parameters were observed at various intervals during the study, but the findings did not occur consistently and were not dose-related. Therefore, the authors concluded that these findings were not direct effects of exposure

to acrylonitrile, but rather were a secondary response to other effects such as weight loss, tumor formation, or inflammatory reactions.

Decreased red blood cell counts, hematocrit, and hemoglobin content have been reported following acute-, intermediate-, and chronic-duration oral studies in animals (Farooqui and Ahmed 1983; Johannsen and Levinskas 2002a, 2002b; NTP 2001; Quast et al. 1975). A single gavage dose of 80 mg/kg resulted in decreases in hematocrit, mean cell hemoglobin concentration, mean cell volume, and platelet count in rats (Farooqui and Ahmed 1983). Although the mechanism of these hemotoxic effects is not clear, the investigators found that acrylonitrile bound covalently to both red blood cell membranes and hemoglobin. Decreases in hemoglobin levels and increases in reticulocyte levels were observed in female rats exposed to 10.9 mg/kg/day for 6–12 months (Johannsen and Levinskas 2002a). Similarly, decreases in hemoglobin levels were observed in female mice administered 5 mg/kg for 14 weeks (NTP 2001). In dogs administered acrylonitrile at doses up to 18 mg/kg/day for 6 months, decreased red cell counts, hematocrit, and hemoglobin content were seen only in animals that died (Quast et al. 1975). As with intermediate-duration studies, chronic-duration exposure has resulted in decreases in hemoglobin levels at doses ≥8.0 mg/kg/day in rats (Johannsen and Levinskas 2002a, 2002b). No effects on red blood cell parameters were observed in rats exposed to up to 25 mg/kg/day for 2 years (Quast 2002).

In addition to the alterations in red cell parameters, decreased lymphocyte counts were observed in male and female mice at administered 20 and 40 mg/kg, respectively, for 14 weeks and decreased total leukocyte counts were observed in females at 40 mg/kg (NTP 2001).

2.8 MUSCULOSKELETAL

In humans, one study of a worker accidentally sprayed with acrylonitrile reported increased levels of muscle enzyme creatinine phosphokinase and myoglobinuria; the data are too limited to draw any firm conclusions (Vogel and Kirkendall 1984).

Laboratory animal studies have not reported histological alterations in muscular/skeletal tissues following intermediate- or chronic-duration oral exposure (NTP 2001; Quast 2002).

2.9 HEPATIC

Acrylonitrile is metabolized in the liver to potentially toxic metabolites; however, there are limited indications that the liver is a target organ for acrylonitrile toxicity.

In humans, mild jaundice lasting several days to 4 weeks has been observed after acute-duration occupational exposure to acrylonitrile vapors at presumably high concentrations (Wilson 1944); however, the concentrations of acrylonitrile to which workers were exposed were not reported. The effects were fully reversible. In factory workers exposed to average acrylonitrile concentrations of 2.1–14.1 ppm for ≥10 years, Sakurai et al. (1978) reported an increase in palpable livers of workers. However, the study authors considered these results to be inconclusive because the increase was not statistically significant and subjective judgments were involved; blood chemistry evaluations did not indicate liver damage. In another study of Japanese acrylic fiber workers with a TWA acrylonitrile concentration of 1.13 ppm, no alterations in serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyl transferase, or total bilirubin levels were found (Muto et al. 1992).

In animals, acrylonitrile does not appear to cause damage to the liver following inhalation or oral exposure. Intermediate- and chronic-duration inhalation exposure in rats did not result in liver injury as evaluated by serum enzyme activity and histopathological evaluation of the tissue (Quast et al. 1980a, 1983). Similarly, intermediate- and chronic-duration oral studies have not reported histological alterations at doses as high as 42 mg/kg/day (Ghanayem et al. 1997; Humiston et al. 1975; NTP 2001; Quast 2002) and 25 mg/kg/day (Johannsen and Levinskas 2002a, 2002b; NTP 2001; Quast 2002), respectively. Some biochemical changes and increases in liver weight were noted. Alterations in liver glutathione levels (Gut et al. 1985; Szabo et al. 1977) have been reported. Alterations in liver weight have also been reported in some studies. Inhalation exposure of rats for 5 days to 129 ppm acrylonitrile resulted in slightly lower liver weight (Gut et al. 1984), whereas increases in liver weight were reported in rats following acute-duration oral exposure to 65 mg/kg/day (Murray et al. 1978) or chronic-duration oral exposure to 10 mg/kg/day (Johannsen and Levinskas 2002b). In the absence of histological alterations or other indications of liver damage, these alterations were considered adaptive changes related to increased metabolic activity by the liver due to the presence of acrylonitrile in the body.

2.10 RENAL

Most studies indicate that inhalation exposure to acrylonitrile does not result in significant kidney injury. For example, physical examination of workers exposed to acrylonitrile vapors in the workplace for ≥10 years provided no indication of renal effects (Sakurai et al. 1978). In animals, no histological or biochemical signs of renal injury were seen following inhalation exposure of rats to 129 ppm of acrylonitrile for 5 days (Gut et al. 1984) or to 80 ppm for 6 or 12 months or 2 years (Quast et al. 1980a, 1983). A decrease in urine specific gravity was observed at ≥20 ppm in rats exposed for 6 months (Quast et al. 1983), but not after 12 months (Quast et al. 1983) or 2 years (Quast et al. 1980a). The investigators suggested that this effect may be secondary to polydipsia and polyuria observed early in the study. Small increases in urinary levels of glucose, gamma-glutamyl transpeptidase, and N-acetyl-glucosaminidase were observed in rats exposed to 200 ppm of acrylonitrile for 4 hours (Rouisse et al. 1986), but this was not accompanied by any significant effect on urinary creatinine or blood urea nitrogen (BUN).

No adverse effects on the renal system have been reported in animals administered acrylonitrile via the oral route. In chronic-duration exposure studies in rats, increased kidney weights relative to body weight were observed (Johannsen and Levinskas 2002a, 2002b). However, the significance of this observation, if any, is not known, because no histopathological, blood chemistry, or urinalysis findings suggestive of kidney injury were observed in intermediate- and chronic-duration studies in rats, mice, or dogs (Humiston et al. 1975; Johannsen and Levinskas 2002a, 2002b; NTP 2001; Quast 2002; Quast et al. 1975).

2.11 DERMAL

In humans, direct skin irritation resulting from exposure to acrylonitrile vapors has been observed. Workers exposed to acrylonitrile vapors at 16–100 ppm for 20–45 minutes complained of intolerable itching of the skin, but no dermatitis was observed (Wilson et al. 1948). This phenomenon is presumably a direct irritant effect of acrylonitrile on the skin. In contrast, no signs of skin irritation were observed in humans following a 2-day patch test with 0.1% acrylonitrile (Kanerva et al. 1999).

A skin redness reported in experimental animals (rats, rabbits, cats, and monkeys) after inhalation exposure to acrylonitrile may be due to a vasodilatory effect, rather than a direct irritant action (Ahmed and Patel 1981).

2.12 OCULAR

There is limited information on ocular effects in humans following exposure to acrylonitrile. Conjunctival irritation was reported by workers at six to seven Japanese acrylic fiber manufacturing facilities (Muto et al. 1992; Sakurai et al. 1978). Since the increased prevalence was only found in workers at one facility, the investigators suggested that the effect may be due to transient exposure to high acrylonitrile levels or to exposure to a different chemical.

Eye irritation was noted in guinea pigs exposed to ≥575 ppm acrylonitrile vapor for 4 hours (Dudley and Neal 1942). No signs of eye irritation or ophthalmological alterations were observed in rats or mice exposed to ≤80 ppm acrylonitrile vapor for intermediate or chronic durations (Johannsen and Levinskas 2002a; NTP 2001; Quast 2002; Quast et al. 1983). No studies were located regarding ocular effects in animals following oral exposure to acrylonitrile.

2.13 ENDOCRINE

No studies were located regarding endocrine effects in humans following exposure to acrylonitrile.

In a series of studies conducted by Szabo et al. (1984), histological alterations were observed in the adrenal gland of rats administered acrylonitrile in drinking water and via gavage for up to 60 days. A 3-week exposure to 70 mg/kg/day resulted in adrenal atrophy. Adrenocortical hyperplasia was reported following 60-day gavage exposure; however, the study does not clearly identify a LOAEL—it notes that lesions were observed in "virtually all of the dose levels of acrylonitrile-gavaged animals," the lowest dose tested was 2 mg/kg/day, and no incidence data were provided. The study also found significant decreases in plasma corticosterone levels. In contrast, no lesions to endocrine tissues, including the adrenals, were observed in rats, mice, or dogs following intermediate- or chronic-duration exposure (NTP 2001; Johannsen and Levinskas 2002a, 2002b; Quast et al. 1983).

2.14 IMMUNOLOGICAL

Although no studies were located regarding immune function in humans or animals following inhalation, oral, or dermal exposure to acrylonitrile, several studies have evaluated immune system tissues. No histopathological alterations were observed in the thymus, lymph nodes, and/or spleen in rats exposed via inhalation to 80 ppm for 6 or 12 months (Quast et al. 1983); rats orally exposed to 21/25 mg/kg/day for

1 or 2 years (Quast 2002), 80 mg/kg/day for 2 years (Quast et al. 1980a), 8.4/10.9 mg/kg/day for 23–26 months (Johanssen and Levinskas 2002a), or 8.0 mg/kg/day for 19–22 months (Johannsen and Levinskas 2002b); or mice exposed to 40 mg/kg/day for 14 weeks or 20 mg/kg/day for 2 years (NTP 2001).

2.15 NEUROLOGICAL

Neurological symptoms in humans associated with acrylonitrile poisoning include limb weakness, labored and irregular breathing, dizziness and impaired judgment, cyanosis, nausea, collapse, and convulsions (Baxter 1979). However, the concentrations that produce these effects were not clearly defined. Workers exposed to 16–100 ppm for 20–45 minutes complained of headaches and nausea, apprehension, and nervous irritation (Wilson et al. 1948). The workers exposed to acrylonitrile vapors fully recovered. In a study with volunteers exposed to acrylonitrile at concentrations of 2.3 and 4.6 ppm, no symptoms attributable to effects on the nervous system were reported by the subjects (Jakubowski et al. 1987). Signs of cyanide poisoning were exhibited by a man accidentally sprayed with acrylonitrile; dizziness, redness, nausea, vomiting, and hallucinations were reported (Vogel and Kirkendall 1984). The symptoms persisted for 3 days.

Laboratory animal studies support the identification of the nervous system as a target of acrylonitrile toxicity. Several mechanisms appear to be involved in acrylonitrile-induced neurotoxicity (Ghanayem et al. 1991). Shortly after exposure, signs of cholinergic overstimulation were observed in laboratory animals; signs included excessive salivation, miosis, polyuria, and/or increased gastric secretions in dogs exposed to 30 ppm for 4 hours (Dudley and Neal 1942), cats exposed to 100 ppm for 4 hours (Dudley and Neal 1942), rats receiving a single gavage dose of 20, 47, or 90 mg/kg (Ahmed and Farooqui 1982; Ahmed and Patel 1981; Ghanayem et al. 1991), and rat dams administered 65 mg/kg/day on GDs 6–15 (Murray et al. 1978). A delayed phase of neurotoxicity followed this acute response; the delayed phase was characterized by respiratory depression, paralysis, and convulsions (Dudley and Neal 1942; Ghanayem et al. 1991).

Other overt signs of toxicity observed in acute-duration exposure studies include “weakness” in one of two monkeys exposed to 90 ppm for 4 hours (Dudley and Neal 1942), tremors and ataxia in rats exposed to 775 and 871 ppm, respectively, for 4 hours (Kiplinger 2005), an unsteady gait in rats exposed to 125 ppm 8 hours/day for 5 days (Gut et al. 1985), and marked central nervous system effects in mice following a single gavage dose of 27 mg/kg (Ahmed and Patel 1981). Guinea pigs showed no measurable signs of neurological effects from acute-duration exposure to acrylonitrile at a dose that caused death

(575 ppm) (Dudley and Neal 1942). It should be noted that this study was based on a small number of animals at each exposure concentration.

Neurological effects have also been reported in intermediate- and chronic-duration inhalation and oral exposure studies. Weakness in hindlimbs and inability to rear occurred in rats administered 50 mg/kg 5 days/week for 12 weeks (Gagnaire et al. 1998). Chronic-duration oral exposure resulted in paralysis, seizures, and decreased activity in rats exposed for 18 months to 65–72 mg/kg/day (Bigner et al. 1986). No overt signs of neurotoxicity were observed in male rats exposed to 37 mg/kg/day or in female rats exposed to 40 mg/kg/day for 48 weeks (Friedman and Beliles 2002). An inhalation study and an oral study conducted by Gagnaire et al. (1998) reported decreased sensory nerve conduction velocity in rats exposed to 25 ppm for 24 weeks or 50 mg/kg/day for 12 weeks, respectively. No histological alterations were observed in rats exposed to 42 mg/kg/day in drinking water for 90 days (Humiston et al. 1975). Chronic-duration exposure resulted in glial cell tumors and perivascular cuffing in the brain of rats exposed to 80 ppm acrylonitrile via gavage 6 hours/day, 5 days/week for 2 years (Quast et al. 1980a) and in rats exposed to 4.4 mg/kg/day acrylonitrile in drinking water for 2 years (Quast 2002). A histopathology peer review and scientific advisory group review of the findings of the 2-year inhalation (Quast et al. 1980a) and oral (Quast 2002) studies was conducted by Experimental Pathology Laboratories (Hardisty et al. 2002). The reviewers concurred with the study investigators' findings; however, they concluded that the glial cell tumors and perivascular cuffing should be considered preneoplastic since they were not associated with evidence of preexisting degeneration or necrosis that could have led to gliosis.

A series of studies conducted by Fechter and Pouyatos and associates have examined the ototoxicity of acrylonitrile, specifically the effect on noise-induced hearing loss. A subcutaneous injection of 50 mg/kg acrylonitrile resulted in a temporary elevation of auditory threshold (Fechter et al. 2003); the impairment lasted 75–100 minutes post-injection. No permanent hearing loss, as measured by distortion product otoacoustic emission, or outer hair cell damage in the organ of Corti was induced in rats administered 50 mg/kg/day acrylonitrile for 5 days via subcutaneous injection (Pouyatos et al. 2005). Administration of two or five subcutaneous injection doses of 50 mg/kg acrylonitrile and exposure to noise (108 dB for 8 hours or 95 or 97 dB 4 hours/day for 5 days) resulted in persistent loss in auditory threshold sensitivity, particularly at higher frequencies, as compared to controls and rats only exposed to noise (Fechter 2004; Fechter et al. 2003; Pouyatos et al. 2005, 2009). Exposure to both acrylonitrile and noise also resulted in outer hair cell loss in the organ of Corti (Pouyatos et al. 2005, 2009).

2.16 REPRODUCTIVE

There is limited information on the reproductive toxicity of acrylonitrile in humans. Xu et al. (2003) reported significant decreases in semen density and the number of sperm per ejaculum in acrylonitrile-exposed workers. There were no significant alterations in semen volume or sperm viability, motility, or morphological defects. The investigators noted that the workers were exposed to a mean concentration at operation sites of 0.36 ppm for 2.8 years; no other additional information was provided including potential exposure to other compounds.

Although some studies have reported reproductive effects in laboratory animals, most studies have not reported histological alterations in reproductive tissues or alterations in reproductive function. Wang et al. (1995) reported increases in sperm aberration rates in mice exposed to 28 ppm acrylonitrile 2 hours/day, 5 days/week for 28 days; this effect was not observed in mice exposed to 55 ppm 2 hours/day 6 days/week for 7 or 14 days (Wang et al. 1995). Decreases in sperm motility and concentration and increases in sperm morphological alterations were observed in rats administered 20 mg/kg/day, 6 days/week for 12 weeks (Dang et al. 2017) or 46 mg/kg/day, 6 days/week for 28 days (Shi et al. 2021). Tandon et al. (1988) observed histological and biochemical evidence of degenerative changes in testicular tubules of mice exposed to 10 mg/kg/day of acrylonitrile for 60 days. These changes were accompanied by a 45% decrease in sperm count. None of the oral studies assessed reproductive function. Reproductive effects have been observed in female mice administered acrylonitrile via gavage for 28 days or 2 years. Impaired ovarian follicular development characterized as increased atretic follicles, decreased preovulatory follicles, and increased follicular inflammation was observed at 5 mg/kg/day (Luo et al. 2022); the study also found decreased oocyte development at this dose level. In the 2-year study, increases in the incidence of ovarian cyst and ovarian atrophy were observed at ≥2.5 and ≥10 mg/kg/day, respectively (NTP 2001). NTP (2001) did not find any histological alterations in the testes of male mice administered 20 mg/kg for 14 weeks or 2 years.

Studies in rats have not found histological alterations following intermediate-duration inhalation exposure to 80 ppm (Quast et al. 1983), intermediate-duration oral exposure to ≥37 mg/kg/day (Friedman and Beliles 2002; Humiston et al. 1975), or chronic-duration oral exposure to ≥8 mg/kg/day (Johannsen and Levinskas 2002a, 2002b).

Multigeneration studies do not provide evidence for impaired reproductive function in rats. No alterations in estrous cycle lengths, mating, gestation length, or reproductive performance were observed

in F0 or F1 rats exposed via inhalation to 90 ppm acrylonitrile (Nemec et al. 2008). The investigators noted a slight, but statistically significant, decrease in sperm motility and percentage of progressive sperm motility in the F0 male rats; however, they did not consider the alterations to be compound-related since the values were within the range of historical controls. In a 3-generation reproduction drinking water study in rats, Friedman and Beliles (2002) found that exposure of animals to acrylonitrile in drinking water at 37 mg/kg/day in males and 40 mg/kg/day in females did not adversely affect reproductive performance indices in the F0, F1, and F2 generations.

2.17 DEVELOPMENTAL

No studies were located regarding developmental effects in humans following exposure to acrylonitrile.

Inhalation and oral exposure studies in laboratory animals have evaluated the potential developmental toxicity of acrylonitrile. Inhalation of 80 ppm acrylonitrile during GDs 6–15 resulted in a significant increase in the total number of fetal malformations (Murray et al. 1978). These malformations included short tail, missing vertebrae, short trunk, omphalocele, and hemivertebra; there were no significant increases in a particular malformation. The mean number of implantations, live fetus and resorptions, fetal body weight, or crown-rump length were not significantly altered by exposure to 40 or 80 ppm of acrylonitrile. Decreases in maternal weight gain were observed at 40 and 80 ppm. In a 2-generation inhalation study, maternal exposure to 90 ppm acrylonitrile resulted in decreases in pup body weight gain on postnatal days (PNDs) 14 and 21 (5.8–.6 and 10.7–12.2%, respectively) in the F1 generation (Nemec et al. 2008). Slight delays in sexual developmental landmarks were also observed in the F1 animals, but this was attributed to the decrease in body weight.

A decreased number of pups was observed in the offspring of mice mated after a 28-day exposure to 5 mg/kg/day (Luo et al. 2022); no alterations in maternal body weight were observed at this dose level. At 10 mg/kg/day, there was a decrease in birth weight. Oral administration of 65 mg/kg/day of acrylonitrile during GDs 6–15 resulted in decreases in fetal body weight, decreases in crown-rump length, and increases in the incidence of short tail, short trunk, and missing vertebrae malformations (Murray et al. 1978). Short trunk and missing vertebrae were only observed in fetuses also having the short trunk malformation. A slight increase in the incidence of litters with short tail malformations was also observed at 25 mg/kg/day (7.4%), but the incidence was not significantly different from controls (2.6%). The number of live pups and resorption per litter were not affected by the administration of acrylonitrile. Decreases in maternal weight gain and increased incidences of maternal hyperexcitability and excessive

salivation were also observed at 65 mg/kg/day. In a second developmental toxicity study, misdirected allantois, trunk, and caudal extremities were observed in the embryos of rats administered 100 mg/kg on GD 10 (Saillenfait and Sabate 2000).

A 3-generation drinking water study reported decreases in pup survival (from birth to PND 4 and from PND 4 to weaning) at maternal doses of ≥40 mg/kg/day (Friedman and Beliles 2002). A decrease in pup viability (birth to postnatal day 4) was also observed at 20 mg/kg/day in the F1b generation, but not in the other generations. Decreases in maternal water consumption, food consumption, and body weight gain were also observed at ≥20 mg/kg/day. The investigators noted that the decrease in pup survival may be secondary to decreases in maternal water intake, which could have resulted in decreased milk production; the investigators noted that the lactation viability (PND 4 to weaning) was not affected more than pup viability (birth to PND 4). Significant decreases in pup body weight at PNDs 4 and/or 21 were also observed at 40 mg/kg/day. When the F1b offspring of dams exposed to 40 mg/kg/day were fostered to unexposed dams, no alterations in pup survival or pup body weight were observed.

In vitro studies conducted by Saillenfait and associates support the developmental toxicity of acrylonitrile. Culturing GD 10 rat embryos with acrylonitrile resulted in dose-related decreases in growth and increases in morphological alterations (Saillenfait and Sabate 2000; Saillenfait et al. 1992, 1993) but did not affect survival (Saillenfait et al. 1992).

2.18 OTHER NONCANCER

Information on the potential of acrylonitrile to induce other noncancer effects is limited to studies examining blood glucose levels in animals. Inhalation exposure of rats to ≥26 ppm for 12 hours or 129 ppm for 5 days (8 hours/day) resulted in increases in blood glucose levels (Gut et al. 1984). In contrast, no alterations in fasting blood glucose levels were observed in male and female rats exposed via drinking water or gavage to approximately 8 or 10 mg/kg/day, respectively (Johannsen and Levinskas 2002b).

2.19 CANCER

A large number of epidemiological studies have been conducted to evaluate the possible association between occupational exposure to acrylonitrile and increases in cancer risk. The studies examined workers involved in acrylonitrile monomer production and the manufacture of fiber and resin. Most of

the studies are retrospective cohort mortality investigations examining between ~100 and 25,500 workers at one or more facilities in the United States or Europe. Most of these studies share several limitations including either the lack of monitoring information or limited monitoring data from which exposure was estimated, lack of control for simultaneous exposure to other chemicals, and no or limited information on smoking. Summaries of the findings of eight of the larger studies are presented in Table 2-4. Several of these studies are updates of older studies; only the most recent examination is included in the table. Lung cancer was the most well-studied cancer endpoint. In general, most studies did not find increased risk of lung or other respiratory cancers. Although less extensively evaluated, most studies have not found increased risk of other cancers among acrylonitrile workers. In addition to the individual studies, two meta-analyses have examined the possible association between acrylonitrile exposure and cancer mortality; a list of the studies included in the analyses are presented in Table 2-5. An older review and meta-analysis of 26 cancer studies (including several unpublished studies) examined cancer mortality and incidence data (Collins and Acquavella 1998). The investigators concluded that "the available studies do not support a causal relation between acrylonitrile exposure and cancer." A more recent meta-analysis conducted by Alexander et al. (2021) focused on lung cancer mortality using the data from 10 cohort studies and 1 case-control study. The meta-analysis generated a summary relative risk estimate of 1.04 (95% confidence interval [CI] 0.89–1.21), and the investigators concluded that the meta-analysis did not support an increased risk of lung cancer mortality among acrylonitrile workers.

The available inhalation and oral exposure animal studies provide strong evidence that acrylonitrile is carcinogenic in rats and mice following chronic-duration exposure. As summarized in Table 2-6, animal studies identified a number of target tissues. Multiple studies have reported glial cell tumors in the brain and spinal cord, carcinomas in the Zymbal gland, and mammary gland following inhalation or oral exposure and forestomach papillomas/carcinomas following oral exposure. Comparisons of chronic-duration oral studies in rats and mice suggest differences between target tissues. NTP (2001) noted that a similar mechanism of carcinogenicity in rats and mice has been reported for other compounds such as 1,3-butadiene, vinyl chloride, benzene, and ethylene oxide, which are epoxides or are metabolized to mutagenic epoxide intermediates.

Table 2-4. Cancer Outcomes in Humans Exposed to Acrylonitrile

Reference, study type, and population	Exposure	Outcome evaluated	Result
Benn and Osborne 1998 Retrospective mortality study of 2,763 male workers at six facilities involved in acrylonitrile polymerization or acrylic fibers spinning in the United Kingdom	Acrylonitrile exposure was based on company work histories categorized into high exposure, possible exposure, or no/little exposure.	Trachea, bronchus, and lung cancer deaths High exposure group Workers <45 years of age	 ↔ ↑
		Stomach cancer deaths	↔
Delzell and Monson 1982 Retrospective cohort mortality study of 327 workers at a nitrile rubber manufacturing facility in the United States	Workers were employed in two departments with potential acrylonitrile exposure.	All cancer deaths	↔
		Lung cancer deaths	↔
		Digestive organ and peritoneum cancer deaths	↔
		Bladder cancer deaths	↔
		Lymphatic and hematopoietic cancer deaths	↔
Koutros et al. 2019 Retrospective cohort mortality study of 25,460 workers at eight acrylonitrile facilities in the United States; this is a follow-up to the Blair et al. (1998) study	An 8-hour TWA estimate of acrylonitrile exposure was estimated using work history, plant records, and monitoring data for each job/department/facility by time period. The 5th quintile for cumulative exposure was >12.1 ppm-years.	Lung and bronchus cancer deaths SMR HR-cumulative exposure	 ↔ ↑, 5th quintile
		Esophageal cancer deaths SMR	 ↔
		Mesothelioma deaths SMR HR	 ↔ ↔
		Breast cancer deaths SMR	 ↔
		Urinary bladder cancer deaths SMR HR-average exposure	 ↔ ↑, 3rd tertile

Table 2-4. Cancer Outcomes in Humans Exposed to Acrylonitrile

Reference, study type, and population	Exposure	Outcome evaluated	Result
		Brain/nervous system cancer deaths SMR	↔
		Lymphoma deaths SMR	↔
Marsh and Zimmerman 2015 Retrospective cohort mortality study of 2,096 workers (789 workers were exposed to acrylonitrile) at a chemical manufacturing facility in the United States. This is a follow-up to the Marsh et al. (1999) study.	Exposure estimated using historical estimates of acrylonitrile exposure, location monitoring data, and job histories. Cumulative exposure estimates and average intensity of exposure estimates were calculated for each worker. Mean cumulative exposure was 39.75 ppm-years and mean average intensity exposure was 3.69 ppm.	All cancer deaths	↔
		Bronchus, trachea, lung cancer deaths	↔
		Bladder and other urinary organs cancer deaths	↔
		Prostate cancer deaths	↔
Mastrangelo et al. 1993 Retrospective cohort mortality study of 671 male workers at an acrylic fiber facility in Italy.	Workers categorized into high exposure, low exposure, and occasionally high exposure groups based on work history. The low and occasionally high exposure groups were also exposed to dimethylacetamide.	All cancer deaths	↔
		Lung cancer deaths	↔
		Intestine and colon cancer deaths	↑, only in workers co-exposed to dimethylacetamide
		Rectum cancer deaths	↔
		Testis cancer deaths	↔
		Brain cancer deaths	↔
		Leukemia	↔

Table 2-4. Cancer Outcomes in Humans Exposed to Acrylonitrile

Reference, study type, and population	Exposure	Outcome evaluated	Result
Scélo et al. 2004 Case-control study of 2,861 workers with lung cancer and 3,118 controls from seven countries (United Kingdom, Romania, Hungary, Poland, Russia, Slovakia, Czech Republic); 39 cases and 20 controls were classified as exposed to acrylonitrile	Acrylonitrile exposure was based on expert assessment, lifetime occupational histories, and specialized questionnaires.	Lung cancer Ever exposed Cumulative exposure	 ↑ ↔
Swaen et al. 2004 Retrospective cohort study of 2,842 workers 6,803 workers (2,842 with potential exposure to acrylonitrile and 3,961 workers at a fertilizer production facility) in The Netherlands. This is a follow-up to the Swaen et al. (1992, 1998) studies; workers were followed through 2000.	Exposure assessment based on monitored data or estimated exposure based on more recent monitoring with adjustments for changes in production, industrial hygiene, and work procedures. Workers were assigned to job categories and associated exposure estimates. High cumulative exposure was 10 ppm-year.	All cancer deaths	↔, all workers ↔, high exposure
		Trachea and lung cancer deaths	↔, all workers ↔, high exposure
		Large intestine cancer death	↔, all workers
		Prostate cancer deaths	↔, all workers
		Brain cancer deaths	↔, all workers
		Leukemia deaths	↔, all workers
Symons et al. 2008 Retrospective cohort study of 2,548 workers at two orlon acrylic facilities in the United States. This is a follow-up to the Wood et al. (1998), Chen et al. (1987), O'Berg et al. (1985), and O'Berg (1980) studies; workers were followed through 2002.	Exposure was estimated for various job titles using personal and area monitoring data, history of use of personal protective equipment, plant production records, and information on work conditions and practices. The mean cumulative exposures were 61.4 and 52.1 ppm-years at the two facilities.	All cancer deaths	↔
		Respiratory cancer deaths	↔
		Prostate cancer deaths	↔
		Colorectal cancer deaths	↔

↔ = no association; ↑ = association; ↓ = inverse association; HR = hazard ratio; SMR = standardized mortality ratio; TWA = time-weighted average

Table 2-5. Occupational Studies Included in Meta Analyses[a]

Collins and Acquavella (1998) meta-analysis	
Benn and Osborne 1998	O'Berg et al. 1985
Blair et al. 1998	Ott et al. 1980, 1989
Burke 1985a, 1985b	Selzell and Monson 1982
Chen et al. 1987	Swaen et al. 1992, 1998
Collins et al. 1989	Theiss et al. 1980
Gaffey and Strauss 1981	Thomas et al.1987
Herman 1981	Werner and Carter 1981
Keisselbach et al. 1980	Wood et al. 1998
Marsh 1983	Zack 1980
Mastrangelo et al. 1993	Zhou and Wan 1991
O'Berg 1980	
Alexander et al. (2021) meta-analysis	
Benn and Osborne 1998	Ott et al. 1980
Delzell and Monson 1982	Swaen et al. 2004
Kiesselbach et al. 1979	Symons et al. 2008
Koutros et al. 2019	Thiess et al. 1980
Marsh 1983	Scelo et al. 2004
Marsh and Zimmerman 2015	
Mastrangelo et al. 1993	

[a]See meta-analysis paper for complete citations for the cited references.

Table 2-6. Neoplastic Tumors Reported in Rats and Mice Chronically Exposed to Acrylonitrile

Tissue and tumor type	Route	Cancer effect level	Reference
Central nervous system			
Brain glial cell tumors[a] (rats)	Inhalation	20 ppm (females) 80 ppm (males)	Quast et al. 1980a
Brain glial cell tumors[a] (rats)	Oral	2.5 (males) 3.7 (females)	Johannsen and Levinskas 2002a
Brain glial cell tumors[a] (rats)	Oral	3.4 mg/kg/day (males) 4.4 mg/kg/day (females)	Quast 2002
Brain glial cell tumors[a] (rats)	Oral	10 mg/kg/day	Johannsen and Levinskas 2002b
Brain and spinal glial cell tumors[a] (rats)	Oral	10.7 mg/kg/day (females)	Johannsen and Levinskas 2002b
Primary brain tumors (rats)	Oral	65 mg/kg/day (males) 72 m/g/kg/day (females)	Bigner et al. 1986
Zymbal gland			
Carcinoma (rats)	Inhalation	60 ppm (males)	Maltoni et al. 1988
Carcinoma (rats)	Inhalation	80 ppm	Quast et al. 1980a
Carcinoma (rats)	Oral	1.3 mg/kg/day (females) 2.5 mg/kg/day (males)	Johannsen and Levinskas 2002a

Table 2-6. Neoplastic Tumors Reported in Rats and Mice Chronically Exposed to Acrylonitrile

Tissue and tumor type	Route	Cancer effect level	Reference
Carcinoma (rats)	Oral	4.4 mg/kg/day (females) 21.3 mg/kg/day (males)	Quast 2002
Carcinoma (rats)	Oral	8.0 mg/kg/day (males) 10.7 mg/kg/day (females)	Johannsen and Levinskas 2002b
Carcinoma (rats)	Oral	10 mg/kg/day	Johannsen and Levinskas 2002b
Squamous carcinoma (rats)	Oral	28 mg/kg/day (males)	Gallagher et al. 1988
Gastrointestinal tract			
Tongue squamous epithelial papilloma or carcinoma (rats)	Inhalation	80 ppm (males)	Quast et al. 1980a
Tongue papilloma or carcinoma (rats)	Oral	21.3 mg/kg/day (males 25.0 mg/kg/day (females)	Quast 2002
Forestomach squamous cell papilloma/carcinoma (rats)	Oral	0.3 mg/kg/day (males) 3.7 mg/kg/day (females)	Johannsen and Levinskas 2002a
Forestomach papillomas and/or carcinoma (rats)	Oral	8.5 mg/kg/day (males) 10.8 mg/kg/day (females)	Quast 2002
Forestomach carcinoma (rats)	Oral	10 mg/kg/day (males)	Johannsen and Levinskas 2002b
Forestomach papilloma (rats)	Oral	10.7 mg/kg/day (females)	Johannsen and Levinskas 2002b
Forestomach papilloma or carcinoma (mice)	Oral	10 mg/kg/day	NTP 2001
Small intestine adenocarcinoma (rats)	Inhalation	80 ppm (males)	Quast et al. 1980a
Small intestine mucous cystadenocarcinoma (rats)	Oral	10.8 mg/kg/day (females)	Quast 2002
Intestinal adenocarcinoma (rats)	Oral	10 mg/kg/day (males)	Johannsen and Levinskas 2002b
Mammary gland			
Adenocarcinoma (rats)	Inhalation	80 ppm (females)	Quast et al. 1980a
Fibroadenomas (rats)	Oral	1.3 mg/kg/day (females)	Johannsen and Levinskas 2002a
Carcinoma (rats)	Oral	10 mg/kg/day (females)	Johannsen and Levinskas 2002b
Malignant tumors (rats)	Oral	25.0 mg/kg/day (females)	Quast 2002
Liver			
Hepatomas (rats)	Inhalation	60 ppm (males)	Maltoni et al. 1988
Harderian gland			
Adenoma or carcinoma (mice)	Oral	10 mg/kg/day	NTP 2001

Table 2-6. Neoplastic Tumors Reported in Rats and Mice Chronically Exposed to Acrylonitrile

Tissue and tumor type	Route	Cancer effect level	Reference
Lungs			
Alveolar/bronchiolar adenoma or carcinoma (mice)	Oral	10 mg/kg/day (females)	NTP 2001
Ovaries			
Granulosa cell tumors or cystadenomas (mice)	Oral	10 mg/kg/day (females)[b]	NTP 2001

[a]Study investigators diagnosed these tumors as astrocytomas.
[b]Nonsignificant increase in incidence but the investigators considered the tumors to be compound-related.

Kolenda-Roberts et al. (2013) conducted an investigation to further characterize acrylonitrile-induced brain tumors observed in rat studies. Immunohistochemical characterization was conducted on 39 spontaneously occurring brain tumors in rats (5 oligodendrogliomas, 14 astrocytomas, 8 gliomas/ mixed gliomas, and 1 severe case of gliosis (which was later considered to be an oligodendroglioma) obtained from the National Toxicology Program (NTP) and 9 astrocytomas from a 2-year acrylonitrile drinking water study (no additional information on the source was provided, likely the Quast [2002] study). Based on immunohistochemical analysis, all nine astrocytomas from acrylonitrile-exposed rats were identified as malignant microglial tumors. Similarly, Experimental Pathology Laboratories (Moore and Hardisty 2014) conducted a re-evaluation of the brain tumors reported in the 2-year inhalation study conducted by Quast et al. (1980a). Immunohistochemical analysis found that the 13 brain tumors identified as astrocytomas in the Quast et al. (1980a) study were malignant microglial tumors. These findings are supported by the results in the Bigner et al. (1986) acrylonitrile study that reported that the observed brain lesions were similar to spontaneously occurring tumors, which have been generally classified as astrocytomas; however, there was no evidence that the tumors were astrocytic in lineage or relatedness, and the tumors were negative for glial fibrillary acidic protein which is an astrocyte marker. These finding suggest that the tumors referred to as astrocytomas in the acrylonitrile studies were likely malignant microglial tumors. For this toxicological profile, ATSDR has opted to refer to these tumors as glial cell tumors.

The mechanism of acrylonitrile carcinogenicity in rats and mice has not been fully elucidated. Kobets et al. (2022) suggested that multiple mechanisms are likely involved, but the mechanisms do not likely involve direct DNA damage. Likely mechanisms for brain and forestomach tumors are direct and indirect (due to oxidative damage) cytotoxicity and compensatory cell proliferation. Kobets et al. (2022)

suggested that glutathione depletion in the brain and forestomach (and various other tissues) is a critical initiating event. Glutathione depletion results in increases in the metabolism of acrylonitrile to 2-cyanoethylene oxide and cyanide. These metabolites, as well as acrylonitrile, could initiate pro-inflammatory signaling and sustained cell and tissue injury, which could lead to compensatory cell proliferation, cell transformation, and neoplastic development (Kobets et al. 2022). Albertini et al. (2023) also suggested that multiple mechanisms are involved in acrylonitrile's mutagenicity. The investigators suggested that acrylonitrile's mutagenic mechanism of action likely involves indirect mutagenicity caused by oxidative DNA damage. Williams et al. (2017) also found no evidence that acrylonitrile exposure resulted in direct DNA damage in the brain or Zymbal's gland but found some evidence of oxidative damage.

HHS has categorized acrylonitrile as "reasonably anticipated to be a human carcinogen" (NTP 2021). EPA has categorized acrylonitrile as a probable human carcinogen (IRIS 2002). IARC (Stayner et al. 2024) concluded that acrylonitrile is "carcinogenic to humans" (Group 1).

2.20 GENOTOXICITY

The genotoxicity of acrylonitrile has been extensively studied in *in vitro* (Table 2-7) and *in vivo* (Table 2-8) studies and reviewed by Albertini et al. (2023). Mixed results have been found in studies of bacterial and mammalian system *in vitro* assays when tested with or without metabolic activation. Increases in gene mutations were observed in *in vivo* studies in rats, mice, and *Drosophila*. In contrast, most studies assessing chromosome level mutations arising in somatic cells *in vivo* in mice or rats administered acrylonitrile by a variety of routes have yielded negative results.

Table 2-7. Genotoxicity of Acrylonitrile *In Vitro*

		Results		
		Activation		
Species (test system)	Endpoint	With	Without	Reference
Prokaryotic organisms				
Salmonella typhimurium plate incorporation	Gene mutation	+	+	Khudoley et al. 1987
S. typhimurium plate incorporation	Gene mutation	+	–	Lijinsky and Andrews 1980
S. typhimurium liquid preincubation	Gene mutation	+	+	Zeiger and Haworth 1985

Table 2-7. Genotoxicity of Acrylonitrile *In Vitro*

Species (test system)	Endpoint	Results		Reference
		Activation		
		With	Without	
S. typhimurium liquid preincubation	Gene mutation	–	–	Matsushima et al. 1985
S. typhimurium gas exposure	Gene mutation	+	–	De Meester et al. 1978
S. typhimurium with plasmid pin3ERb$_5$	Gene mutation	–	–	Emmert et al. 2006
Escherichia coli	Gene mutation	ND	+	Venitt et al. 1977
Eukaryotic organisms				
Saccharomyces cerevisiae D7	Gene conversion	–	+	Arni 1985
S. cerevisiae JD1	Gene conversion	+	–	Brooks et al. 1985
S. cerevisiae RS112	Intrachromosomal recombination	+	+	Carls and Schiestl 1994
Mammalian cells				
Human lymphocytes	Gene mutation	+	–	Recio and Skopek 1988
Mouse lymphoma L5178Y thymidine kinase locus	Gene mutation	NA	+	Myhr et al. 1985
Mouse lymphoma L5178Y thymidine kinase locus	Gene mutation	+	+	Amacher and Turner 1985
Mouse lymphoma L5178Y thymidine kinase locus	Gene mutation	+	+	Lee and Webber 1985
Mouse lymphoma L5178Y ouabain resistance	Gene mutation	–	–	Garner and Campbell 1985
Mouse lymphoma L5178Y 6-thioguanine resistance	Gene mutation	+	+	Garner and Campbell 1985
Chinese hamster V79/HGPT	Gene mutation	–	–	Lee and Webber 1985
Mouse lymphoma P388F thymidine kinase locus	Gene mutation	+	–	Anderson and Cross 1985
Human lymphoblasts AHH-1 TK6	Gene mutation	+	–	Crespi et al. 1985
Human lymphoblastoid TK6	Gene mutation	+	–	Recio and Skopek 1988
Human lymphoblasts	Gene mutation	NA	+	Crespi et al. 1985
Rat liver RL4	Sister chromatid exchange	NA	–	Priston and Dean 1985
Human lymphocytes	Sister chromatid exchange	–	–	Obe et al. 1985
Human lymphocytes	Sister chromatid exchange	+	–	Perocco et al. 1982
Human bronchial epithelial cells	Sister chromatid exchange	NA	+	Chang et al. 1990

Table 2-7. Genotoxicity of Acrylonitrile *In Vitro*

Species (test system)	Endpoint	Results: Activation With	Results: Activation Without	Reference
Chinese hamster ovary	Sister chromatid exchange	+	–	Brat and Williams 1982
Human testicular cells	DNA damage	NA	–	Bjorge et al. 1996
Rat testicular cells	DNA damage	NA	–	Bjorge et al. 1996
Rat astrocytes	DNA damage	NA	–	Pu et al. 2006
Human hepatocytes	DNA strand breaks	NA	+	Robbiano et al. 1994
Human bronchial epithelial cells	DNA strand breaks	NA	+	Chang et al. 1990
Rat hepatocytes	DNA strand breaks	NA	+	Robbiano et al. 1994
Hepatocyte primary cultures	DNA synthesis	NA	+	Williams et al. 1985
Hepatocyte primary cultures	DNA synthesis	NA	+	Glauert et al. 1985
Hepatocyte primary cultures	DNA synthesis	NA	–	Probst and Hill 1985
Human mammary epithelial cells	Unscheduled DNA synthesis	NA	–	Butterworth et al. 1992
Rat hepatocytes	Unscheduled DNA synthesis	NA	–	Butterworth et al. 1992
Syrian hamster embryo cells	Cell transformation	NA	+	Sanner and Rivedal 1985; Parent and Casto 1979
Balb/C-3T3	Cell transformation	+	–	Matthews et al. 1985
C3H/10TI/2	Cell transformation	+	–	Lawrence and McGregor 1985
C3H/10TI/2	Cell transformation	NA	+	Banerjee and Segal 1986
NIH/3T3	Cell transformation	NA	+	Banerjee and Segal 1986

– = negative result; + = positive result; +/– = inconclusive results; DNA = deoxyribonucleic acid; NA = not applicable; ND = no data

Table 2-8. Genotoxicity of Acrylonitrile *In Vivo*

Species (exposure route)	Endpoint	Results	Reference
Mammalian systems			
Human lymphocytes (inhalation)	Chromosomal aberrations	–	Thiess and Fleig 1978
Human lymphocytes (inhalation)	Chromosomal aberrations	+	Major et al. 1998
Human lymphocytes (inhalation)	Chromosomal aberrations	–	Sram et al. 2004
Mouse bone marrow (i.p.)	Chromosomal aberrations	–	Leonard et al. 1981
Mouse bone marrow (i.p.)	Chromosomal aberrations	–	Sharief et al. 1986
Mouse bone marrow (oral)	Chromosomal aberrations	–	Rabello-Gay and Ahmed 1980
Human lymphocytes (inhalation)	Sister chromatid exchange	+	Major et al. 1998

Table 2-8. Genotoxicity of Acrylonitrile *In Vivo*

Species (exposure route)	Endpoint	Results	Reference
Mouse bone marrow (i.p.)	Micronuclei	–	Leonard et al. 1981
Mouse (i.p.)	Dominant lethals	–	Leonard et al. 1981
Human lymphocytes (inhalation)	Unscheduled DNA synthesis	+	Major et al. 1998
Rat lung tissue (oral)	Unscheduled DNA synthesis	+	Ahmed et al. 1992
Rat brain (oral)	Unscheduled DNA synthesis	+	Hogy and Guengerich 1986
Rat liver (oral)	Unscheduled DNA synthesis	–	Hogy and Guengerich 1986
Rat gastric mucosal tissue (oral)	Unscheduled DNA synthesis	+	Ahmed et al. 1996
Rat hepatocytes, spermatocytes (i.p.)	Unscheduled DNA synthesis	–	Butterworth et al. 1992
Human spermatozoa (inhalation)	DNA strand breaks	+	Xu et al. 2003
Rat stomach, colon, kidney, urinary bladder, lung (i.p.)	DNA strand breaks	+	Sekihashi et al. 2002
Rat liver, brain (i.p.)	DNA strand breaks	–	Sekihashi et al. 2002
Mouse stomach, colon, urinary bladder, lung, brain (i.p.)	DNA strand breaks	+	Sekihashi et al. 2002
Mouse liver, kidney (i.p.)	DNA strand breaks	–	Sekihashi et al. 2002
Rat white blood cells, brain cortical cells (oral)	DNA strand breaks	–	Pu et al. 2009
Rat lymphocytes (oral)	Gene mutations	+	Walker et al. 2020a
Mouse lymphocytes (oral)	Gene mutations	+	Walker et al. 2020b
Non-mammalian systems			
Drosophila melanogaster	Gene mutations	+	Fujikawa et al. 1985; Vogel 1985; Wurgler et al. 1985
D. melanogaster	Gene mutations	(+)	Vogel and Nivard 1993

– = negative result; + = positive result; (*) = marginally positive results associated with cytotoxicity;
DNA = deoxyribonucleic acid; i.p. = intraperitoneal injection

In vitro studies in human and rat cells have not shown increases in the occurrence of deoxyribonucleic acid (DNA) damage (Bjorge et al. 1996; Pu et al. 2006) but found increases in DNA strand breaks (Chang et al. 1990; Robbiano et al. 1994). Mixed results were found for DNA strand breaks in *in vivo* studies (Pu et al. 2009; Sekihashi et al. 2002; Xu et al. 2003). Mixed results were also found for DNA synthesis in *in vitro* studies (Butterworth et al. 1992; Glauert et al. 1985; Probst and Hill 1985; Williams et al. 1985). In contrast, the *in vivo* data generally suggest that acrylonitrile exposure resulted in increases in unscheduled DNA synthesis (Ahmed et al. 1992, 1996; Hogy and Guengerich 1986; Major et al. 1998).

Conflicting results for sister chromatid exchange have been observed, with some *in vitro* studies finding positive results (Brat and Williams 1982; Chang et al. 1990; Perocco et al. 1982) and others not finding effects (Obe et al. 1985; Priston and Dean 1985); an *in vivo* study found increases in the occurrence of

sister chromatid exchanges in the lymphocytes of workers (Major et al. 1998). Most *in vivo* studies did not find increases in chromosomal aberrations (Leonard et al. 1981; Major et al. 1998; Rabello-Gay and Ahmed 1980; Sram et al. 2004; Thiess and Fleig 1978). A study in mice did not find increases in micronuclei formation or dominant lethality (Leonard et al. 1981).

CHAPTER 3. TOXICOKINETICS, SUSCEPTIBLE POPULATIONS, BIOMARKERS, CHEMICAL INTERACTIONS

3.1 TOXICOKINETICS

- Acrylonitrile is well absorbed following inhalation and oral exposure; approximate absorption rates are 50 and 90%, respectively. Data are not available to estimate dermal absorption rates.
- It is widely distributed throughout the body, with higher levels in the liver, kidneys, lungs, and stomach.
- The primary metabolic pathway is conjugation with glutathione. It is also metabolized by the microsomal enzyme system to form 2-cyanoethylene, which is metabolized to thiocyanate or thiodiglycolic acid.
- Acrylonitrile is primarily excreted in the urine as conjugates or thiocyanate. A small percentage is excreted in air as carbon dioxide.
- Physiologically based pharmacokinetic (PBPK) models of rats and humans have been developed for predicting internal doses of acrylonitrile and cyanoethylene oxide.

3.1.1 Absorption

In a well-controlled and conducted study with volunteers, Jakubowski et al. (1987) reported that an average of 52% of the inhaled dose of acrylonitrile (5 or 10 mg/m^3) is absorbed by the lungs. Similar results were reported by Rogaczewska and Piotrowski (1968), who found that 46% of inhaled acrylonitrile is retained by the lungs of humans.

Pilon et al. (1988b) demonstrated in rats exposed to 4 mg/kg acrylonitrile (2,3-^{14}C) in a closed-circuit inhalation chamber that the absorption of acrylonitrile was biphasic, characterized by a rapid dose-dependent phase that was followed by a slower dose-independent phase.

Results of studies in laboratory animals with [^{14}C]-acrylonitrile indicate acrylonitrile is rapidly and extensively absorbed by the oral route. Radiolabeled acrylonitrile is detected in blood within 30 minutes after administration of an oral dose and peak plasma concentrations are reached 6 hours after administration (Farooqui and Ahmed 1982). Extensive absorption is indicated by the fact that only 2–10% of administered radioactivity is recovered in the feces (Ahmed et al. 1982, 1983; Farooqui and Ahmed 1982; Young et al. 1977).

In studies in volunteers conducted by Rogaczewska and Piotrowski (1968), absorption by skin was estimated to be 0.6 mg/cm^2/hour. Although no quantitative estimates of dermal absorption could be made, absorption of acrylonitrile via the dermal route by humans was demonstrated in a case study by Vogel and Kirkendall (1984). Accidental spraying of a man with acrylonitrile resulted in marked symptoms of acrylonitrile toxicity, indicating that significant amounts of acrylonitrile had been absorbed, primarily through the skin.

3.1.2 Distribution

Acrylonitrile is rapidly distributed throughout the body after inhalation exposure. Measurable amounts of acrylonitrile derived radiolabel were present in the brain, stomach, liver, kidney, lung, and blood of rats within 1 hour of initiation of exposure (Pilon et al. 1988b).

Tissue distribution of radioactivity in rats after a single oral dose of [^{14}C]-acrylonitrile indicates that acrylonitrile and its metabolites are rapidly distributed to all tissues (Ahmed et al. 1982, 1983; Burka et al. 1994; Silver et al. 1987; Young et al. 1977). Species differences are apparent. In mice, cyanide levels in the blood peaked at 1 hour, while in rats, peak levels were not reached until 3 hours after administration (Ahmed and Patel 1981). The highest levels of radioactivity were recovered in the gastrointestinal tract, in particular in the stomach. The retention of acrylonitrile and its metabolites in the stomach appears to be due, at least in part, to covalent binding (Ahmed et al. 1982; Silver et al. 1987). Following intravenous administration of [^{14}C]-labeled acrylonitrile, radiolabel was distributed to the gastrointestinal tract, suggesting enterohepatic circulation of acetonitrile or its metabolites (Ahmed et al. 1996; Jacob and Ahmed 2004; Young et al. 1977).

Distribution studies by whole-body autoradiography in rats and monkeys revealed accumulation of radiolabel in the liver, kidney, lung, adrenal cortex, and stomach. In fetuses exposed *in utero*, only the eye lens accumulated radiolabel at a higher concentration than that observed in maternal blood (Sandberg and Slanina 1980).

No studies were located regarding distribution in humans or animals following dermal exposure to acrylonitrile.

3.1.3 Metabolism

Proposed pathways for the metabolism of acrylonitrile are presented in Figure 3-1 (Ahmed et al. 1983; EPA 1980b; Langvardt et al. 1980; Linhart et al. 1988; Muller et al. 1987; Pilon et al. 1988a; Roberts et al. 1989, 1991; Sumner et al. 1997, 1999). Studies indicate that the metabolism of acrylonitrile in animals proceeds by the same pathways whether exposure is by the oral (Ahmed et al. 1983; Langvardt et al. 1980; Pilon et al. 1988a) or the inhalation route (Gut et al. 1985; Muller et al. 1987; Tardif et al. 1987). No data were located regarding the metabolism of acrylonitrile following dermal exposure.

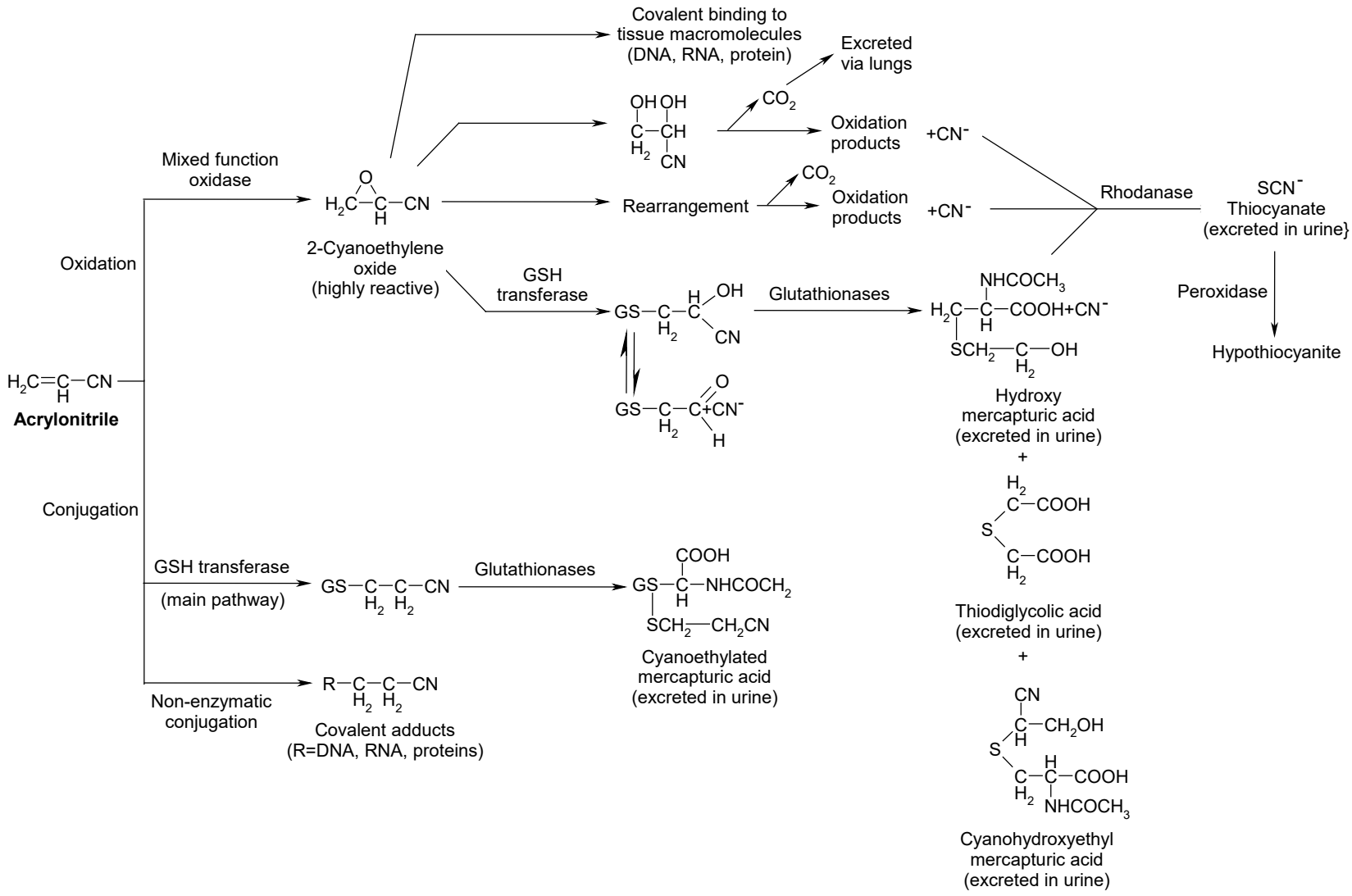
Both enzymatic and nonenzymatic biotransformation of acrylonitrile occurs. Acrylonitrile is capable of covalently binding to proteins and other macromolecules such as lipids or nucleic acids, or acrylonitrile can also be directly conjugated to glutathione and excreted in urine as cyanoethylmercapturic acid.

Alternatively, acrylonitrile is metabolized to 2-cyanoethylene oxide by the microsomal enzyme system. Cytochrome P450 2E1 is the major contributor in the microsomal pathway (Subramanian and Ahmed 1995; Sumner et al. 1999). Cytochrome c peroxidase has also been shown to oxidize acrylonitrile (Chinchilla et al. 2014). 2-Cyanoethylene oxide can react directly with tissue macromolecules, or it can be further metabolized to oxidation products that release cyanide. Cyanide is converted to thiocyanate and excreted in the urine. 2-Cyanoethylene oxide is also conjugated with glutathione and metabolized to 2-hydroxyethylmercapturic acid, which is excreted in the urine.

Acrylonitrile is also metabolized to CO_2, which is eliminated through the lungs. Carbon dioxide is produced when acrylonitrile is metabolized to ethylene oxide and degraded to oxidation products and cyanide via the epoxide hydratase pathways (Farooqui and Ahmed 1982; Young et al. 1977).

Studies indicate that acrylonitrile conjugation with glutathione is the preferred pathway for metabolism (Ghanayem and Ahmed 1982; EPA 1978; Pilon et al. 1988a). However, if glutathione is depleted or the pathway is overloaded (as may be the case at high doses), microsomal metabolism to the thiocyanate via 2-cyanoethylene oxide is increased. Following an oral dose of acrylonitrile to rats (0.09–28.8 mg/kg) or mice (0.09–10.0 mg/kg), excretion of urinary metabolites from the microsomal pathway increased linearly with dose, whereas excretion of metabolites from the direct glutathione conjugation pathway plateaued, suggesting saturation of the glutathione pathway (Kedderis et al. 1993). Increased thiocyanate excretion with glutathione depletion or increased dose was demonstrated by Pilon et al. (1988a). Glutathione depleted rats excreted 58% of an orally administered dose as thiocyanate, while

Figure 3-1. Proposed Metabolic Scheme for Acrylonitrile



Sources: Ahmed et al. 1983; Albertini et al. 2023; Linhart et al. 1988; Muller et al. 1987; Roberts et al. 1989, 1991; Sumner et al. 1997, 1999

normal rats (glutathione sufficient) given the same dose (4 mg/kg) of acrylonitrile excreted only 16% as thiocyanate. Normal rats (glutathione sufficient) given acrylonitrile at 10 mg/kg excreted 23% of the dose as thiocyanate.

The increased metabolism of acrylonitrile to 2-cyanoethylene oxide has significant implications in acrylonitrile toxicity. 2-Cyanoethylene oxide has been shown to react with cell macromolecules (including nucleic acids) both *in vivo* and *in vitro* (Guengerich et al. 1981; Hogy and Guengerich 1986). This metabolite may be responsible for the carcinogenic effects of acrylonitrile.

Urinary excretion patterns of thiocyanate suggest that there are quantitative species differences in acrylonitrile metabolism (Ahmed and Patel 1981). Thiocyanate was identified as a metabolite in rats, mice, rabbits, and Chinese hamsters. About 20–23% of the administered dose was excreted as thiocyanate in rats, rabbits, and Chinese hamsters, while 35% was excreted as thiocyanate in mice (Gut et al. 1975). A larger portion of the urinary metabolites were derived from the microsomal pathway in mice compared to rats (Fennell et al. 1991; Kedderis et al. 1993). It has also been observed that mice metabolize acrylonitrile more rapidly than rats (Ahmed and Patel 1981; Gut et al. 1975; Jacob and Ahmed 2004). Maximum blood cyanide concentrations were observed 1 hour after dosing in mice, but 3 hours after dosing in rats (Ahmed and Patel 1981). In mice, thiocyanate was present in the urine within 4 hours of dosing, while in rats, thiocyanate was present in urine only at time intervals >4 hours (Gut et al. 1975).

In humans, metabolites of acrylonitrile have been identified in urine following occupational exposure (assumed to be by the inhalation route) and in controlled exposure studies. Metabolites identified in humans were the same as those in animals (Jakubowski et al. 1987; Sakurai et al. 1978). Acrylonitrile and thiocyanate were quantified in urine of workers exposed to acrylonitrile. Dose-related increases in thiocyanate were observed, indicating that cyanide is liberated with the metabolism of acrylonitrile. In a study with volunteers under controlled conditions, N-acetyl-S-(2-cyanoethyl)-L-cysteine (2CyEMA) was monitored in urine as an indication of exposure. On average, 22% of the absorbed acrylonitrile was metabolized to 2CyEMA; however, considerable individual variability was observed. The 2CyEMA excretion ranged from 13 to 39% of the absorbed dose (Jakubowski et al. 1987).

In a case study of a human male accidentally sprayed with acrylonitrile, recurring signs of cyanide poisoning were seen over a 3-day period (Vogel and Kirkendall 1984). This indicates that acrylonitrile is also metabolized to cyanide following predominantly dermal exposure.

3.1.4 Excretion

Studies on workers in an occupational setting showed a dose-response relationship between the concentration of acrylonitrile of inspired air and the recovery of metabolites in the urine (Houthuijs et al. 1982; Sakurai et al. 1978). In a controlled study using volunteers, urinary metabolite data suggested that the elimination of acrylonitrile followed first-order kinetics, with a half-life of 7–8 hours (Jakubowski et al. 1987).

The predominant route of excretion in rats exposed by inhalation is via urine (Gut et al. 1985; Tardif et al. 1987; Young et al. 1977). In rats exposed to 5 ppm of [$^{1\text{-}14}$C]-acrylonitrile for 6 hours, 68% of the absorbed radioactivity was excreted in the urine within 220 hours, with 3.9% in the feces, 6.1% in expired air as $^{14}CO_2$, and 18% of the radioactivity being retained in the body tissues. Following exposure to a higher concentration (100 mm), a larger fraction of the dose was recovered in urine (82%) and a smaller fraction (2.6%) was retained in the body (Young et al. 1977), indicating that urinary excretion is dose-dependent. Percent fecal excretion was similar at both doses.

Following oral exposure, the major route of excretion of acrylonitrile in rats is via the urine, either as thiocyanate or as other products of conjugation. Within the first 24 hours of a single oral dose, 40–60% was recovered in the urine (Ahmed et al. 1983). Farooqui and Ahmed (1982) reported that 10 days after the administration of a single dose, 61, 3, and 13% of the dose had been accounted for in the urine, feces, and expired air, respectively. Approximately 25% was retained in the body covalently bound to tissues.

A study by Young et al. (1977) showed that retention and excretion of acrylonitrile are not directly proportional to dose. The data suggest a saturation process, perhaps due to covalent binding to tissue macromolecules. Seventy-two hours after administration of single oral doses of either 0.1 or 10 mg/kg, the proportion of the dose retained in the carcass was 37% at the low dose (0.1 mg/kg) and 27% at the high dose (10 mg/kg).

A study by Jacob and Ahmed (2004) compared elimination of acrylonitrile in mice and rats following intravenous doses of [^{14}C]-labeled acrylonitrile (mice, 3.4 mg/kg; rats, 11.5 mg/kg). In mice, 74% of the radiolabel was eliminated in 48 hours: 4% in expired air, 16% in urine, and 54% in feces. In rats, 26% of the radiolabel was eliminated: 2% in expired air, 4% in urine, and 20% in feces.

No studies were located regarding excretion in humans or animals following dermal exposure to acrylonitrile.

3.1.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

Models are simplified representations of a system with the intent of reproducing or simulating its structure, function, and behavior. PBPK models are more firmly grounded in principles of biology and biochemistry. They use mathematical descriptions of the processes determining uptake and disposition of chemical substances as a function of their physicochemical, biochemical, and physiological characteristics (Andersen and Krishnan 1994; Clewell 1995; Mumtaz et al. 2012a; Sweeney and Gearhart 2020). PBPK models have been developed for both organic and inorganic pollutants (Ruiz et al. 2011) and are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Mumtaz et al. 2012b; Ruiz et al. 2011; Sweeney and Gearhart 2020; Tan et al. 2020). PBPK models can also be used to more accurately extrapolate from animal to human, high dose to low dose, route to route, and various exposure scenarios and to study pollutant mixtures (El-Masri et al. 2004). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic endpoints (Clewell 1995).

Gargas et al. (1995) Rat Model

Description. Gargas et al. (1995) developed a model to simulate the kinetics of acrylonitrile and its microsomal metabolite, cyanoethylene oxide, in the rat. The model consists of two modules: one representing acrylonitrile and the other representing cyanoethylene oxide. Each model includes compartments representing arterial and venous blood, brain, fat, liver, lung, and two lumped compartments representing rapidly perfused and slowly perfused tissues. The acrylonitrile and cyanoethylene oxide modules are connected by conversion of acrylonitrile to cyanoethylene oxide in the liver compartment. Acrylonitrile absorbed from the gastrointestinal tract is assumed to undergo first-order transfer to the liver ($hour^{-1}$). Exchange between blood and each tissue compartment is assumed to be flow-limited and governed by the tissue blood flow rate and the arterial-venous concentration difference. The concentration of acrylonitrile or cyanoethylene oxide in tissue is assumed to be in equilibrium with tissue venous blood concentration, determined by tissue:blood partition coefficient. Two pathways for metabolism of acrylonitrile are represented in the liver: a saturable pathway that

converts acrylonitrile to cyanoethylene oxide (V_{max}, K_m) and an unlimited first-order pathway that conjugates acrylonitrile with glutathione ($hour^{-1}$). Cyanoethylene oxide is assumed to be eliminated by conjugation with glutathione in brain, liver, rapidly perfused tissues, and slowly perfused tissues. Both acrylonitrile and cyanoethylene oxide are assumed to undergo unsaturable first-order binding to blood sulfhydryls and hemoglobin ($hour^{-1}$).

A fixed fraction (88%) of the acrylonitrile metabolized through the cyanoethylene oxide pathway or through the direct glutathione or sulfhydryl binding pathway is assumed to be excreted in urine. The model includes a pathway for elimination of acrylonitrile and cyanoethylene oxide in exhaled air.

Calibration and Evaluation. Tissue:blood partition coefficients were calculated from measured tissue:air partition coefficients (Gargas et al. 1995). Rate constants for reaction of acrylonitrile and cyanoethylene oxide with hemoglobin were determined from observations of the time course for [^{14}C] binding to hemoglobin isolated from rat erythrocytes and incubated with [^{14}C]-labeled acrylonitrile (Gargas et al. 1995). Parameters for conversion of acrylonitrile to cyanoethylene oxide, conjugation of acrylonitrile and cyanoethylene oxide with glutathione, and binding of cyanoethylene oxide to blood sulfhydryls were optimized against observations of the time course of blood acrylonitrile and cyanoethylene oxide concentrations following a single intravenous dose of acrylonitrile (3.4–84 mg/kg) or a single oral dose of cyanoethylene oxide (0.6 or 5.3 mg/kg) administered to male Fisher 344 rats.

The model was evaluated against data from studies conducted in rats that were not included in the model calibration. These data consisted of observations of the fraction of an oral dose of [^{14}C], administered as [^{14}C]-labeled acrylonitrile, excreted in urine and identified as being derived from either the cyanoethylene oxide pathway or from the direct conjugation of acrylonitrile with glutathione (Kedderis et al. 1993). The comparison between the observations and predictions are presented in plots without measures of variance in the observations; however, the model appeared to predict the observed dose-response relationship for both urinary metabolite pathways. The model also predicted the observed dose-response relationship for covalent binding of [^{14}C] to rat hemoglobin, following an oral dose of [^{14}C]-labeled acrylonitrile (Fennell et al. 1991).

Kedderis et al. (1996) Rat Model

Description. Kedderis et al. (1996) modified the Gargas et al. (1995) model to include a stomach compartment and parameters to simulate the kinetics of the chemical reaction of acrylonitrile with glutathione in brain, liver, stomach, rapidly perfused tissues, and slowly perfused tissues.

Calibration and Evaluation. The rate of reaction of acrylonitrile with glutathione was measured in incubations of acrylonitrile and glutathione at concentrations above and below the non-protein sulfhydryl concentration measured in rat liver (mean 8.83±0.49 nmol/L) (Kedderis et al. 1996). Parameters for the oral absorption rate coefficient, conversion of acrylonitrile to cyanoethylene oxide, conjugation of acrylonitrile and cyanoethylene oxide with glutathione, and binding of cyanoethylene oxide were optimized against observations of the time course of blood acrylonitrile and cyanoethylene oxide concentrations following a single intravenous dose of acrylonitrile (3.4–84 mg/kg administered to male Fisher 344 rats) (Gargas et al. 1995), or following a single oral dose of acrylonitrile (3 or 30 mg/kg) (Kedderis et al. 1996).

The model was evaluated against data from studies conducted in rats that were not included in the model calibration (Kedderis et al. 1996). Rats were exposed (whole-body) to acrylonitrile in air (186, 254, or 291 ppm) or were administered a single oral dose of acrylonitrile (10 mg/kg). The model predicted the observed post-inhalation exposure time course for concentrations of acrylonitrile and cyanoethylene oxide in venous blood, brain, and liver, with most predictions within ±2 standard deviations of the observed means. The model predicted the observed time course for the concentrations of acrylonitrile in brain and liver, and cyanoethylene oxide in liver following the oral dose of acrylonitrile; however, it overpredicted the observed concentrations of cyanoethylene oxide in brain.

Applications to Dosimetry Extrapolation. Kirman et al. (2000) used the Kedderis et al. (1996) model to predict various internal dose metrics achieved in rat inhalation and oral bioassays of acrylonitrile in which brain tumors were assessed. Internal doses (peak concentrations of acrylonitrile or cyanoethylene oxide blood or brain) were predicted for several inhalation and oral bioassays, and the predicted internal doses and observed brain tumor responses for each route of exposure were pooled across studies. The pooled data were then used in dose-response models to estimate oral or inhalation exposure concentrations (mg/L drinking water, $\mu g/m^3$ air) corresponding to a $1x10^{-6}$ extra risk of brain tumors.

Sweeney et al. (2003) Human Model

Description. Sweeney et al. (2003) used the structure and parameters of the Kedderis et al. (1996) model to develop a corresponding human model. The human model included estimates of variation in human parameter values, represented by the coefficients of variation of normal distributions of the parameters.

Calibration and Evaluation. The rat liver V_{max} for conversion of acrylonitrile to cyanoethylene oxide was scaled to the human liver based on the observed ratio of the V_{max} observed in *in vitro* preparations of rat and human liver microsomes, the microsomal protein content of rat and human livers, and mass of rat and human livers (Lipscomb et al. 2003; Ploemen et al. 1997). The rate coefficient for cyanoethylene oxide hydrolysis was scaled to humans, assuming the same scaling factors used for microsomal conversion of acrylonitrile to cyanoethylene oxide. Rates of conjugation of acrylonitrile and cyanoethylene oxide with glutathione were scaled from the *in vivo* rates in the rat adjusted for differences in rates measured *in vitro* in rat and human liver, liver mass, and liver glutathione levels. Human tissue:blood partition coefficients for acrylonitrile and cyanoethylene oxide were calculated from a measured human blood:air partition coefficient and rat tissue:air coefficients (Teo et al. 1994).

Evaluations of the model against observations in humans were not reported. Sweeney et al. (2003) compared predicted concentrations of acrylonitrile and cyanoethylene oxide in blood and brain of rats and humans, performed sensitivity analyses of these internal dose metrics to parameter values, and estimated the contribution of parameter variability to variability in predicted internal dose metrics (acrylonitrile or cyanoethylene oxide blood and brain concentration area under the curve).

3.1.6 Animal-to-Human Extrapolations

The Kedderis et al. (1996) and Sweeney et al. (2003) PBPK models provide a theoretical basis for dose-response extrapolation from rats to humans, based on predicted internal doses of acrylonitrile or cyanoethylene oxide. The Kedderis et al. (1996) rat model has been evaluated for predicting observed levels of acrylonitrile and cyanoethylene oxide in blood, brain, and liver of rats. However, the Sweeney et al. (2003) human model has not been evaluated with observations made in humans.

As reviewed by Albertini et al. (2023), there are species differences in the metabolism of acrylonitrile. *In vitro* studies examining the oxidation by cytochrome P450 by liver microsomes have found greater rates in the formation of 2-cyanoethylene oxide in mice and rats than in humans; the rates were 4 times higher

in mice and 1.5 times higher in rats. The rate of 2-cyanoethylene oxide hydrolysis was significant in humans and undetectable in rats and mice, although it is inducible in all three species. Additionally, the rate of conjugation of 2-cyanoethylene oxide with glutathione is 1.5 times faster in humans than in rats or mice. Species differences have also been observed in the ratio of the oxidative urinary metabolite, N-acetyl-S-(1-cyano-2-hydroxyethyl)-L-cysteine (CHEMA), and the conjugated metabolite, N-acetyl-S-(2-cyanoethyl)-L-cysteine (CEMA). The ratios of CHEMA:CEMA were 0.3–0.4 in rats, 0.4–0.9 in mice, 0.26 in humans exposed to acrylonitrile, and 0.19 in the general population. These findings suggest that the oxidative pathway has a much larger role in rodents and that the glutathione conjugation pathway plays a larger role in humans.

3.2 CHILDREN AND OTHER POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Children may be more or less susceptible than adults to health effects from exposure to hazardous substances and the relationship may change with developmental age.

This section also discusses unusually susceptible populations. A susceptible population may exhibit different or enhanced responses to certain chemicals than most persons exposed to the same level of these chemicals in the environment. Factors involved with increased susceptibility may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters can reduce detoxification or excretion or compromise organ function.

Populations at greater exposure risk to unusually high exposure levels to acrylonitrile are discussed in Section 5.7, Populations with Potentially High Exposures.

There are limited data on potential differences in the toxicity or toxicokinetics of acrylonitrile between children and adults. Developmental effects, including malformations, decreased fetal body weight, and decreased pup viability have been reported in laboratory animal studies (Friedman and Beliles 2002; Murray et al. 1978; Nemec et al. 2008); it is noted that these effects typically occurred at doses associated with maternal toxicity. Szabo et al. (1984) found possible age-related differences in toxicity between young and adult rats. The levels of plasma corticosterone and aldosterone were significantly lower in the young rats, as compared to the adult rats.

Several polymorphisms have been evaluated to assess whether they increase the susceptibility to acrylonitrile. A study of workers handling low levels of acrylonitrile found no relationship between N-(cyanoethyl)valine, an acrylonitrile hemoglobin adduct, and the genetic states of polymorphic glutathione transferases, GSTM1 and GSTT1 (Thier et al. 1999). Similar findings were reported for CYP2E1 polymorphisms (Thier et al. 2002).

3.3 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as biomarkers of exposure, biomarkers of effect, and biomarkers of susceptibility (NAS/NRC 2006).

The National Report on Human Exposure to Environmental Chemicals provides an ongoing assessment of the exposure of a generalizable sample of the U.S. population to environmental chemicals using biomonitoring (see http://www.cdc.gov/exposurereport/). If available, biomonitoring data for acrylonitrile from this report are discussed in Section 5.6, General Population Exposure.

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 2006). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. Biomarkers of exposure to acrylonitrile are discussed in Section 3.3.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that (depending on magnitude) can be recognized as an established or potential health impairment or disease (NAS/NRC 2006). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effect caused by acrylonitrile are discussed in Section 3.3.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.2, Children and Other Populations that are Unusually Susceptible.

3.3.1 Biomarkers of Exposure

The parent acrylonitrile molecule and its metabolites have been measured in blood and urine. Measurement of thiocyanate, CEMA, and 2CyEMA have been used as biomarkers of exposure to acrylonitrile; however, thiocyanate and CEMA are not specific to acrylonitrile.

Factory workers exposed to an average of 0.1, 0.5, or 4.2 ppm of acrylonitrile in the air during an 8-hour workday averaged 3.9, 19.7, and 360 µg/L acrylonitrile in the urine, respectively, and 4.5, 5.78, and 11.4 mg/L thiocyanate in the urine, respectively (Sakurai et al. 1978). No acrylonitrile was detected in the urine of a control group, but an average of 4.00 mg/L of thiocyanate was found in the urine. The presence of thiocyanate in the urine of workers not exposed to acrylonitrile has been related to cigarette smoking (Houthuijs et al. 1982; Sakurai et al. 1978). Houthuijs et al. (1982) reported post-shift acrylonitrile values of 39 µg/L when the mean acrylonitrile concentration in the air was 0.13 ppm.

2CyEMA is formed by glutathione conjunction and is excreted in the urine. 2CyEMA is considered an adequate biomarker of acrylonitrile exposure (de Jesús et al. 2021) and has been used to monitor acrylonitrile exposure in the U.S. general population (see Section 5.6 for monitoring data).

Increased levels of the hemoglobin adduct N-(2-cyanoethyl)valine have been found in acrylonitrile workers and in smokers (Thier et al. 1999, 2002); the levels in smokers were much lower than in the acrylonitrile workers (Thier et al. 2002). Two studies have evaluated exposure to high levels of acrylonitrile resulting from a train derailment in Wetteren, Belgium using the hemoglobin adduct, N-2-cyanoethylvaline, as a biomarker of exposure. De Smedt et al. (2014) reported that 53% of the nonsmoking residents living in the evacuation zone had N-2-cyanoethylvaline levels that exceeded the reference value of 10 pmol/g globin, as compared to1% in controls. In smokers, 22% exceeded the reference value of 200 pmol/g globin versus 8% of controls. The mean N-2-cyanoethylvaline levels were 206.7 and 212.1 pmol/g globin in the nonsmokers and smokers, respectively. A study of emergency responders found that 25.7 and 55% of nonsmokers and smokers had N-2-cyanoethylvaline levels

exceeding the reference values (Van Nieuwenhuyse et al. 2014). Several investigators have used N-2-cyanoethylvaline levels to estimate individual body burdens (Huizer et al. 2014; Leng and Gries 2014). Huizer et al. (2014) used a BioNormtox PBPK model and N-2-cyanoethylvaline levels to predict initial exposure levels in four workers rescuing a colleague exposed to high levels of acrylonitrile at a train depot. The predicted air concentrations ranging between 5.6 and 17.9 ppm were similar among the workers; however, the results could not be validated with measured concentrations. Another study of these workers estimated an elimination interval of 148 days (Bader and Wrbitzky 2006). In a study in rats exposed to various doses of acrylonitrile (3–300 ppm) in drinking water for 105 days, a dose-related increase in N-(2-cyanoethyl)valine levels were found (Osterman-Golkar et al. 1994). At doses of 0.74 mg acrylonitrile/kg (10 ppm in drinking water) and lower, there was a linear relationship between dose and hemoglobin adduct levels. A sublinear relationship, indicative of saturation, was observed at higher doses.

3.3.2 Biomarkers of Effect

A variety of effects have been demonstrated following acrylonitrile exposure in humans and animals. These effects show a close similarity to an underlying cyanide effect, particularly for acute-duration exposures. Effects can be detected in groups of exposed individuals by monitoring signs and symptoms such as increased salivation, dizziness, and labored and irregular breathing. In some cases, convulsions and coma may occur. Because the release of cyanide for producing toxic effects is common for other compounds, measuring these effects is not specific for acrylonitrile exposure. These effects do identify potential health impairment. It should be noted that the toxicity of acrylonitrile resides not only in the cyanide radical, but also in the entire molecule. The latter structure explains various chronic-duration exposure effects such as cancer that result from acrylonitrile, as opposed to cyanide for which effects are more relevant for acute-duration toxicity. Studies that identify subtle physiological changes that can be used to detect or predict risk of disease following long-term exposure to acrylonitrile are not available.

3.4 INTERACTIONS WITH OTHER CHEMICALS

The interaction between acrylonitrile and other chemicals has not been thoroughly studied. O'Berg (1980) noted that out of eight workers exposed to acrylonitrile who developed lung cancer, seven were smokers (smoking history was not available for the eighth individual). This suggests that smoking might increase lung cancer risk from acrylonitrile exposure, but the data are too limited to draw any firm conclusions on this point.

Radimer et al. (1974) described four cases of severe epidermal necrolysis in individuals who had been exposed to the residual fumes of a mixture of acrylonitrile and carbon tetrachloride used to fumigate their homes. Three of the people died. The study authors thought that this was most likely due to the effects of acrylonitrile but noted that an interaction between carbon tetrachloride and acrylonitrile was possible.

In animals, the hemorrhagic effects of acrylonitrile exposure on the adrenals may be reduced by prior exposure of the animals to adrenergic blockers or chemicals that deplete the adrenal cortex of catecholamines (Silver et al. 1987; Szabo et al. 1980). It is difficult to judge whether adrenergic antagonists would have a similar protective effect in humans, because effects of acrylonitrile on the adrenal have not been described in humans.

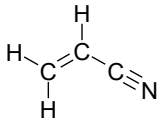
Acrylonitrile alone has little tendency to produce duodenal ulcers in animals, but pretreatment with phenobarbital or Aroclor results in a marked increase in the incidence of such ulcers (Szabo et al. 1983, 1984). Although the mechanism of the ulcerogenic effect is not obvious, these data indicate that agents that enhanced mixed-function oxidase activity may also increase the toxicity of acrylonitrile.

CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

Information regarding the chemical identity of acrylonitrile is presented in Table 4-1.

Table 4-1. Chemical Identity of Acrylonitrile

Characteristic	Information
Chemical name	Acrylonitrile
Synonym(s) and registered trade name(s)	Cyanoethylene; 2-Propenenitrile; Vinyl cyanide; Acritet, Caswell No. 010; ENT 54; Fumigrain; Ventox
Chemical formula	C_3H_3N
SMILES	C=CC#N
Chemical structure	
CAS Registry Number	107-13-1

CAS = Chemical Abstracts Service; SMILES = simplified molecular-input line-entry system

Source: NLM 2022

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Information regarding physical and chemical properties of acrylonitrile is presented in Table 4-2.

Table 4-2. Physical and Chemical Properties of Acrylonitrile

Property	Information	Reference
Molecular weight	53.06	Weast 1985
Color	Colorless	Verschueren 1983
Physical state	Liquid	Verschueren 1983
Melting point	-83°C	Verschueren 1983
Boiling point	77.4°C	Verschueren 1983
Density at 20°C	0.8060	Verschueren 1983
Odor	Pungent (onion, garlic)	Verschueren 1983
Odor threshold:		
Water	18.6 mg/L	Verschueren 1983
Air	47 mg/m^3	Verschueren 1983

Table 4-2. Physical and Chemical Properties of Acrylonitrile

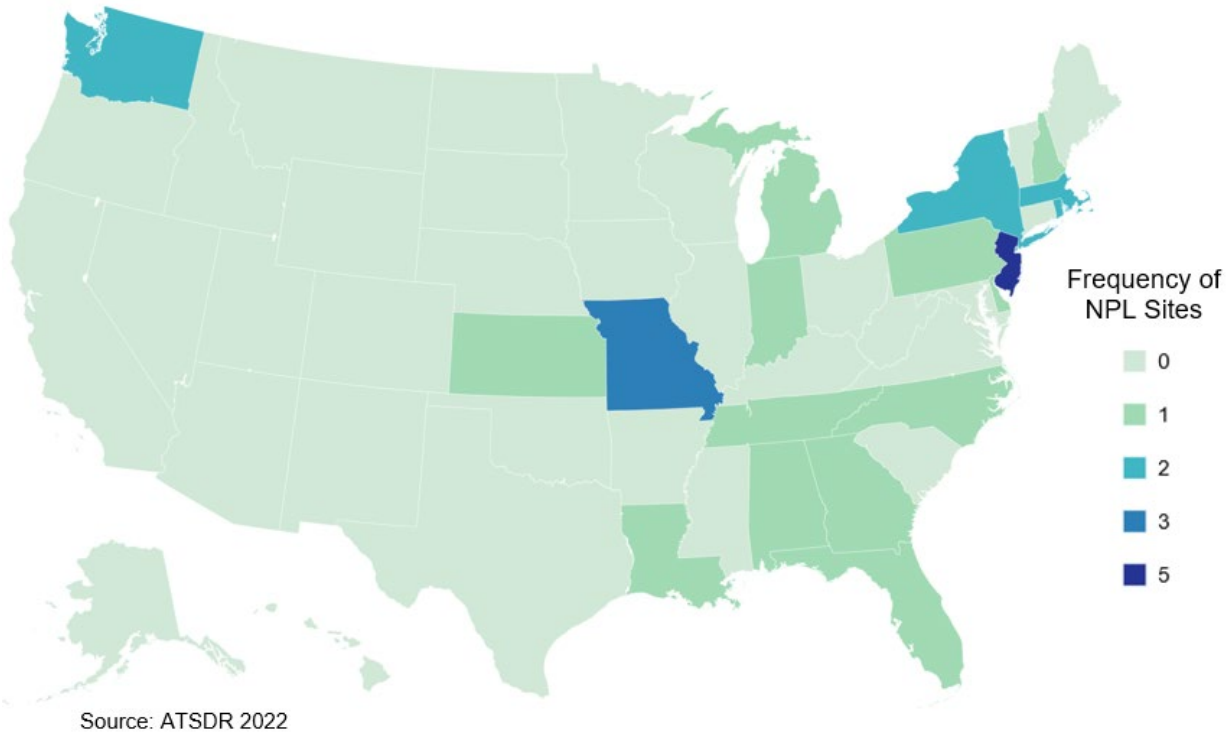
Property	Information	Reference
Solubility:		
Water at 20°C	79,000 mg/L 6,803 mg/L	Klein et al. 1957 Yalkowsky et al. 2010
Organic solvents	Soluble in all common organic solvents	Sax and Lewis 1987
Partition coefficients:		
Log K_{ow}	0.25	EPA 1982a
Log K_{oc}	1.00 and 1.10 -0.07 (estimated from Log K_{ow})	EPA 1992 EPA 1982a
Vapor pressure at 22.8°C at 25°C	 100 mm Hg 109 mm Hg	 EPA 1982a NLM 2022
Henry's law constant at 25°C	1.18×10^{-5} atm-m^3/mol 8.8×10^{-5} atm-m^3/mol (calculated from vapor pressure/water solubility)	Sander 2015 EPA 1982a
Autoignition temperature	481°C	Sax 1984
Flashpoint	-1°C	Sax 1984
Explosive limits	3–17%	Sax and Lewis 1987
Conversion factors	1 ppm=2.203 mg/m^3 1 mg/m^3=0.454 ppm	Verschueren 1983

CHAPTER 5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Acrylonitrile has been identified in at least 28 of the 1,868 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (ATSDR 2022). However, the number of sites in which acrylonitrile has been evaluated is not known. The number of sites in each state is shown in Figure 5-1.

Figure 5-1. Number of NPL Sites with Acrylonitrile Contamination



- The primary routes of exposure for the general population are the oral and inhalation routes. Members of the general public are most likely exposed to acrylonitrile through the use of products that contain acrylonitrile, such as acrylic fiber clothing or carpeting, and acrylonitrile-based plastics. Environmental exposures through air and water, especially for people near industrial or chemical waste sites, are also possible.

- Acrylonitrile may enter human food materials by leaching from plastic food containers. Data regarding acrylonitrile in food or drinking water were not available.

- Acrylonitrile is primarily released via underground injection and to the air. It has been detected at low levels in ambient air and groundwater, and in sediment, surface water, and groundwater at Superfund sites.

- Based on its volatility and water solubility, acrylonitrile will preferentially volatilize to air or remain dissolved in water. It has high mobility in soils and may migrate to groundwater. It is not expected to be persistent in air or water; however, biodegradation may be inhibited in water at high concentrations.

Acrylonitrile is primarily used to make acrylic fibers and plastics (Brazdil 2012). Previously, acrylonitrile, in combination with carbon tetrachloride, was used as a fumigant for flour milling, bakery food processing equipment, and stored tobacco; these fumigants were voluntarily withdrawn in the late 1970s (IARC 1979). Cigarette smoke is expected to still be a source of exposure for smokers based on presumed formation of acrylonitrile during combustion (Chen et al. 2019; Moldoveanu 2010).

Acrylonitrile is readily volatile (EPA 1982a), and significant quantities may escape into air during manufacture and use. Volatilization may also occur from chemical waste sites. In air, acrylonitrile is degraded primarily by reaction with hydroxyl radicals, with an estimated half-life of 1.2–12 hours (EPA 1980a; Harris et al. 1981; Teruel et al. 2007). Historically, acrylonitrile has been detected in air in the vicinity of various industrial sources at concentrations up to 150 ppbv (EPA 1980a), and recently in ambient air at up to 0.446 ppbv (EPA 2022a).

Acrylonitrile is readily soluble in water, and current total discharges to water via industrial effluents are likely low (TRI23 2024). Water contamination may occur following a spill or near a chemical site. In water, acrylonitrile has little tendency to adsorb to sediment, but is subject to biodegradation by microorganisms. The rate and extent of degradation depend upon conditions and upon the time for microbial acclimation. Degradation may approach 100% under favorable circumstances but may be inhibited by high concentrations of acrylonitrile. Acrylonitrile has not been detected in ambient surface water but was detected in surface water and groundwater at Superfund sites (WQP 2022). The vast majority of releases to the environment are via underground injection (TRI23 2024); acrylonitrile has been detected in ambient groundwater at concentrations up to 1.82 ppb (WQP 2022).

Acrylonitrile is expected to be highly mobile in soils (EPA 1992) and showed reduced biodegradation at high concentrations (Donberg et al. 1992). Acrylonitrile was not detected in ambient soil or sediment; at Superfund sites, it was detected at a maximum of 89,000 ppb in sediment (WQP 2022).

The highest exposures are expected for people working in facilities that manufacture or use acrylonitrile, and, to a lesser degree, people who smoke (Moldoveanu 2010; Stewart et al. 1998). For members of the general public who do not live near an industrial source or a chemical waste site, exposure to very low levels of acrylonitrile may occur through leaching/volatilization from consumer products, such as acrylic carpeting, or by ingestion of food stored in acrylic plastic containers (EPA 1978; IARC 1979; Lickly et al. 1991). Contact with consumer products is expected to be a primary exposure pathway, although no data quantifying this route were available. No drinking water monitoring data were available. Low environmental exposures may occur through ambient air (EPA 2022a). For people who do live near industrial or hazardous waste sites, inhalation of acrylonitrile in air is likely to be the main route of exposure (EPA 1980a), although intake through water could also be of concern.

5.2 PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.2.1 Production

Acrylonitrile is produced commercially by the process of propylene ammoxidation, in which propylene, ammonia, and air are reacted in a fluidized bed in the presence of a catalyst (EPA 1984, 1985). The propylene ammoxidation process was first patented in 1949 but became the primary process after the development of a bismuth molybdate catalyst in 1959 (Brazdil 2012). The majority of the world's production of acrylonitrile has shifted to the Asia Pacific, accounting for an estimated 58.1% of the production capacity, in comparison to 22.8% production capacity in North America (Brazdil 2012). The nationally aggregated production of acrylonitrile has held steady between 1,000,000,000 and <5,000,000,000 pounds between 2016 and 2019 (EPA 2020a).

Acrylonitrile manufacturing was reported to the Chemical Data Reporting (CDR) Rule in 2019 by three companies: Ascend Performance Materials Holdings Inc. in Harris Texas; INEOS Nitriles USA LLC, at two plants in Aurora, Illinois; and CSTN Holdings Inc. in Waggaman, Louisiana (EPA 2020a). This is not an exhaustive list; companies must meet a threshold to trigger reporting to the CDR, and other manufacturers may therefore be unreported. Table 5-1 summarizes information on companies that reported the production, import, or use of acrylonitrile for the Toxics Release Inventory (TRI) in 2023 (TRI23 2024). TRI data should be used with caution since only certain types of industrial facilities are required to report. This is not an exhaustive list.

Table 5-1. Facilities that Produce, Process, or Use Acrylonitrile

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AL	5	10,000	49,999,999	6, 7, 12, 14
AR	1	10,000	99,999	9, 12
CA	1	100,000	999,999	6
CT	2	100,000	999,999	6
GA	1	1,000,000	9,999,999	6
IL	3	10,000	9,999,999	6
IN	3	1,000	99,999	6, 9, 12
KS	1	100,000	999,999	6
KY	4	10,000	9,999,999	6, 7
LA	8	100	49,999,999	1, 4, 5, 6, 10, 12
MA	1	10,000	99,999	6
MI	3	1,000,000 (or N/A)	9,999,999 (or N/A)	6
MO	2	100	999,999	6, 12
MS	2	100,000	9,999,999	6, 7
NC	3	1,000	99,999	6
NJ	2	10,000	999,999	6
NY	2	1,000	99,999	1, 5, 6
OH	10	1,000	9,999,999	1, 4, 6, 8, 12, 14
PA	2	100,000	9,999,999	6
SC	6	1,000 (or N/A)	9,999,999 (or N/A)	6, 12
TN	3	100 (or N/A)	99,999 (or N/A)	1, 5, 6
TX	15	1,000 (or N/A)	99,999,999 (or N/A)	1, 4, 5, 6, 7, 8, 9, 10, 11, 12
VA	2	1,000	999,999	1, 3, 4, 6
WA	1	N/A	N/A	
WI	2	1,000 (or N/A)	999,999 (or N/A)	6, 8
WV	3	0	9,999,999	6, 10, 14

[a]Post office state abbreviations used.
[b]Amounts on site reported by facilities in each state. Facilities may report N/A instead of a numeric value "if the waste stream that contains or contained the EPCRA Section 313 chemical is not directed to the relevant environmental medium, or if leaks, spills, and fugitive emissions cannot occur" (EPA 2022d).
[c]Activities/Uses:

1. Produce
2. Import
3. Used Processing
4. Sale/Distribution
5. Byproduct
6. Reactant
7. Formulation Component
8. Article Component
9. Repackaging
10. Chemical Processing Aid
11. Manufacture Aid
12. Ancillary
13. Manufacture Impurity
14. Process Impurity

Note: Facilities that report N/A for amounts on site do not report activities/uses.

EPCRA = Emergency Planning and Community Right-to-Know Act; N/A = not applicable

Source: TRI23 2024 (Data are from 2023)

5.2.2 Import/Export

Imports of acrylonitrile have been relatively small. In 2019, about 1,840,000 pounds of acrylonitrile were reported as imported to the CDR (EPA 2020a). Values reported by the CDR may be lower than actual import or export quantities; companies must meet a threshold to trigger reporting, and some information may not be available in the public dataset.

A substantial fraction of the acrylonitrile produced in the United States is exported. In 2019, about 528,000,000 pounds of acrylonitrile were reported as exported to the CDR (41% of reported U.S. production) (EPA 2020a).

5.2.3 Use

The primary use of acrylonitrile is as the raw material for the manufacture of acrylic and modacrylic fibers. Other major uses include the production of plastics (acrylonitrile-butadiene-styrene [ABS] and styrene-acrylonitrile [SAN]), nitrile rubbers, nitrile barrier resins, adiponitrile, and acrylamide (EPA 1984). ABS plastics may be used for food packaging, but the residual acrylonitrile content must be <11 ppm (FDA 2022).

Acrylonitrile has been used, in a mixture with carbon tetrachloride, as a fumigant for flour milling and bakery food processing equipment and for stored tobacco. However, pesticide products containing acrylonitrile were voluntarily withdrawn by the manufacturers (IARC 1979). Registration of pesticide products in the United States containing acrylonitrile was cancelled in the late 1980s (EPA 2022b).

U.S. commercial use of acrylonitrile is 42% for acrylic fibers, 34% for ABS resins, 8% for adiponitrile, 7% for acrylamide, 3% for nitrile rubber, and 2% for carbon fiber or other uses (Brazdil 2012). Industrial uses for acrylonitrile as reported to the 2020 CDR are reproduced in Table 5-2; six companies reported consumer and commercial use of acrylonitrile, as part of chemical manufacturing (EPA 2020a).

Table 5-2. Industrial Uses of Acrylonitrile Reported Under the Chemical Data Reporting (CDR)

Industrial function category	Sector
Catalyst	Synthetic rubber manufacturing
Other; bulk liquid storage terminal	Wholesale and retail trade
Monomers	All other basic organic chemical manufacturing
	All other chemical product and preparation manufacturing
	Organic fiber manufacturing
	Paint and coating manufacturing
	Plastics material and resin manufacturing
	Synthetic rubber manufacturing
Intermediates	All other basic organic chemical manufacturing
	All other chemical product and preparation manufacturing
	Paint and coating manufacturing
	Petrochemical manufacturing
	Plastics material and resin manufacturing
	Synthetic rubber manufacturing

Source: EPA 2020a (data are from 2016–2019)

5.2.4 Disposal

Acrylonitrile is listed as a hazardous substance under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), as amended by the Superfund Amendments and Reauthorization Act (SARA), and wastes containing acrylonitrile are considered hazardous wastes under Resource Conservation and Recovery Act (RCRA) (EPA 2022c). Because acrylonitrile is listed as a hazardous substance, disposal of waste acrylonitrile is controlled by a number of federal regulations (see Chapter 7). Rotary kiln, fluidized bed, and liquid injection incineration are acceptable methods of acrylonitrile disposal (EPA 1981). Biological treatment of hazardous leachate containing acrylonitrile is very effective; activated carbon treatment was also investigated but was not as effective (EPA 1982b). Underground injection is another commonly implemented disposal method (TRI23 2024).

5.3 RELEASES TO THE ENVIRONMENT

The Toxics Release Inventory (TRI) data should be used with caution because only certain types of facilities are required to report (EPA 2022d). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ ≥10 full-time employees; if their facility's North American Industry Classification System (NAICS) codes is covered

under EPCRA Section 313 or is a federal facility; and if their facility manufactures (defined to include importing) or processes any TRI chemical in excess of 25,000 pounds, or otherwise uses any TRI chemical in excess of 10,000 pounds, in a calendar year (EPA 2022d).

5.3.1 Air

Estimated releases of 293,212 pounds (~133 metric tons) of acrylonitrile to the atmosphere from 88 domestic manufacturing and processing facilities in 2023, accounted for about 3.7% of the estimated total environmental releases from facilities required to report to the TRI (TRI23 2024). These releases are summarized in Table 5-3.

Table 5-3. Releases to the Environment from Facilities that Produce, Process, or Use Acrylonitrile[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
AL	5	120,279	62	0[l]	12,002	0	132,301	42	132,343
AR	1	1	0	0	0	0	1	0	1
CA	1	324	0	0	2	0	324	2	326
CT	2	140	0	0	0	0	140	0	140
GA	1	2,533	0	0	0	0	2,533	0	2,533
IL	3	13,645	4	0	60	372	13,649	432	14,081
IN	3	949	0	0	0	0	949	0	949
KS	1	1,130	0	0	0	0	1,130	0	1,130
KY	4	3,200	7	0	2,218	0	3,207	2,218	5,425
LA	8	19,767	53	73,569	9	0	93,389	9	93,398
MA	1	5	0	0	0	0	5	0	5
MI	3	3,346	5	0	5	0	3,356	0	3,356
MS	2	3,656	0	0	0	0	3,656	0	3,656
MO	2	32	0	0	0	0	32	0	32
NJ	2	39	0	0	0	0	39	0	39
NY	2	323	0	0	5	0	323	5	328
NC	3	792	0	0	0	0	792	0	793
OH	10	23,133	2,312	1,076,683	250	422	1,099,827	2,973	1,102,801
PA	2	408	3	0	0	0	411	0	411
SC	6	36,690	0	0	13	0	36,690	13	36,703
TN	3	1,093	123	0	0	0	1,093	123	1,216
TX	15	58,598	16	6,300,202	8	0	6,358,808	16	6,358,825
VA	2	1,669	0	0	0	0	1,669	0	1,669

Table 5-3. Releases to the Environment from Facilities that Produce, Process, or Use Acrylonitrile[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
WA	1	<RQ	<RQ	<RQ	<RQ	<RQ	<RQ	<RQ	<RQ
WV	3	1,200	179	0	0	0	1,202	177	1,379
WI	2	261	2	0	0	0	261	2	262
Total	88	293,212	2,768	7,450,454	14,572	794	7,755,787	6,014	7,761,801

[a]The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, wastewater treatment (metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II-V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other onsite landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown.
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off-site, including to POTWs.
[l]Due to reporting guidelines, a zero may represent that the facility or facilities in each state's row reported "0", and "NA", or left the cell blank in their Form R submission.

RF = reporting facilities; RQ = reportable quantity; UI = underground injection

Source: TRI23 2024 (Data are from 2023)

Because acrylonitrile is readily volatile, significant releases to air may occur during acrylonitrile production and use. EPA's National Emission Inventory (NEI) database contains information regarding sources that emit criteria air pollutants (CAPs) and their precursors and hazardous air pollutants (HAPs) for the 50 states, Washington DC, Puerto Rico, and the U.S. Virgin Islands. Emissions are estimated from multiple sources, including state and local environmental agencies; the TRI database; computer models for on- and off-road emissions; and databases related to EPA's Maximum Achievable Control Technology (MACT) programs to reduce emissions of HAPs. Acrylonitrile emissions estimated from the 2017 inventory are summarized in Table 5-4.

Table 5-4. Acrylonitrile Emissions Estimated by Sector

Sector	Emissions (pounds)
Industrial processes, chemical manufacturing	291,274.66
Waste disposal	229,796.53
Industrial processes, not elsewhere classified	23,342.01
Industrial processes, storage and transfer	20,135.49
Fuel combustion, electric generation, coal	7,908.17
Solvent, industrial surface coating and solvent use	3,044.18
Fuel combustion, industrial boilers, internal combustion engines, coal	2,539.87
Fuel combustion, electric generation, other	2,168.22
Industrial processes, petroleum refineries	1,734.29
Industrial processes, pulp and paper	378.38
Bulk gasoline terminals	318.74
Solvent, degreasing	264.32
Fuel combustion, commercial/institutional, other	149.05
Fuel combustion, industrial boilers, internal combustion engines, natural gas	113.22
Fuel combustion, commercial/institutional, natural gas	87.44
Industrial processes, cement manufacturing	47.58
Fuel combustion, electric generation, biomass	34.86
Fuel combustion, industrial boilers, internal combustion engines, other	32.95
Industrial processes, non-ferrous metals	19.61
Fuel combustion, commercial/institutional, biomass	10.20
Industrial processes, ferrous metals	9.42
Fuel combustion, commercial/institutional, oil	5.83
Fuel combustion, electric generation, natural gas	0

Source: EPA 2017

5.3.2 Water

Estimated releases of 2,768 pounds (~1.26 metric tons) of acrylonitrile to surface water from 88 domestic manufacturing and processing facilities in 2022, accounted for about <1% of the estimated total environmental releases from facilities required to report to the TRI (TRI23 2024).

Acrylonitrile may be released to water during production and use. No data were located on acrylonitrile releases to water from other sources, but because acrylonitrile is readily soluble and is not strongly adsorbed to soil or sediment, large accidental spills or leaks from chemical waste sites could lead to significant water contamination. Several examples of groundwater contamination following spills have

been reported (EPA 1978). Acrylonitrile may also be released to water by leaks or emissions from hazardous waste sites.

5.3.3 Soil

Estimated releases of 14,572 pounds (~6.61 metric tons) of acrylonitrile to soil from 88 domestic manufacturing and processing facilities in 2023 accounted for about <1% of the estimated total environmental releases from facilities required to report to the TRI (TRI23 2024). Estimated releases of 7,450,454 pounds (~3,379 metric tons) of acrylonitrile via underground injection from 88 domestic manufacturing and processing facilities in 2023 accounted for about 95.99% of the estimated total environmental releases from facilities required to report to the TRI (TRI23 2024). These releases are summarized in Table 5-3.

Direct release of acrylonitrile to soil during acrylonitrile production and use is believed to be minimal (<1 metric ton/year) (EPA 1982c).

5.4 ENVIRONMENTAL FATE

5.4.1 Transport and Partitioning

Air. No data regarding the transportation and partitioning of acrylonitrile in the environment were located. However, physical-chemical properties can be used to estimate environmental behavior. Acrylonitrile is both readily volatile to air from dry surfaces (0.13 atm at 23°C) (EPA 1982a) and highly soluble in water (6,803–79,000 mg/L) (Klein et al. 1957; Yalkowsky et al. 2010). These characteristics dominate the behavior of acrylonitrile in the environment. Based on these properties, acrylonitrile will be primarily in the vapor phase in the atmosphere and may be removed through precipitation. EPA (1980c) estimated the half-time of acrylonitrile clearance from air in wet precipitation to be >10 months. While present in air, acrylonitrile has little tendency to adsorb to particulate matter (EPA 1980c), so air transport of volatilized material is determined mainly by wind speed and direction.

Water. Based on the measured Henry's law constant of 1.18×10^{-5} atm-m^3/mol (Sander 2015), acrylonitrile is moderately volatile from surface water. Further, based on its relatively high water solubility and relatively low log K_{ow} (0.25) (EPA 1982a), acrylonitrile dissolved in water has a low tendency to adsorb to suspended soils or sediments (Roy and Griffin 1985). Surface transport is

determined by water flow parameters. In addition, acrylonitrile may penetrate into groundwater from surface spills or from contaminated surface water.

Sediment and Soil. In two low-organic carbon soils, log K_{oc} values for acrylonitrile were determined to be 1.10 in silt loam (1.49% organic carbon) and 1.00 in sandy loam (0.66% organic carbon) (EPA 1992). Based on these relatively low log K_{oc} values, supported by its relatively high water solubility, acrylonitrile is expected to be highly mobile in moist soils. The high vapor pressure indicates that evaporation from dry soil is expected to occur rapidly, and the Henry's law constant indicates that it will be moderately volatile from moist soils.

Other Media. Based on the relatively low log K_{ow} value, it would not be expected that acrylonitrile would bioaccumulate greatly in the tissues of aquatic organisms (Kenaga 1980; Neely et al. 1974). Data in aquatic organisms exposed to water containing acrylonitrile support some accumulation. Barrows et al. (1978) measured a steady-state bioconcentration factor (BCF) of 48 in bluegill sunfish. Based on the relative proportion of fat in sunfish and other aquatic organisms, EPA (1980b) estimated an average BCF of about 30 for the edible portions of freshwater and marine species.

5.4.2 Transformation and Degradation

Air. The principal pathway leading to degradation of acrylonitrile in air is believed to be photooxidation, mainly by reaction with hydroxyl radicals (OH). The rate constant for acrylonitrile reaction with OH has been measured as 4.1×10^{-12} and 1.11×10^{-11} cm^3/molecule/second (Harris et al. 1981; Teruel et al. 2007). This would correspond to an atmospheric half-life of about 1.2–3.1 hours based on a 12-hour daylight OH concentration of 1.50×10^6 molecules/cm^3. This is similar to the half-life of 9–10 hours measured in a smog chamber (EPA 1980a).

The photooxidation of acrylonitrile by hydroxyl radicals in the presence of nitric oxide has been observed to yield formaldehyde (HCHO) and formyl cyanide (HCOCN) (Hashimoto et al. 1984). From these results, the following reaction was proposed:

$$OH + CH_2CHCN + 2NO + 2O_2 \rightarrow HCHO + HCOCN + 2NO_2 + OH$$

Data given by Hashimoto et al. (1984) suggest that the half-life of acrylonitrile in the atmosphere may be on the order of 12 hours.

Acrylonitrile may also be oxidized by other atmospheric components such as ozone and oxygen, but the rates of these reactions are much lower than for OH; the experimentally determined tropospheric lifetime based on ozone oxidation is 84 days (Munshi et al. 1989). This is not considered to be an important degradative pathway.

Water. Very little is known about nonbiologically mediated transformations of acrylonitrile in water. It is not expected to hydrolyze under ambient conditions (EPA 1979). While it is known that acrylonitrile photooxidizes in air, no reliable information was found on photochemical reactions in water. There were also no data on the oxidation of acrylonitrile in water. Acrylonitrile is susceptible to oxidation by strong oxidants such as chlorine used to disinfect drinking water.

Acrylonitrile is readily degraded by aerobic microorganisms in water, especially if there is time for acclimation (Cherry et al. 1956; Mills and Stack 1954, 1955; Stover and Kincannon 1983). After 27 days of acclimation, about 70% of the acrylonitrile initially present in river water was degraded under laboratory conditions, yielding acrylic acid and ammonia. Complete degradation occurred under ideal conditions where nutrients were added to promote microbial growth (Cherry et al. 1956).

A bacterium classified as *Nocardia rhodochrous* LL 100-2 has been reported to be able to degrade acrylonitrile (DiGeronimo and Antoine 1976). An aerobic bacterium classified as Arthrobacter in an acclimated sludge completely degraded acrylonitrile after 48 hours yielding acrylic acid (Yamada et al. 1979). It was proposed that acrylonitrile was biodegraded by the following reaction:

$$CH_2CHCN + H_2O \rightarrow CH_2CHCONH_2 + H_2O \rightarrow CH_2CHCOOH + NH_3$$

It has been shown that low concentrations of acrylonitrile in solution (≤10 mg/L) can be completely degraded in a laboratory, static-culture batch experiment where domestic sewage water was the source of the microbial inoculum (Tabak et al. 1981). A solution of acrylonitrile (152 mg/L) was degraded to <0.05 mg/L in a continuous flow activated sludge system under laboratory conditions (Kincannon et al. 1983). Under simulated aerobic wastewater treatment conditions, acrylonitrile was degraded by 61–100% after 2 weeks (NITE 2022).

Studies performed using sewage sludge indicate that acrylonitrile may also be degraded by methanogenic bacteria under anaerobic conditions, although concentrations of 50–1,000 mg/L led to moderate inhibition

of bacterial fermentation (EPA 1978). This suggests that microbial degradation of acrylonitrile in anaerobic groundwater may not proceed efficiently if acrylonitrile levels were high, as might occur after a spill.

Sediment and Soil. One study regarding biodegradation of acrylonitrile in soil was located. In a study with sandy (0.53% organic carbon), sandy loam (2.6% organic carbon), and loamy clay (4.0% organic carbon) soil, mineralization half-lives were 11–19 days in the sandy soil, 0.5–1 day in the sandy loam, and 0.5 days in the loamy clay soil (Donberg et al. 1992). Decreased biodegradation was observed with increased concentrations; in the sandy soil, degradation was observed at acrylonitrile concentrations between 10 and 50 ppm, but negligible degradation was observed at 100 ppm after 78 days. In the sandy loam soil, rapid degradation occurred between 10 and 100 ppm, with decreased >50 and 80% acrylonitrile remaining after 21 days at 500 and 1,000 ppm. Data regarding transformation in sediment were not located, but similar behavior as seen in soil would be expected.

5.5 LEVELS IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to acrylonitrile depends, in part, on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of acrylonitrile in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical methods. In reviewing data on acrylonitrile levels monitored or estimated in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable.

Table 5-5 shows the lowest limit of detections that are achieved by analytical analysis in environmental media. An overview summary of the range of concentrations detected in environmental media is presented in Table 5-6.

Table 5-5. Lowest Limit of Detection Based on Standards[a]

Media	Detection limit	Reference
Air	0.003–0.14 ppb 0.012 ppmv	EPA 2022a OSHA 2001
Drinking water	0.02–20 ppb	EPA 1994b, 1994c
Surface water and groundwater	0.02–20 ppb	EPA 1994b, 1994c, 1995
Soil	9–360 ppb	EPA 1990

Table 5-5. Lowest Limit of Detection Based on Standards[a]

Media	Detection limit	Reference
Sediment	30–900 ppb	EPA 2018d
Whole blood	–	–[b]

[a]Detection limits based on using appropriate preparation and analytics. These limits may not be possible in all situations.
[b]No method located.

Table 5-6. Summary of Environmental Levels of Acrylonitrile[a]

Media	Low	High	For more information
Outdoor air (ppbv)	0.446	1.1	Section 5.5.1
Indoor air (ppbv)[b]	1.2	2.2	Section 5.5.1
Surface water (ppb)	Not detected	Not detected	Section 5.5.2
Groundwater (ppb)	1.82	13.0	Section 5.5.2
Drinking water (ppb)[b]	–	–	
Food (ppb)[b]	–	–	
Soil	Not detected	Not detected	Section 5.5.3

[a]Unit conversion: ppb = µg/L (aqueous); = µg/kg (sediment and soil); = [concentration ppbc] / 4 carbons
ppbv = 24.45 * [concentration µg/m^3] / 53.06 g/mol. Summary values represent most recent (2015–2022) ambient data available.
[b]No data located.

Detections of acrylonitrile in air at NPL sites are summarized in Table 5-7. No data are available on levels of acrylonitrile in water or soil at NPL sites (ATSDR 2022).

Table 5-7. Acrylonitrile Levels in Water, Soil, and Air of National Priorities List (NPL) Sites

Medium	Median[a]	Geometric mean[a]	Geometric standard deviation[a]	Number of quantitative measurements	NPL sites
Water (ppb)			No data		
Soil (ppb)			No data		
Air (ppbv)	2.2	2.5	10.5	5	3

[a]Concentrations found in ATSDR site documents from 1981 to 2022 for 1,868 NPL sites (ATSDR 2022). Maximum concentrations were abstracted for types of environmental media for which exposure is likely. Pathways do not necessarily involve exposure or levels of concern.

5.5.1 Air

Acrylonitrile is a pollutant included in the national Air Quality System (AQS) database, which contains ambient air pollution data collected by EPA, state, local, and tribal air pollution control agencies from monitors throughout the country. Table 5-8 shows the yearly mean 24-hour percentile distributions of acrylonitrile at monitoring stations across the United States. Average concentrations have been decreasing over the 5-year intervals. No air monitoring data was available in the Water Quality Portal (WQP 2022).

Table 5-8. Summary of Annual Concentration of Acrylonitrile (ppbv) Measured in Ambient Air at Locations Across the United States[a,b]

Year	Number of monitoring locations	Number of samples	Average of the arithmetic mean at all locations	Maximum concentration
2020–2022[c]	63	18,277	0.0101	0.446
2015–2019	86	22,094	0.0198	0.985
2010–2014	86	25,806	0.0485	1.42
2005–2009	110	23,925	0.0617	2.14
2000–2004	103	17,773	0.110	5.98

[a]Values were originally reported in parts per billion carbon (ppbC) and converted to ppbv.
[b]24-hour sampling period.
[c]As of July 28, 2022.

Source: EPA 2022a

Measurable levels of atmospheric acrylonitrile are typically associated with industrial sources; however, no recent monitoring data around industrial sites were available. Air samples collected in one acrylonitrile-fiber plant ranged from 1.4 to 9.2 ppmv (3–20 mg/m^3) (EPA 1980b). Mean 24-hour acrylonitrile concentrations in atmospheric samples collected within 5 km of 11 factories producing or using acrylonitrile ranged from <0.05 to 150 ppbv (<0.1–325 µg/m^3) (EPA 1980a). The occurrence of acrylonitrile was correlated to wind patterns; the highest concentrations were downwind of, and in close proximity to, the plant. The median concentration of acrylonitrile for 43 measurements in "source-dominated areas" (i.e., near chemical plants) was 0.97 ppbv (2.1 µg/m^3) (EPA 1983b). From Table 5-7, acrylonitrile was detected at 1.04±4.47 ppbv in air at NPL sites; there were no other data available on the concentration of acrylonitrile in air near chemical waste sites. However, air is an exposure pathway of concern due to the volatility of acrylonitrile.

A review of 148 vapor intrusion public health assessments and health consultations by ATSDR found three sites with air concentrations of acrylonitrile above 0.9 ppb (2.0 µg/m^3) (ATSDR 2005, 2007, 2008; Burk and Zarus 2013). Indoor air concentrations in three residential buildings ranged from 1.2 ppb (2.7 µg/m^3) to 2.2 ppb (4.8 µg/m^3) (ATSDR 2005, 2008). Outdoor air was detected in a play yard at 1.1 ppb (2.4 µg/m^3) (ATSDR 2007).

5.5.2 Water

Acrylonitrile is not a common contaminant of typical surface water or groundwater. The most likely source of acrylonitrile in water is industrial discharges. Recent water monitoring data around industrial sites, including NPLs, was not available, and water releases of acrylonitrile accounts for a low percentage of total reported releases (Table 5-3). Acrylonitrile was not detected in 19 wastewater samples collected between 2003 and 2009 (WQP 2022).

The Water Quality Portal (WQP) is an aggregated database of environmental monitoring data collected by EPA, U.S. Department of Agriculture (USDA), the National Water Quality Monitoring Council, state, local, and tribal water pollution control agencies, and other volunteer groups. Table 5-9 reports the concentrations of acrylonitrile detected in surface water and groundwater. Acrylonitrile was not detected in ambient surface water and was detected in low amounts in groundwater. Concentrations and detection frequency in groundwater have generally continued to decrease across the 5-year time intervals.

Table 5-9. Summary of Concentrations of Acrylonitrile (ppb) Measured in Surface Water and Groundwater Across the United States

Year range	Average	Maximum concentration	Number of samples	Percent detected
Surface water				
2020–2022[a]	–	–	87	0%
2015–2019	–	–	381	0%
2010–2014	–	–	717	0%
2005–2009	–	–	980	0%
2000–2004	–	–	1,107	0%
Groundwater				
2020–2022[a]	1.82	1.82	1,121	0.089%
2015–2019	5.89	13.0	1,337	0.67%
2010–2014	16.6	1,000	3,651	8.93%

Table 5-9. Summary of Concentrations of Acrylonitrile (ppb) Measured in Surface Water and Groundwater Across the United States

Year range	Average	Maximum concentration	Number of samples	Percent detected
2005–2009	25.5	2,500	6,969	27.4%
2000–2004	–	–	4,448	0%

[a]As of July 28, 2022.

Source: WQP 2022

Limited sampling campaigns of Superfund sites are reported in Table 5-10. More recent data were not available. No general conclusions can be determined without more data, but the detections of acrylonitrile support the possibility of increased exposure at polluted sites.

Table 5-10. Summary of Concentrations of Acrylonitrile (ppb) Measured in Surface and Groundwater at Superfund Sites

Year rage	Average	Maximum concentration	Number of samples	Percent detected
Palermo Wellfield Superfund Site				
Surface water				
2010–2014	10.0	10.0	8	100%
Groundwater				
2010–2014	10.0	10.0	53	100%
EPA Region 10 Boomsnub Superfund Site				
Groundwater				
2010–2014	0.786	1.0	42	100%
2000– 2004	10.1	100	71	100%
EPA Region 10 Superfund Portland Harbor Site				
Surface water				
2005–2009	1.0	1.0	23	100%
Groundwater				
2005–2009	6.51	250	382	100%
2000–2004	1.88	5.0	31	100%

Source: WQP 2022

Acrylonitrile is not regulated under the Safe Drinking Water Act (SDWA) and is not monitored under the Unregulated Contaminant Monitoring Rule. No data regarding acrylonitrile concentrations in drinking water were located.

5.5.3 Sediment and Soil

Limited monitoring data of acrylonitrile in soil and sediment were available. Historical data did not detect acrylonitrile in 351 sediment samples collected from lake and river bottoms across the United States (Staples et al. 1985). From sampling campaigns across the country, acrylonitrile was not detected in 87 sediment samples collected between 2010 and 2019, or in 97 samples collected between 2000 and 2009 (WQP 2022).

In 2004, acrylonitrile was detected at a maximum of 210.0 ppb (average of 47.5 ppb, n=11) in soil samples collected from Bainbridge Island, Seattle, Washington (WQP 2022). It is unclear if these are ambient samples, or if they are impacted by the Wyckoff Eagle Harbor Superfund Site on Bainbridge Island. Acrylonitrile was not detected in 274 soil samples collected between 2005 to 2009, or in 144 samples collected between 2000 to 2004 (WQP 2022). No recent data were available.

Limited sampling campaigns of Superfund sites are reported in Table 5-11. The presence of acrylonitrile at these sites supports the possibility of increased exposure at hazardous waste and other impacted sites.

Table 5-11. Summary of Concentrations of Acrylonitrile (ppb) Measured in Sediment at Superfund Sites

Year range	Average	Maximum concentration	Number of samples	Percent detected
EPA Region 10 Superfund Portland Harbor Site				
2005–2009	427	89,000	450	100%
2000–2004	85.9	12,000	406	100%
EPA Region 10 Superfund Lower Duwamish Waterway Site				
2005–2009	8.57	9.9	12	100%
2000–2004	5.34	6.9	11	100%

Source: WQP 2022

5.5.4 Other Media

As part of a biomonitoring campaign in Honolulu, Hawaii, acrylonitrile was not detected in *Lutjanus kasmira* (n=22), *Myripristis berndti* (n=22), or *Selar crumenophthalmus* (n=22) collected between 2004 and 2014 (WQP 2022). No other biomonitoring data were located.

Foods may become contaminated with acrylonitrile as a result of the migration of the monomer from chemical containers made of acrylonitrile polymers. Acrylonitrile has been found to desorb from polyacrylonitrile resins and partition into cooking oil (Gilbert et al. 1980). Other foods that may be contaminated by acrylonitrile from their containers include luncheon meat, peanut butter, margarine, fruit juice, and vegetable oil (EPA 1980b, 1983a; FDA 2022). There are few data on the extent of food-related acrylonitrile exposure. The FDA reported typical acrylonitrile concentrations in margarine of 25 µg/kg (FDA 2022), and the Commission of European Communities (CEC 1983) reported that the levels of acrylonitrile in contaminated foods are generally about 1 µg/kg. While past data suggested potential exposure, somewhat more recent data showed that there was little migration of the monomer from packaging materials because food was packaged in vastly different resins that have been drastically improved (AN Group 1990). Migration increased under simulated conditions when heated to ≥120°F, especially when heated for increasing durations of time (Lickly et al. 1991). A linear relationship between the residual acrylonitrile in the polymer and the amount that migrated was observed.

Acrylonitrile was detected in the smoke of cigarettes made in the United States in the 1960s and 1970s, usually at levels of 1–2 mg per cigarette (IARC 1979). At that time, acrylonitrile was used as a fumigant for stored tobacco. Most pesticide registrations for acrylonitrile were cancelled in 1978, and the use of acrylonitrile as a fumigant has been discontinued. This was previously believed to be the only source of acrylonitrile in cigarettes; however, the formation of acrylonitrile from nitrate and nitrite during cigarette burning has been proposed (Chen et al. 2019). This is supported by more recent detections of acrylonitrile in smoking products, at 5.10–11.59 µg/cigarette in tobacco cigarettes, and even 6.63 and 15.82 µg/cigarette in herbal cigarettes, long after the ending of usage of acrylonitrile as a fumigant (Moldoveanu 2010).

Residual acrylonitrile monomer may also occur in commercially made polymeric materials used in rugs and other products. Estimated levels include acrylic and modacrylic fibers (<1 mg acrylonitrile/kg polymeric material), acrylonitrile-based resins (15–50 mg/kg), and nitrile rubber and latex (0–750 mg/kg) (EPA 1978; IARC 1979). It is possible that acrylonitrile may evaporate into air or leach into water from these products, but no data on this topic were located.

5.6 GENERAL POPULATION EXPOSURE

Recent general population exposure estimates, based on environmental exposure measures of acrylonitrile in air and water, were not located. Based on a study published in 1979, as shown in Table 5-12, only

people living near chemical factories or work sites are likely to be exposed to measurable amounts of acrylonitrile in air and water (EPA 1980a). Because acrylonitrile has been detected recently at low levels in ambient air, some environmental exposure may occur. Members of the general population may also be potentially exposed to acrylonitrile through the consumption of acrylonitrile-contaminated food. However, it should be recalled that only foods in direct contact with acrylonitrile-based plastics are subject to contamination, and then only at very low levels. The acrylonitrile metabolite, 2CyEMA, has been used as a biomarker of exposure and was measured in urine using National Health and Nutrition Examination Survey (NHANES) 2005–2006, 2011–2012, and 2013–2014, 2015–2016, and 2017–2018 data. These monitoring data are presented in Table 5-13.

Table 5-12. Estimated Levels of Human Exposure to Acrylonitrile for Nonoccupational and Occupational Exposure

Population type	Medium	Typical concentration in medium	Assumed rate of intake of medium	Assumed absorption fraction	Estimated dose (µg/kg/day)
General[a] (70-kg adult)	Air	0.0 µg/m^3	20 m^3/day	0.9	0
	Water	0.0 µg/L	20 L/day	0.9	0
	Food	1 µg/kg	2 kg/day	0.5	0.01
Population living within 5 km of a chemical factory or waste site	Air	2–12 µg/m^3	20 m^3/day	0.9	0.5–3.0
	Water[b]	0.1 µg/L	20 L/day	0.9	0.003
Workers in an acrylonitrile factory	Air	0.1–4 mg/m^3	10 m^3/day	0.9	12.9–514

[a]Potential exposures from chemical spills and acrylic clothing were not considered.
[b]Untreated well water assuming waste effluent or leachate initially containing 10 µg/L is reduced by a factor or 100 by groundwater dilution and biodegradation before it reaches the well.

Source: EPA 1980a

Table 5-13. Urinary N-Acetyl-S-(2-Cyanoethyl)-L-Cysteine (2CyEMA) Levels (Creatinine Adjusted) (µg/g Creatinine) in the U.S. General Population

	Geometric mean	50th Percentile	75th Percentile	90th Percentile	95th Percentile	Sample size
Survey year 2005–-2006						
Total population	4.04 (3.38–4.84)	1.61 (1.46–1.82)	10.2 (4.55–34.4)	159 (124–192)	271 (234–290)	3,334
Age 12–19 years	2.24 (1.89–2.66)	1.33 (1.22–1.42)	3.24 (2.29–4.51)	37.4 (13.4–57.2)	86.9 (57.2–119)	1,029
Age 20+ years	4.44 (3.64–5.41)	1.67 (1.50–1.88)	21.2 (5.38–52.1)	182 (147–206)	281 (250–306)	2,305
Males	4.53 (3.61–5.70)	1.59 (1.41–1.84)	35.4 (8.66–63.0)	165 (124–196)	235 (206–281)	1,583
Females	3.62 (3.02–4.34)	1.63 (1.43–1.89)	4.41 (3.26–8.17)	147 (115–188)	284 (242–316)	1,751
Mexican Americans	2.34 (1.96–2.79)	1.42 (1.32–1.49)	3.03 (2.64–3.96)	31.7 (11.7–73.5)	91.0 (44.2–126)	817
Non-Hispanic Blacks	4.79 (3.95–5.81)	1.83 (1.51–2.46)	35.3 (10.2–63.3)	147 (109–183)	217 (183–259)	897
Non-Hispanic Whites	4.36 (3.41–5.56)	1.61 (1.43–1.94)	19.1 (4.11–57.2)	184 (138–225)	287 (259–315)	1,365
Survey years 2011–2012						
Total population	3.89 (3.44–4.40)	1.83 (1.73–1.93)	5.28 (4.08–7.59)	157 (119–194)	256 (224–300)	2,464
Age 6–11 years	2.11 (1.91–2.33)	2.00 (1.81–2.22)	2.95 (2.53–3.59)	5.00 (3.92–5.78)	6.31 (5.74–7.95)	393
Age 12–19 years	2.58 (2.10–3.18)	1.73 (1.51–1.88)	3.28 (2.35–5.84)	19.3 (7.61–58.9)	157 (17.6–228)	384
Age 20+ years	4.43 (3.85–5.09)	1.82 (1.66–2.00)	8.86 (5.46–20.6)	188 (151–224)	292 (238–339)	1,687
Males	4.02 (3.34–4.83)	1.76 (1.61–1.93)	7.71 (4.18–20.2)	153 (116–220)	238 (220–278)	1,250
Females	3.77 (3.01–4.73)	1.87 (1.71–2.09)	4.37 (3.22–6.59)	158 (86.4–228)	292 (229–315)	1,214
Mexican Americans	2.84 (2.20–3.66)	1.65 (1.49–1.86)	3.52 (2.40–7.27)	41.8 (20.0–93.2)	128 (39.4–345)	313
Non-Hispanic Blacks	3.91 (3.18–4.81)	1.92 (1.74–2.10)	7.14 (3.58–33.5)	120 (92.2–139)	199 (145–241)	662
Non-Hispanic Whites	4.25 (3.67–4.92)	1.85 (1.74–1.97)	6.40 (4.02–13.7)	200 (157–230)	292 (238–342)	808
All Hispanics	2.88 (2.37–3.49)	1.62 (1.53–1.78)	3.38 (2.65–4.56)	54.1 (31.6–91.7)	146 (67.8–230)	566
Asians	2.55 (2.26–2.87)	1.76 (1.61–2.15)	3.50 (2.89–4.18)	13.0 (5.64–37.8)	68.0 (26.8–98.5)	341
Survey years 2013–2014						
Total population	3.72 (3.29–4.20)	1.87 (1.71–2.02)	5.83 (4.37–8.61)	121 (97.0–144)	227 (180–286)	2,575
Age 6–11 years	2.04 (1.80–2.31)	1.87 (1.62–2.29)	3.18 (2.77–3.97)	5.74 (4.30–7.22)	7.27 (5.91–9.83)	387
Age 12–19 years	2.21 (1.77–2.75)	1.46 (1.29–1.78)	3.47 (2.35–4.83)	14.1 (5.53–84.7)	89.7 (15.1–152)	438
Age 20+ years	4.27 (3.74–4.87)	1.95 (1.76–2.08)	9.07 (6.10–17.0)	144 (122–176)	272 (215–332)	1,750
Males	3.56 (3.05–4.15)	1.73 (1.56–1.97)	6.39 (4.64–8.89)	110 (67.2–146)	228 (168–281)	1,275

Table 5-13. Urinary N-Acetyl-S-(2-Cyanoethyl)-L-Cysteine (2CyEMA) Levels (Creatinine Adjusted) (µg/g Creatinine) in the U.S. General Population

	Geometric mean	50th Percentile	75th Percentile	90th Percentile	95th Percentile	Sample size
Females	3.88 (3.21–4.68)	1.95 (1.72–2.21)	5.43 (3.91–9.19)	135 (91.6–172)	223 (176–353)	1,300
Mexican Americans	2.24 (1.85–2.71)	1.44 (1.33–1.53)	2.72 (2.07–3.68)	26.4 (6.62–57.4)	71.0 (36.3–184)	447
Non-Hispanic Blacks	5.26 (4.35–6.34)	2.28 (2.00–2.79)	31.0 (13.5–60.5)	177 (121–226)	280 (206–387)	558
Non-Hispanic Whites	3.98 (3.35–4.72)	1.95 (1.74–2.18)	7.21 (4.45–12.0)	126 (99.3–172)	260 (179–332)	934
All Hispanics	2.51 (1.96–3.23)	1.49 (1.40–1.69)	2.97 (2.28–4.51)	43.2 (8.51–89.7)	146 (51.3–235)	693
Asians	2.46 (1.94–3.12)	1.97 (1.61–2.31)	3.22 (2.72–4.12)	9.28 (4.23–82.3)	82.3 (8.63–144)	286
Survey years 2015–2016						
Total population	2.82 (2.33–3.40)	1.37 (1.26–1.48)	3.57 (2.61–6.83)	105 (65.5–143)	190 (153–225)	3,012
Age 3–5 years	2.27 (2.11–2.44)	2.13 (1.89–2.31)	3.34 (3.06–3.58)	5.06 (4.19–6.20)	7.39 (6.12–9.35)	458
Age 6–11 years	1.54 (1.35–1.75)	1.42 (1.26–1.61)	2.07 (1.74–2.51)	3.37 (2.51–4.55)	5.37 (3.28–8.85)	373
Age 12–19 years	1.39 (1.10–1.76)	.991 (.887–1.11)	1.76 (1.39–2.43)	6.40 (2.72–25.4)	35.7 (5.79–85.0)	395
Age 20+ years	3.34 (2.70–4.13)	1.41 (1.30–1.51)	6.83 (3.25–27.7)	135 (94.8–171)	216 (173–255)	1,786
Males	3.08 (2.47–3.83)	1.34 (1.23–1.47)	6.14 (2.90–19.9)	114 (70.2–161)	188 (149–222)	1,499
Females	2.59 (2.08–3.22)	1.41 (1.22–1.54)	3.03 (2.36–4.32)	85.0 (57.6–129)	196 (140–240)	1,513
Mexican Americans	1.88 (1.69–2.08)	1.20 (1.11–1.30)	2.22 (1.89–2.75)	21.5 (10.0–33.7)	81.4 (31.0–142)	577
Non-Hispanic Blacks	4.57 (3.38–6.19)	1.78 (1.48–2.49)	32.2 (7.79–66.8)	134 (106–163)	205 (163–252)	654
Non-Hispanic Whites	2.95 (2.30–3.78)	1.38 (1.23–1.49)	3.73 (2.36–12.9)	117 (61.2–184)	206 (159–251)	912
All Hispanics	2 (1.78–2.24)	1.24 (1.14–1.34)	2.40 (2.00–2.75)	30.2 (15.2–51.8)	96.4 (61.7–145)	969
Asians	1.77 (1.51–2.09)	1.34 (1.18–1.46)	2.10 (1.82–2.45)	6.93 (3.80–21.6)	38.2 (6.93–110)	329
Survey years 2017–2018						
Total population	2.77 (2.48–3.10)	1.38 (1.24–1.54)	3.44 (2.63–4.32)	106 (74.7–134)	186 (155–240)	2,653
Age 3–5 years	2.21 (1.94–2.53)	2.08 (1.79–2.36)	3.22 (2.73–3.37)	5.00 (3.76–9.31)	9.31 (4.69–14.8)	334
Age 6–11 years	1.77 (1.58–1.98)	1.63 (1.40–1.86)	2.45 (2.08–3.07)	4.23 (3.10–5.14)	5.50 (4.50–7.57)	314
Age 12–19 years	1.39 (1.12–1.73)	1.01 (0.901–1.12)	1.75 (1.46–2.42)	4.84 (2.88–33.3)	33.3 (3.41–68.5)	351
Age 20+ years	3.22 (2.78–3.73)	1.40 (1.22–1.58)	4.88 (3.41–14.2)	134 (102–162)	225 (170–278)	654
Males	3.00 (2.46–3.67)	1.35 (1.18–1.55)	4.31 (3.03–11.4)	115 (83.9–158)	212 (144–274)	1,310
Females	2.56 (2.25–2.92)	1.42 (1.24–1.61)	2.72 (2.21–3.93)	74.0 (45.2–116)	179 (127–250)	1,343

Table 5-13. Urinary N-Acetyl-S-(2-Cyanoethyl)-L-Cysteine (2CyEMA) Levels (Creatinine Adjusted) (µg/g Creatinine) in the U.S. General Population

	Geometric mean	50th Percentile	75th Percentile	90th Percentile	95th Percentile	Sample size
Mexican Americans	1.49 (1.23–1.79)	1.05 (0.957–1.25)	1.67 (1.54–2.14)	9.53 (2.63–23.5)	58.7 (16.4–86.7)	412
Non-Hispanic Blacks	4.52 (3.55–5.76)	1.67 (1.38–2.14)	36.5 (14.8–63.4)	160 (119–209)	253 (208–303)	601
Non-Hispanic Whites	2.77 (2.33–3.31)	1.36 (1.21–1.56)	3.41 (2.36–4.43)	107 (72.3–144)	179 (134–286)	861
All Hispanics	1.54 (1.34–1.78)	1.08 (0.994–1.25)	1.79 (1.64–2.07)	6.32 (3.15–20.2)	62.7 (18.2–90.3)	639
Asians	1.79 (1.51–2.12)	1.53 (1.28–1.69)	2.36 (2.03–2.85)	3.93 (3.23–5.78)	25.6 (4.40–111)	354

Source: CDC 2022

Acrylonitrile in water is expected to rapidly volatilize; thus, there is potential for inhalation exposure during showering and bathing. ATSDR's three-compartment Shower and Household-Use Exposure (SHOWER) model predicts air concentrations in the shower stall, bathroom, and main house throughout the day by estimating the contribution from showering or bathing and the contribution from other water sources in the house, such as the dishwasher, clothes washer, and faucets. The SHOWER model also estimates dermal uptake from showering, bathing, and handwashing. This information, along with human activity patterns, is used to calculate a daily TWA exposure concentration via inhalation exposure and from dermal uptake from skin contact. ATSDR's SHOWER model is a stand-alone application and is available by sending a request to showermodel@cdc.gov.

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Occupational exposures via inhalation of acrylonitrile vapor at the workplace are likely to be considerably greater than exposures outside the workplace (see Tables 5-12 and 5-14). Exposure levels may be highest for workers in plants where the chemical is used as a feedstock (EPA 1984).

Table 5-14. Estimated Levels of Worker Exposure to Acrylonitrile (ppm) at Plants Across Three Decades

		Estimated exposure per decade[a]			
Job title	Plant type	1952–1959	1960–1969	1970–1979	1980–1983
Assistant reactor operator	Fiber	6.89	6.89	4.36	1.85
Monomer operator	Monomer	0.71–1.91	0.63–16.82	0.49–6.18	0.31–1.26
Wet tow operator	Fiber	20.82	15.38	9.13	0.80
Polymer operator and helper	Fiber	18.78	18.05	3.73	1.24
Production laborer	Resin	–	7.50	3.04	0.68
Maintenance mechanic	Fiber	2.05–7.72	2.05–6.44	1.50–2.70	0.36–0.67
	Monomer	0.02–1.52	0.03–8.17	0.04–2.07	0.01–0.58
	Resin	0.36	1.57	0.09	0.05
Quality control technician[b]	Fiber	0.23–2.24	0.25–2.03	0.24–1.58	0.20–0.93
	Monomer	0.05–0.06	0.07–3.57	0.08–2.07	0.07–0.81
	Resin	0.17	0.16	0.13	0.10

[a]Expressed as 8-hour time-weighted averages.
[b]This job was performed in a laboratory in a building separate from production and was not directly related to production.

Source: Stewart et al. 1998

Occupational exposures to acrylonitrile include plastic and polymer manufacturers, polymer molders, polymer combustion workers, furniture makers, and manufacturers of fibers and synthetic rubber (EPA 1980b). Other populations that could have elevated exposure to acrylonitrile include residents in the vicinity of industrial sources or chemical waste sites.

In a cohort study of workers in facilities which manufacture acrylonitrile monomer (n=4), acrylic fiber (n=3), and acrylic resins (n=1) in Virginia, Ohio, Texas, Louisiana, Florida, and Alabama, exposure to acrylonitrile was estimated based on short-term area samples collected prior to 1977 or personal air samples collected after 1977 (Stewart et al. 1998). Exposure estimates are reported in Table 5-14. The decreasing estimated exposure reflects plant operation and engineering changes, including exhaust ventilation, process and work practice changes, and equipment. Of these changes, 47% were implemented after 1977. While occupational exposures are likely to be the highest exposure setting for acrylonitrile, steps can be taken to limit this exposure.

Case studies of acrylonitrile poisoning in humans following fumigation of living quarters in post-World War II Germany suggest that children are more susceptible to acrylonitrile than adults (Grunske 1949). Children died after sleeping in rooms recently fumigated with acrylonitrile for lice and bed bugs, while adults sharing the same quarters reported few, if any, effects (skin or eye irritation).

CHAPTER 6. ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of acrylonitrile is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the adverse health effects (and techniques for developing methods to determine such health effects) of acrylonitrile.

Data needs are defined as substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.1 Information on Health Effects

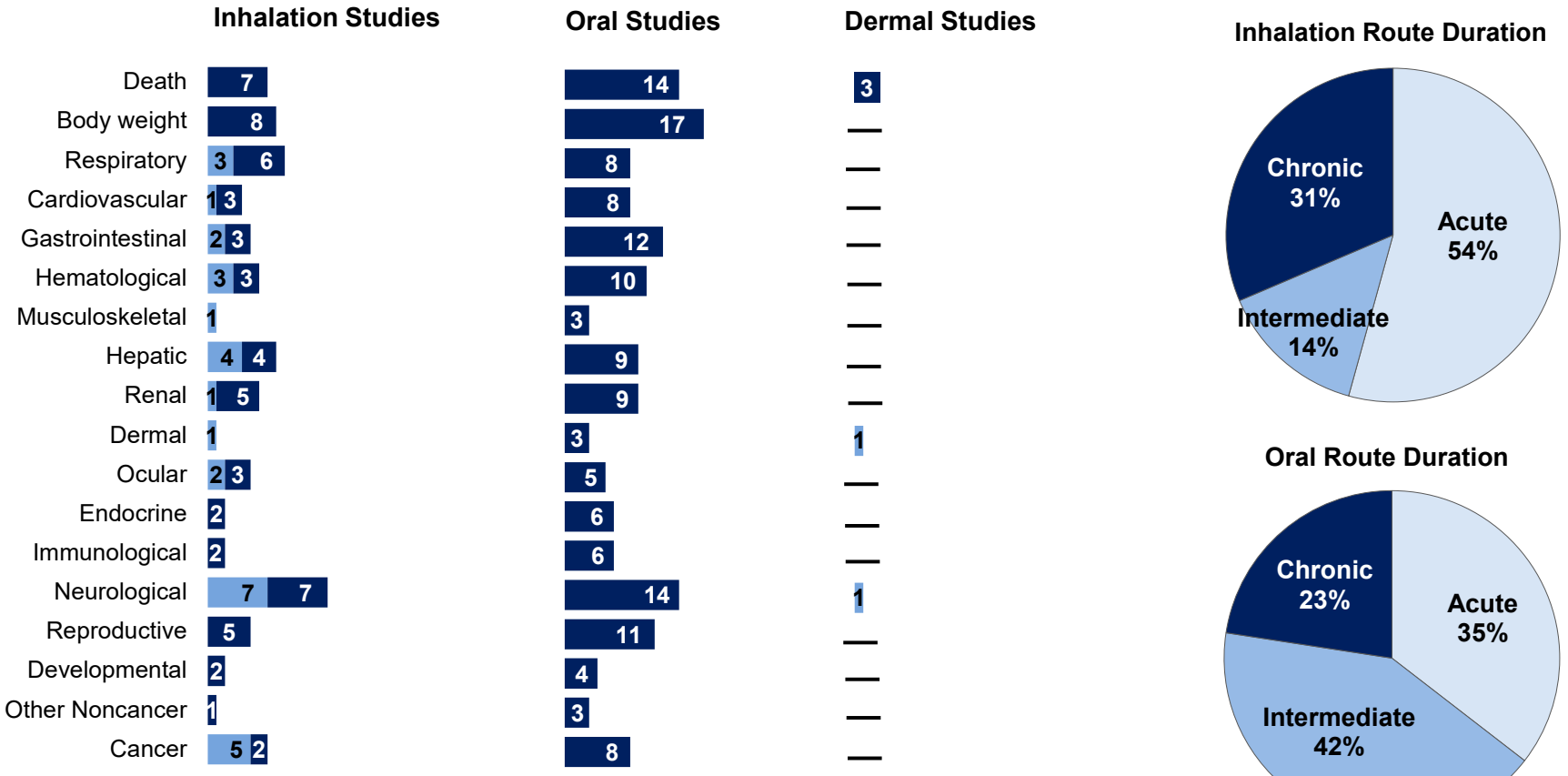
Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to acrylonitrile that are discussed in Chapter 2 are summarized in Figure 6-1. The purpose of this figure is to illustrate the information concerning the health effects of acrylonitrile. The number of human and animal studies examining each endpoint is indicated regardless of whether an effect was found and the quality of the study or studies. Note that some studies examined more than one organ system.

6.2 Identification of Data Needs

Missing information in Figure 6-1 should not be interpreted as a "data need." A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Figure 6-1. Summary of Existing Health Effects Studies on Acrylonitrile by Route and Endpoint*

Potential body weight, liver, and kidney effects were the most studied endpoints
The majority of the studies examined oral exposure in **animals** (versus **humans**)



*Includes studies discussed in Chapter 2; the number of studies include those finding no effect.

Acute-Duration MRLs. Information is available regarding the effects of acute-duration inhalation exposure of humans to acrylonitrile, and the effects are characteristic of cyanide-type toxicity. Quantitative data are limited and were not considered adequate for derivation of an acute-duration inhalation MRL. Further studies of humans exposed to low levels of acrylonitrile in the workplace would increase the confidence in derivation of an acute-duration MRL. Reliable studies in animals are needed to identify sensitive targets of toxicity and establish concentration-response relationships. No studies are available on the effects of acute-duration oral exposure in humans; however, exposure to acrylonitrile reveals neurological disturbances characteristic of cyanide-type toxicity and lethal effects in rats and mice. Rats also develop birth defects. Animal data were considered adequate for derivation of an acute-duration oral MRL. Additional studies employing several species and various dose levels would be useful in confirming target tissues and determining thresholds for these effects.

Intermediate-Duration MRLs. No information is available on the effects of intermediate-duration inhalation or oral exposure in humans. Several animal inhalation studies were identified and were considered adequate for derivation of an intermediate-duration inhalation MRL for acrylonitrile. There is information on intermediate-duration oral exposure in animals. Studies revealed decreased hemoglobin, forestomach lesions, and neurological effects in animals. Data in animals were sufficient to derive an intermediate-duration oral MRL. Further studies in animals would be useful in defining thresholds for these effects.

Chronic-Duration MRLs. Several occupational exposure studies have been identified that examined symptoms, hematological, and serum clinical chemistry parameters. No studies were located evaluating health effects associated with chronic-duration oral or dermal exposure in humans. One animal study evaluated noncancer endpoints following chronic-duration inhalation exposure; this study could not be used to derive an MRL for acrylonitrile because death was observed at the lowest dose level. Additional chronic-duration inhalation studies testing low concentrations would be useful for identifying sensitive target tissues and concentration-response relationships. Several studies have evaluated the chronic oral toxicity of acrylonitrile in rats and mice; these studies were considered adequate to identify a sensitive target of toxicity. Thus, the database was considered adequate for derivation of a chronic-duration oral MRL. Since the MRL is based on a LOAEL (lowest dose tested in the study), additional studies would be useful to establish dose-response relationships in the low dose range.

Health Effects.

Reproductive Toxicity. Information on the potential reproductive toxicity of acrylonitrile is limited to an occupational exposure study and several inhalation or oral exposure studies in animals. Studies in male rats and mice have shown that exposure to acrylonitrile results in increases in sperm aberrations, decreases in sperm motility and concentrations, and increases in sperm head and tail morphological alterations. Testicular tubular degeneration has also been observed. Studies to further evaluate the significance of the testicular effects on reproductive capability in rats, mice, and other species would be very valuable.

Developmental Toxicity. No information is available on developmental effects of acrylonitrile in humans by any route of exposure. Developmental toxicity has been observed in rats both by the oral and inhalation routes of exposure; however, effects have only been observed at maternally toxic doses. Additional studies providing insight into whether the observed effects are due to direct fetal toxicity or are secondary to the maternal toxicity would provide valuable information. Developmental studies on other animal species have not been conducted. Because species differences for acute-duration acrylonitrile toxicity and metabolism have been demonstrated, additional developmental studies in other species using various dose levels would be valuable in evaluating the potential for acrylonitrile to cause developmental effects in humans.

Immunotoxicity. Information on the immunotoxicity of acrylonitrile is limited to intermediate- and chronic-duration studies in rats and mice that examined the tissues in the immune system. No studies examined immune function. Studies evaluating potential functional impairment of the immune system are warranted at this time.

Neurotoxicity. Clinical signs indicative of disturbances of the nervous system in exposed humans have been well-documented in short-term studies at high doses and appear to be reversible. These effects are characteristic of cyanide toxicity. Animal studies confirm findings in humans. In longer-term studies, effects on the nervous system have also been reported, but it is not certain if these effects are permanent or reversible following termination of acrylonitrile exposure.

Epidemiology and Human Dosimetry Studies. There are studies on the adverse effects of acrylonitrile in humans. Most of these studies evaluated the potential carcinogenicity of acrylonitrile

exposure in workers. Many of the studies have major limitations including insufficient quantification of exposure, short follow-up, small study population, and inadequate evaluation of confounding associations. Additional studies would be useful in estimating the exposure levels associated with adverse effects.

Biomarkers of Exposure and Effect. Several biomarkers of acrylonitrile exposure have been identified. These include thiocyanate and 2CyEMA in urine and the hemoglobin adduct, N-(2-cyanoethyl)valine. Additional studies on 2CyEMA and N-(2-cyanoethyl)valine, which are specific to acrylonitrile, would be useful for assessing acrylonitrile exposure.

Effects produced by exposure to acrylonitrile, particularly after acute-duration exposures, are characteristic of cyanide toxicity. These effects can be detected in people exposed by evaluating signs and symptoms such as limb weakness, labored and irregular breathing, dizziness and impaired judgement, cyanosis, and convulsions. While tests are not specific for acrylonitrile-induced toxicity, they do identify potential health impairment. Studies to develop more specific biomarkers of acrylonitrile-induced effects would be useful in assessing the potential health risk of acrylonitrile near hazardous waste sites.

Absorption, Distribution, Metabolism, and Excretion. Metabolism and excretion in animals exposed to acrylonitrile by the inhalation and oral routes have been studied extensively. However, only limited data on absorption and distribution are available. Some data on humans exposed by inhalation are available. No data are available on the toxicokinetics of acrylonitrile when the exposure route is dermal. More extensive information on absorption and distribution of acrylonitrile would be valuable to fully understand the toxicokinetics of acrylonitrile. Some data on the toxicokinetics of acrylonitrile by the dermal route would be valuable in order to determine if metabolism of acrylonitrile differs by route of exposure.

Comparative Toxicokinetics. The absorption, distribution, metabolism, and excretion of acrylonitrile in rats has been studied. Limited work in other species suggests that important species differences do exist. Further evaluation of these differences, and comparison of metabolic patterns in humans with those of animals would assist in determining the most appropriate animal species for evaluating the hazard and risk of human exposure to acrylonitrile.

Children's Susceptibility. There are limited data to evaluate potential differences between the toxicity of acrylonitrile in children and adults. One study found differences in corticosterone and

aldosterone between young animals and adult animals; however, the biological significance of these alterations is not known. Additional studies examining a wide range of effects, especially neurological, respiratory, and gastrointestinal would be useful to identify potential age-related differences.

Physical and Chemical Properties. Most of the important physical-chemical properties of acrylonitrile have been determined (see Table 4-2). However, the partitioning of acrylonitrile between the air and water has been evaluated by using an estimated value for a Henry's law constant. This general approach assumes that the concentration of the chemical in water is low. Because acrylonitrile is soluble in water, this approach may not be accurate. Experimental measurement of the partition coefficient for acrylonitrile at water-air interfaces would be useful in refining models on the behavior of acrylonitrile in the environment.

Production, Import/Export, Use, Release, and Disposal. Substantial data exist on production, use, and emissions of acrylonitrile in the United States. Additional studies are not needed at this time because these data are readily available.

Environmental Fate. Laboratory studies indicate that acrylonitrile is biodegraded in aqueous systems promoting microbial growth, but typical degradation rates in lakes or rivers have not been studied in detail. Data on the chemical oxidation, photodegradation, and biodegradation of acrylonitrile in surface and groundwater would be helpful.

Bioavailability from Environmental Media. There are limited data on the bioavailability of acrylonitrile in different environmental media. Data on the bioavailability of acrylonitrile would be valuable.

Food Chain Bioaccumulation. Little data are available on the bioaccumulation of acrylonitrile in the food chain. This is not considered a major limitation, because the available data suggest that acrylonitrile has a relatively low tendency to be bioconcentrated by lower trophic levels.

Exposure Levels in Environmental Media. There are limited data on the levels present in soil and sediment, but because acrylonitrile is not expected to accumulate in these compartments, this may not be a major data limitation. Because higher levels of exposure are most likely near industrial sources or chemical waste sites, additional data on the occurrence of acrylonitrile in the atmosphere, surface water, and groundwater near such sites would be useful.

Exposure Levels in Humans. Human exposure levels to acrylonitrile can only be estimated based on average concentrations in air, food, and water and by measurement of biomarkers of exposure. Direct studies of personal exposure levels for individuals with exposures judged to be average and above average (e.g., people living near industrial sources or hazardous waste sites) would be helpful in improving total dose estimates, and in identifying exposure pathways of concern. More recent data regarding exposure from ingestion of food, as well as data on the potential exposure from contact with consumer products containing acrylonitrile, would useful.

Exposures of Children. Biomonitoring data in children as young as 3 years of age have been reported in the most recent National Report on Human Exposure to Environmental Chemicals (2017–2018). Continued monitoring of children would be useful.

6.3 Ongoing Studies

No ongoing studies were identified in the National Institute of Health (NIH) RePORTER (2024) database.

CHAPTER 7. REGULATIONS AND GUIDELINES

Pertinent international and national regulations, advisories, and guidelines regarding acrylonitrile in air, water, and other media are summarized in Table 7-1. This table is not an exhaustive list, and current regulations should be verified by the appropriate regulatory agency.

ATSDR develops MRLs, which are substance-specific guidelines intended to serve as screening levels by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites. See Section 1.3 and Appendix A for detailed information on the MRLs for acrylonitrile.

Table 7-1. Regulations and Guidelines Applicable to Acrylonitrile

Agency	Description	Information	Reference
		Air	
EPA	RfC	$2x10^{-3}$ mg/m^3 (0.001 ppm)	IRIS 2002
WHO	Air quality guidelines for Europe		WHO 2000
	Guideline	Treated as if a human carcinogen, no safe level can be recommended	
	Lifetime unit risk (at air concentration of 1 µg/m^3)	$2x10^{-5}$	
		Water & Food	
EPA	Drinking water standards and health advisories		EPA 2018a
	10^{-4} Cancer risk	0.006 mg/L	
	National primary drinking water regulations	Not listed	EPA 2023
	RfD	Not evaluated	IRIS 2002
WHO	Drinking water quality guidelines	Not listed	WHO 2022
FDA	Substances added to food[a]	Acrylonitrile monomer not listed	FDA 2024
		Cancer	
HHS	Carcinogenicity classification	Reasonably anticipated to be a human carcinogen	NTP 2021
EPA	Carcinogenicity classification	B1[b]	IRIS 2002
	Inhalation unit risk	$6.8x10^{-5}$ per µg/m^3	
	Oral slope factor	$5.4x10^{-1}$ per mg/kg/day	
IARC	Carcinogenicity classification	Group 1[c]	Stayner et al. 2024

Table 7-1. Regulations and Guidelines Applicable to Acrylonitrile

Agency	Description	Information	Reference
	Occupational		
OSHA	PEL (8-hour TWA) for general industry, shipyards, and construction	2 ppm	OSHA 2023a, 2023b, 2023c
	Ceiling limit (15-minute) for general industry, shipyards, and construction	10 ppm	
	Dermal and eye exposure for general industry, shipyards, and construction	No skin or eye contact with liquid acrylonitrile	
NIOSH	REL (up to 10-hour TWA)	1 ppm[d,e]	NIOSH 2019
	Ceiling limit (15-minute)	10 ppm	
	IDLH	60 ppm	NIOSH 2016
	Emergency Criteria		
EPA	AEGLs-air		EPA 2018b
	AEGL 1[f]		
	10-minute	1.5 ppm	
	30-minute	1.5 ppm	
	60-minute	NR[g]	
	4-hour	NR[g]	
	8-hour	NR[g]	
	AEGL 2[f]		
	10-minute	8.6 ppm	
	30-minute	3.2 ppm	
	60-minute	1.7 ppm	
	4-hour	0.48 ppm	
	8-hour	0.26 ppm	
	AEGL 3[f]		
	10-minute	130 ppm	
	30-minute	50 ppm	
	60-minute	28 ppm	
	4-hour	9.7 ppm	
	8-hour	5.2 ppm	

Table 7-1. Regulations and Guidelines Applicable to Acrylonitrile

Agency	Description	Information	Reference
DOE	PACs-air		DOE 2024a
	PAC-1[h]	0.15 ppm	
	PAC-2[h]	1.7 ppm	
	PAC-3[h]	28 ppm	

[a]The Substances Added to Food inventory replaces EAFUS and contains the following types of ingredients: food and color additives listed in FDA regulations, flavoring substances evaluated by FEMA or JECFA, GRAS substances listed in FDA regulations, substances approved for specific uses in food prior to September 6, 1958, substances that are listed in FDA regulations as prohibited from use in food, delisted color additives, and some substances "no longer FEMA GRAS".
[b]Group B1: probable human carcinogen, based on limited evidence of carcinogenicity in humans.
[c]Group 1: carcinogenic to humans.
[d]Skin designation.
[e]Potential occupational carcinogen.
[f]Definitions of AEGL terminology are available from U.S. Environmental Protection Agency (EPA 2018c).
[g]NR: Not recommended due to insufficient data.
[h]Definitions of PAC terminology are available from U.S. Department of Energy (DOE 2024b).

AEGL = acute exposure guideline levels; DOE = Department of Energy; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; FEMA = Flavor and Extract Manufacturers Association of the United States; GRAS = generally recognized as safe; HHS = Department of Health and Human Services; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; JECFA = Joint FAO/WHO Expert Committee on Food Additives; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PAC = protective action criteria; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TLV = threshold limit value; TWA = time-weighted average; WHO = World Health Organization

CHAPTER 8. REFERENCES

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APPENDIX A. ATSDR MINIMAL RISK LEVEL WORKSHEETS

MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified route and duration of exposure. MRLs are based on noncancer health effects only; cancer effects are not considered. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the NOAEL/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (≥365 days) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive substance-induced endpoint considered to be of relevance to humans. LOAELs for serious health effects (such as irreparable damage to the liver or kidneys, or serious birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

APPENDIX A

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Office of Innovation and Analytics, Toxicology Section, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published MRLs. For additional information regarding MRLs, please contact the Office of Innovation and Analytics, Toxicology Section, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop S106-5, Atlanta, Georgia 30329-4027.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Acrylonitrile
CAS Numbers: 107-13-1
Date: April 2025
Profile Status: Final
Route: Inhalation
Duration: Acute

MRL Summary: None of the studies identifying the lowest LOAELs were considered an adequate principal study.

Rationale for Not Deriving an MRL: Sensitive targets of toxicity can be identified from the available acute-duration inhalation database: neurotoxicity, body weight, and developmental toxicity. A summary of the NOAEL and LOAEL values for these effects is presented in Table A-1.

Table A-1. Summary of NOAEL and LOAEL Values for Sensitive Targets of Acute-duration Inhalation Exposure to Acrylonitrile

Species, duration	Effect	NOAEL (ppm)	LOAEL (ppm)	Reference
Human 8 hours		4.6		Jakubowski et al. 1987
Human 20–45 minutes	Irritability		16–100	Wilson et al. 1948
Monkey 4 hours	Weakness	65	90	Dudley and Neal 1942
Rat 8 hours/day, 5 days	Unsteady gait		125	Gut et al. 1985
Dog 4 hours	Slight salivation		30	Dudley and Neal 1942
Rat 8 hours/day, 5 days	Weight loss (magnitude not reported)		125 (serious LOAEL)	Gut et al. 1985
Rat 6 hours/day, GDs 6–15	25% decreased maternal body weight		40 (serious LOAEL)	Murray et al. 1978
Rat 6 hours/day, GDs 6–15	Increased total number of malformations	40	80	Murray et al. 1978

GD = gestation day; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level

The inhalation database was not considered suitable for derivation of an acute-duration inhalation MRL. Although two human studies evaluated possible neurological effects, they were considered inadequate principal studies. Jakubowski et al. (1987) is a toxicokinetic study, which noted that "no subjective symptoms such as headache, nausea, or general weakness" were reported; additionally, it is not ATSDR's practice to derive an MRL based on a free-standing NOAEL. Wilson et al. (1948) is not an experiment, rather it is a note about observations of workers; a wide range of concentrations were reported, and no information was provided on whether effects were observed at all concentrations. The lowest LOAELs reported in animal studies are 30 ppm for slight salivation in dogs (Dudley and Neal 1942) and 40 ppm for decreased maternal body weight in rats (Murray et al. 1978). The Dudley and Neal (1942) study is a

poorly reported study in which observations were limited to overt signs of toxicity and was not considered an adequate principal study. The Murray et al. (1978) study cannot be used as a principal study because the lowest concentration tested is a serious LOAEL.

Agency Contacts (Chemical Managers): Mohammad Shoeb

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Acrylonitrile
CAS Numbers: 107-13-1
Date: April 2025
Profile Status: Final
Route: Inhalation
Duration: Intermediate
MRL: 0.0008 ppm ($8x10^{-4}$ ppm)
Critical Effect: Hyperplasia of nasal respiratory/transitional zone epithelium
Reference: Nemec et al. 2008
Point of Departure: $BMCL_{10\text{-model average}}$ of 0.73 ppm ($BMCL_{HEC}$ of 0.024 ppm)
Uncertainty Factor: 30
LSE Graph Key: 16
Species: Rat

MRL Summary: An intermediate-duration inhalation MRL of 0.0008 ppm ($8x10^{-4}$ ppm) was derived for acrylonitrile based on an increased incidence of hyperplasia of nasal respiratory/transitional zone epithelium in F1 male rats exposed to 15 ppm acrylonitrile for 6 hours/day, 5 days/week for 18 weeks in a 2-generation study (Nemec et al. 2008). The MRL is based on a model averaged benchmark concentration lower confidence limit 10% ($BMCL_{10\text{-model average}}$) of 0.73 ppm, which was adjusted to continuous duration exposure and converted to a human equivalent concentration ($BMCL_{HEC}$) of 0.024 ppm and divided by a total uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustments and 10 for human variability).

Selection of the Critical Effect: Four studies have evaluated the intermediate-duration toxicity of inhaled acrylonitrile. A summary of the lowest LOAEL values for adverse effects is presented in Table A-2. Exposure to ≤90 ppm resulted in respiratory, body weight, gastrointestinal, neurological, and developmental effects. Based on the available data, the respiratory tract appears to be the most sensitive target. The lowest LOAEL was 15 ppm for nasal lesions (Nemec et al. 2008). Nasal lesions (slight irritation of the nasal turbinates) were also reported in rats exposed to 80 ppm 6 hours/day, 5 days/week (NOAEL of 20 ppm) for 6 or 12 months (Quast et al. 1983).

Table A-2. Summary of Lowest LOAEL Values for Targets of Intermediate-duration Inhalation Exposure to Acrylonitrile

Species, duration	Effect	NOAEL (ppm)	LOAEL (ppm)	Reference
Rat 18 weeks, 6 hours/day, 5 days/week	Hyperplasia of respiratory/ transitional zone epithelium, squamous metaplasia, subacute inflammation in nasal cavity in F1 animals	5	15	Nemec et al. 2008
Rat 12 months, 6 hours/day, 5 days/week	Decreased body weight gain in females (12%)	20	80	Quast et al. 1983
Rat 12 months, 6 hours/day, 5 days/week	Gastric irritation	20	80	Quast et al. 1983

Table A-2. Summary of Lowest LOAEL Values for Targets of Intermediate-duration Inhalation Exposure to Acrylonitrile

Species, duration	Effect	NOAEL (ppm)	LOAEL (ppm)	Reference
Rat 24 weeks, 6 hours/day, 5 days/week	Decreased sensory nerve conduction velocity		25	Gagnaire et al. 1998
Rat 28 days, 2 hours/day, 6 days/week	Increased sperm aberrations		28	Wang et al. 1995
Rat 18 weeks, 6 hours/day, 5 days/week	Decreased F1 pup body weight on PNDs 14 and 21 (5.8–12.2%)	45	90	Nemec et al. 2008

LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; PND = postnatal day

Selection of the Principal Study: The Nemec et al. (2008) study was selected as the principal study because it identified the lowest LOAEL for respiratory effects.

Summary of the Principal Study:

Nemec MD, Kirkpatrick DT, Sherman J, et al. 2008. Two-generation reproductive toxicity study of inhaled acrylonitrile vapors in CRL:CD(SD) rats. Int J Toxicol 27:11-29.

Groups of 25 male and 25 female Sprague Dawley rats were exposed to 0, 5, 15, 45, or 90 ppm acrylonitrile 6 hours/day, 7 days/week in a 2-generation study. The F0 rats were exposed for a 10-week premating period, during the 2 weeks of mating, 3 weeks of gestation (no exposure from GD 21 to PND 4), and 3 weeks of lactation; the F1 rats were similarly exposed beginning at 4 weeks of age. Exposure of F1 rats to 90 ppm was terminated after 16–29 exposures due to excessive toxicity. The following parameters were used to assess toxicity: body weight, parenteral food consumption, estrous cyclicity, number of stillborn and live pups, external malformations, pup body weight, plasma and red blood cell cholinesterase (10 rats/group in F0 control and 90 ppm groups and 10 rat/pup in F1 control and 5, 15, and 45 ppm groups), sperm parameters in F0 and F1 males, organ weights, and histopathology of adrenal glands, prostate, brain, pituitary, male and female reproductive tissues, lungs, and nasal cavity (0, 5, 15, and 45 ppm groups only) in F0 and F1 rats.

No compound-related deaths were noted. Signs of irritation (clear/red material around the nose, eyes, and mouth and on forelimbs) were observed in the F0 rats exposed to 90 ppm. Significant decreases in body weight gain were observed in the F0 rats exposed to 45 or 90 ppm, up to 11.8% at 90 ppm, and <10% at 45 ppm in males and at 45 and 90 ppm in females. A decrease in food consumption was also observed at these concentrations. In the F1 adults, clinical signs of toxicity (sensitivity to touch, vocalization upon handling, and evidence of local irritation), 10–15% decrease in food consumption, and decreases in body weight gain (>20% in males and 12% in females) were observed at 90 ppm. Significant decreases in body weight gain were also observed at 45 ppm but were <10%. No compound-related alterations in estrous cycle lengths, mating, gestation length, or reproductive performance were observed in the F0 or F1 rats. Slight, but statistically significant, decreases in sperm motility and percentage of progressive sperm motility were observed in the F0 male rats; the investigators noted that the values were within the range of historical controls and were not considered compound related. No significant alterations were noted in the numbers of F1 and F2 pups born, live litter sizes, or sex ratios, and postnatal survival was not

affected. A slight increase in male anogenital distance was observed in F1 weanlings in the 45 and 90 ppm groups, but not in F2 pups in the 45 ppm group. Given that there are no mechanisms for increasing male anogenital distance and the effect was not observed in the F2 rats, the alteration was not considered compound-related. Significant decreases in F1 pup body weight were observed at 90 ppm on PNDs 14 and 21; the magnitudes of the decreases were 6.6–12.2% for males and 5.8–10.7% in females. Slight delays in sexual development landmarks were also observed in these animals, but this was considered secondary to the decrease in body weight. In the F2 pups, decreases in male body weight were found in the 5, 15, and 45 ppm groups on PND 28; however, the changes were not dose-related and were within historical controls.

A significant decrease (40%) in plasma cholinesterase was observed in the F0 females exposed to 90 ppm, but not in males. The investigators did not consider this to be toxicologically significant in the absence of a corresponding change in red blood cell cholinesterase levels or clinical observed functional deficits. Significant alterations in organ weights were limited to an increase in absolute liver weights in F0 males at 90 ppm and decreased absolute pituitary gland weight in F0 females at 90 ppm. Histological alterations were observed in the nasal cavity and included transitional zone epithelium in F0 males at 45 ppm, F1 males at 15 and 45 ppm, and F1 females at 15 and 45 ppm; squamous metaplasia in F1 males at 15 and 45 ppm and F1 females at 15 ppm; subacute inflammation in F1 males at 15 and 45 ppm and F1 females at 15 ppm; and degeneration of the olfactory epithelium in F0 males and females at 45 ppm and F1 males and females at 45 ppm.

Selection of the Point of Departure for the MRL: The $BMCL_{10}$ is 0.80 ppm for hyperplasia of the respiratory/transitional zone epithelium in F1 male rats estimated using Bayesian model averaging was selected as the point of departure (POD) for the MRL.

A benchmark dose (BMD) approach was used to identify a potential POD for derivation of the intermediate-duration inhalation MRL for acrylonitrile. The incidence data for hyperplasia of respiratory/ transitional zone epithelium, squamous metaplasia, and subacute inflammation of the nasal cavity of the F1 rats were amenable to BMD modeling. The incidence data (Table A-3) were fit to all available dichotomous models in EPA's Benchmark Dose Software (BMDS, version 3.2) with extra risk. Adequate model fit was judged by four criteria: goodness-of-fit statistics (p-value >0.1), scaled residual at the data point (except the control) closest to the predefined benchmark response (BMR), BMCL that is not 10 times lower than the lowest non-zero dose, and visual inspection of the dose-response curve. A BMR of 10% extra risk was used.

Table A-3. Incidence Data of Nasal Cavity Lesions in F1 Rats Exposed to Acrylonitrile

	Concentration (ppm)			
Effect	0	5	15	45
Males				
Hyperplasia	2/10	6/10	10/10	10/10
Squamous metaplasia	0/10	2/10	8/10	8/10
Subacute inflammation	2/10	4/10	9/10	9/10
Females				
Hyperplasia	0/10	0/10	7/10	9/10
Squamous metaplasia	0/10	0/10	6/10	4/10
Subacute inflammation	0/10	0/10	6/10	3/10

Table A-3. Incidence Data of Nasal Cavity Lesions in F1 Rats Exposed to Acrylonitrile

	Concentration (ppm)			
Effect	0	5	15	45
Males and females combined				
Hyperplasia	2/20	6/20	17/20	19/20
Squamous metaplasia	0/20	2/20	14/20	12/20
Subacute inflammation	2/20	4/20	15/20	12/20

Source: Nemec et al. (2008)

The modeling results for hyperplasia of respiratory/transitional zone epithelium are presented in Table A-4. The Dichotomous Hill, Log-Logistic, Logistic, Log-Probit, and Probit models provided adequate fit to the male incidence data using the four model-fit criteria. However, the *p*-values of approximately 1 and scaled residuals of 0.0 suggest that the Log-Logistic and Log-Probit models are overfit and their BMCLs are not considered for MRL derivation. The benchmark concentration (BMC) and BMCL values for the suitable models were 1.13–3.82 and 0.66–0.69 ppm, respectively. Rather than using the results of one of these models, ATSDR opted to model average the results for the Dichotomous Hill, Logistic, and Probit models using EPA's BMDS Bayesian Model Average feature and using equal prior weights (33.33%) as recommended by EPA (2020b). (See Section *Other Additional Studies or Pertinent Information that Lend Support to this MR**L*** for additional information on the model averaging). Using model averaging, the posterior probabilities were 0.029, 0.326, and 0.643 for the Dichotomous Hill, Logistic, and Probit models, respectively.

Although the female incidence data provided adequate fit for three of the criteria, it did not provide adequate visual fit. For the male and female combined incidence data, the Log-Logistic model had the lowest Akaike Information Criterion (AIC) estimated BMC and BMCL values of 2.87 and 1.11 ppm, respectively.

Table A-4. Results from BMD Analysis of Incidence of Hyperplasia of Respiratory/Transitional Zone Epithelium in F1 Rats Exposed to Acrylonitrile in a 2-Generation Study (Nemec et al. 2008)

					Scaled residuals[c]	
Model	BMC_{10}[a] (ppm)	$BMCL_{10}$[a] (ppm)	p-value[b]	AIC	Concentration below BMC[d]	Concentration above BMC[d]
Males						
Dichotomous Hill	3.82	0.66	0.975	29.47	0.00	0.00
Gamma[d]			1.000	27.47	0.00	0.00
Log-Logistic[e]			1.000	27.47	0.00	0.00
Multistage Degree 3[f]			NA	31.47	0.00	0.00
Multistage Degree 2[f]			0.992	27.50	0.02	0.02
Multistage Degree 1[f]			0.642	28.76	0.14	0.14
Weibull[d]			0.999	27.47	0.00	0.00
Logistic	1.17	0.68	0.922	27.73	0.16	0.16

Table A-4. Results from BMD Analysis of Incidence of Hyperplasia of Respiratory/Transitional Zone Epithelium in F1 Rats Exposed to Acrylonitrile in a 2-Generation Study (Nemec et al. 2008)

Model	BMC_{10}[a] (ppm)	$BMCL_{10}$[a] (ppm)	p-value[b]	AIC	Scaled residuals[c]	
					Concentration below BMC[d]	Concentration above BMC[d]
Log-Probit			1.000	29.47	0.00	0.00
Probit	1.13	0.69	0.969	27.57	0.10	0.10
Bayesian Model average[g]	**1.28**	**0.73**				
Males and females combined						
Dichotomous Hill			NA	70.29	3.31×10^{-8}	-1.24×10^{-7}
Gamma[d]			0.088	71.13	0.113	0.113
Log-Logistic[e,g]	**2.87**	**1.11**	**0.339**	**69.12**	**-0.297**	**0.0815**
Multistage Degree 3[f]	1.29	0.919	0.244	69.16	0.148	0.148
Multistage Degree 2[f]	1.29	0.919	0.244	69.16	0.148	0.148
Multistage Degree 1[f]	1.29	0.919	0.244	69.16	0.148	0.148
Weibull[d]	1.29	0.919	0.244	69.16	0.148	0.148
Logistic			0.000	73.15	-0.226	-0.904
Log-Probit	2.73	1.02	0.228	69.67	-0.437	0.0905
Probit			0.003	75.84	-0.334	-1.26

[a]BMC and BMCL values for models that do not provide adequate fit are not included in this table.
[b]Values <0.1 fail to meet conventional χ^2 goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the BMC.
[d]Power restricted to ≥1.
[e]Slope restricted to ≥1.
[f]Betas restricted to ≥0.
[g]Recommended model. BMCLs for models providing adequate fit differed by <3-fold; therefore, the model with the lowest AIC was selected.

AIC = Akaike Information Criterion; BMC = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMCL = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., $_{10}$ = exposure dose associated with a 10% extra risk); BMD = benchmark dose

The results of the BMD modeling for squamous metaplasia are presented in Table A-5. In male rats, the Gamma, Multistage 2, and Weibull models were recommended because they identified the lowest AIC. These models estimated a BMC and BMCL of 1.93 and 1.27 ppm, respectively. In female rats, the lowest AIC was identified for the Dichotomous Hill model with an estimated BMC of 8.23 ppm and BMCL of 4.75 ppm. For males and females combined, the BMC and BMCL values are 5.00 and 3.41 ppm, respectively, estimated using the dichotomous model, which had the lowest AIC.

Table A-5. Results from BMD Analysis of Incidence of Squamous Metaplasia in F1 Rats Exposed to Acrylonitrile in a 2-Generation Study (Nemec et al. 2008)

Model	BMC_{10}[a] (ppm)	$BMCL_{10}$[a] (ppm)	p-Value[b]	AIC	Scaled residuals[c]	
					Concentration below BMC[d]	Concentration above BMC[d]
Males						
Dichotomous Hill			NA	38.02	0.00	0.00
Gamma[d,e]	**1.93**	**1.27**	**0.250**	**35.93**	**0.00**	**0.00**
Log-Logistic[f]	1.94	0.55	0.332	36.27	0.00	0.00
Multistage Degree 3[g]	1.93	1.27	0.250	35.93	0.00	0.00
Multistage Degree 2[g]	**1.93**	**1.27**	**0.250**	**35.93**	**0.00**	**0.00**
Multistage Degree 1[g]	1.93	1.27	0.128	37.93	0.00	0.00
Weibull[d]	**1.93**	**1.27**	**0.250**	**35.93**	**0.00**	**0.00**
Logistic			0.011	44.71	-0.41	-1.50
Log-Probit			0.127	38.44	0.00	0.00
Probit			0.011	44.85	-0.38	-1.49
Females						
Dichotomous Hill[e]	**8.23**	**4.75**	**0.663**	**31.75**	**-0.07**	**0.00**
Gamma[d]			0.013	39.58	-1.03	0.00
Log-Logistic[f]			0.081	36.49	-1.21	0.00
Multistage Degree 3[g]			0.034	37.58	-1.03	0.00
Multistage Degree 2[g]			0.034	37.58	-1.03	0.00
Multistage Degree 1[g]			0.013	39.58	-1.03	0.00
Weibull[d]			0.034	37.58	-1.03	0.00
Logistic			0.002	44.19	2.96	-1.19
Log-Probit			0.011	40.22	-1.22	0.00
Probit			0.002	43.90	2.98	-1.12
Males and females combined						
Dichotomous Hill[e]	**5.00**	**3.41**	**0.507**	**70.80**	**0.00**	**0.00**
Gamma[d]			0.008	77.67	-0.65	0.00
Log-Logistic[e,f]			0.021	76.39	0.00	0.00
Multistage Degree 3[g]			0.008	77.67	-0.65	0.00
Multistage Degree 2[g]			0.008	77.67	-0.65	0.00
Multistage Degree 1[g]			0.008	77.67	-0.65	0.00
Weibull[d]			0.008	77.67	-0.65	0.00
Logistic			<0.0001	90.86	-1.17	-1.97

Table A-5. Results from BMD Analysis of Incidence of Squamous Metaplasia in F1 Rats Exposed to Acrylonitrile in a 2-Generation Study (Nemec et al. 2008)

Model	BMC_{10}[a] (ppm)	$BMCL_{10}$[a] (ppm)	p-Value[b]	AIC	Scaled residuals[c]	
					Concentration below BMC[d]	Concentration above BMC[d]
Log-Probit			0.006	78.29	0.00	0.00
Probit			<0.0001	90.39	-1.09	-1.89

[a]BMC and BMCL values for models that do not provide adequate fit are not included in this table.
[b]Values <0.1 fail to meet conventional χ^2 goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the BMC.
[d]Power restricted to ≥1.
[e]Recommended model(s). BMDLs for models providing adequate fit differed by <3-fold; the model(s) with the lowest AIC was selected. For male rats, the Gamma, Multistage 2, and Weibull models were recommended because they identified the lowest AIC. For female rats and combined males and females, the Dichotomous Hill model was the only model providing adequate fit.
[f]Slope restricted to ≥1.
[g]Betas restricted to ≥0.

AIC = Akaike Information Criterion; BMC = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMCL = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., $_{10}$ = exposure dose associated with a 10% extra risk); BMD = benchmark dose

All of the models providing adequate fit to the subacute inflammation male data (Gamma; Multistage 1, 2, and 3; and Weibull models) resulted in the same BMC and BMCL values of 1.50 and 0.89 ppm, respectively (Table A-6). The incidence data in females only provided fit using the dichotomous model. However, the visual fit for this model was considered poor. None of the models provided adequate fit for the male and female combined data for subacute inflammation.

Table A-6. Results from BMD Analysis of Incidence of Subacute Inflammation in F1 Rats Exposed to Acrylonitrile in a 2-Generation Study (Nemec et al. 2008)

Model	BMC_{10}[a] (ppm)	$BMCL_{10}$[a] (ppm)	p-Value[b]	AIC	Scaled residuals[c]	
					Concentration below BMC[d]	Concentration above BMC[d]
Males						
Dichotomous Hill			NA	44.47	0.00	0.00
Gamma[d,e]	**1.50**	**0.89**	**0.224**	**43.34**	**-0.11**	**-0.11**
Log-Logistic[f]			0.221	43.97	0.10	0.10
Multistage Degree 3[g]	**1.50**	**0.89**	**0.224**	**43.34**	**-0.11**	**-0.11**
Multistage Degree 2[g]	**1.50**	**0.89**	**0.224**	**43.34**	**-0.11**	**-0.11**
Multistage Degree 1[g]	**1.50**	**0.89**	**0.224**	**43.34**	**-0.11**	**-0.11**
Weibull[d]	**1.50**	**0.89**	**0.224**	**43.34**	**-0.11**	**-0.11**
Logistic			0.074	45.45	-0.23	-0.83

Table A-6. Results from BMD Analysis of Incidence of Subacute Inflammation in F1 Rats Exposed to Acrylonitrile in a 2-Generation Study (Nemec et al. 2008)

Model	BMC_{10}[a] (ppm)	$BMCL_{10}$[a] (ppm)	p-Value[b]	AIC	Scaled residuals[c]	
					Concentration below BMC[d]	Concentration above BMC[d]
Log-Probit			0.197	44.22	0.08	0.08
Probit			0.074	46.14	-0.25	-0.97

[a]BMC and BMCL values for models that do not provide adequate fit are not included in this table.
[b]Values <0.1 fail to meet conventional χ^2 goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the BMC.
[d]Power restricted to ≥1.
[e]Recommended model. BMDLs for models providing adequate fit differed by <3-fold; therefore, the models with the lowest AIC were selected (Gamma, Multistage 1, 2, and 3, and Weibull models).
[f]Slope restricted to ≥1.
[g]Betas restricted to ≥0.

AIC = Akaike Information Criterion; BMC = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMCL = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., $_{10}$ = exposure dose associated with a 10% extra risk); BMD = benchmark dose

BMD modeling was also conducted for the altered nerve conduction velocity observed in the Gagnaire et al. (1998) study. The BMCL for sensory nerve conduction velocity was at least 10 times higher than the BMCL for hyperplasia in the nasal cavity; no models provided adequate fit for the amplitude of the sensory action potential data or motor nerve conduction velocity.

The potential PODs for the nasal lesions are presented in Table A-7.

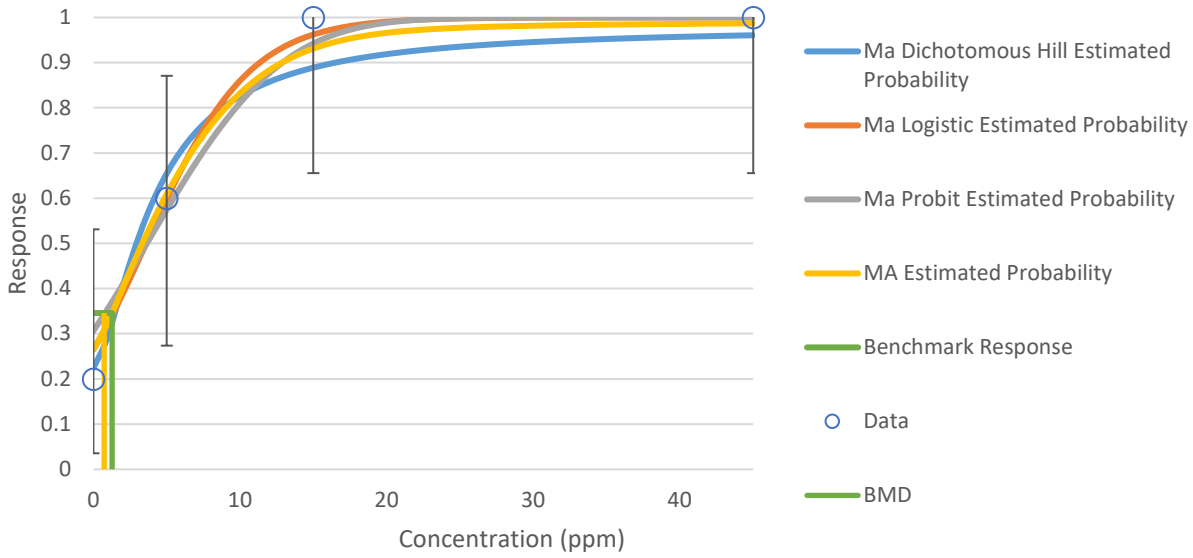
Table A-7. Potential Points of Departure for Intermediate-Duration Inhalation MRL for Acrylonitrile

Endpoint	BMC (ppm)	BMCL (ppm)
Hyperplasia of respiratory/ transitional zone epithelium in males	1.27	0.73
Hyperplasia of respiratory/ transitional zone epithelium in males and females	2.87	1.11
Squamous metaplasia in males	1.93	1.27
Squamous metaplasia in females	8.23	4.75
Squamous metaplasia in males and females	5.00	3.41
Subacute inflammation in males	1.50	0.89

BMC = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMCL = 95% lower confidence limit on the BMC

The lowest BMCL is 0.73 ppm for hyperplasia of the respiratory/transitional zone epithelium in F1 male rats estimated using the Bayesian model average of the frequentist, restricted Dichotomous Hill, Logistic, and Probit models; this was selected as the POD for the MRL. The fit of the Bayesian Model Averaging models is illustrated in Figures A-1, A-2, and A-3.

Figure A-1. Model Averaging Estimated Probabilities for Hyperplasia of Respiratory/Transitional Zone Epithelium in F1 Male Rats Exposed to Acrylonitrile via Inhalation



Calculations

Adjustment for Intermittent Exposure: The $BMCL_{10\text{-model average}}$ of 0.73 ppm was adjusted from intermittent exposure to account for a continuous exposure scenario:

$BMCL_{ADJ}$ = $BMCL_{10}$ of 0.73 ppm x (6 hours/24 hours) x (5 days/7 days) = 0.13 ppm

Human Equivalent Concentration: A HEC was calculated by multiplying the duration adjusted $BMCL_{ADJ}$ by the regional gas dose ratio (RGDR). The RGDR for extrathoracic respiratory tract effects was calculated using the following equation:

$$RDGR_{ET} = ([V_E/SA_{ET}]_A) /([V_E/SA_{ET}]_H)$$

Where:

V_E is the minute volume and SA_{ET} is the surface area of the extrathoracic (ET) region of the respiratory tract.

Minute volume (V_E)

Human: 13.8 L/minute (EPA 1994a)

Rat: 0.190 L/minute; calculated using the following EPA equation:

$$\ln(V_E) = b_0 + b_1\ln(BW)$$

For rats, b_0 equals -0.578 and b_1 equals 0.821.

- Because limited body weight data were reported in the study, a reference body weight of 0.267 kg (EPA 1988) was used.

EPA (1994a) rat and human respiratory surface area reference values for the extrathoracic region:

Human: 200 cm^2
Rat: 15.0 cm^2

$BMCL_{HEC\text{-}model\ average} = BMCL_{ADJ} \times RGDR_{ET}$
$BMCL_{HEC\text{-}model\ average} = 0.13$ ppm x 0.184 = 0.024 ppm

Uncertainty Factors: The $BMCL_{HEC\text{-}model\ average}$ is divided by a total uncertainty factor (UF) of 30:

- 3 UF for extrapolation from animals to humans with dosimetric adjustments
- 10 UF for human variability

$MRL = BMCL_{HEC\text{-}model\ average} \div UFs$
$0.024 \text{ ppm} \div (3x10) = 0.0008 \text{ ppm } (8x10^{-4} \text{ ppm})$

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Selection of nasal lesions in rats as the critical effect is support by studies in humans which reported nose irritation (Simons et al. 2016; Wilson 1944; Wilson et al. 1948).

EPA's BMDS (version 3.2) includes a model-averaging solution for dichotomous incidence data of the type reported here by Nemec et al. (2008). Their implementation uses Bayesian equivalents of the frequentist models. Through a Laplacian approximation, a model-average is calculated based on a distribution of solutions from the models selected by the assessor. Discussion and recommendations for using BMD averaging are available in Wheeler et al. (2020), EPA (2020b), and Hardy et al. (2017).

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APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Acrylonitrile
CAS Numbers: 107-13-1
Date: April 2025
Profile Status: Final
Route: Inhalation
Duration: Chronic

MRL Summary: The database was not considered adequate for derivation of a chronic-duration inhalation MRL for acrylonitrile. Three studies evaluated acrylonitrile toxicity in workers; the highest average exposure level of 14.1 ppm was considered a NOAEL. Because these studies identified a free-standing NOAEL, they cannot be used as the basis of an MRL. In the only chronic-duration study examining noncancer endpoints, death was observed at the lowest concentration tested and thus, the study cannot be used as the basis of an MRL.

Rationale for Not Deriving an MRL: Three studies evaluated workers at six to seven acrylic fiber manufacturing facilities in Japan (Kaneko and Omae 1992; Muto et al. 1992; Sakurai et al. 1978). The evaluation consisted of a symptom questionnaire (Kaneko and Omae 1992) or a medical examination that included a physical examination and measurement of hematological and serum clinical chemistry parameters (Muto et al. 1992; Sakurai et al. 1978). At the time of the studies, the average acrylonitrile exposure levels were ≤14.1 ppm. Increases in the prevalence of upper respiratory tract and conjunctival irritation were observed in workers at one facility; however, the investigators suggested that these effects were likely caused by exposure to high levels of acrylonitrile due to the lack of relationship with the duration of employment (Kaneko and Omae 1992) and was only found at one facility (Muto et al. 1992; Sakurai et al. 1978). No dose-related alterations in serum clinical chemistry or hematological parameters or in the physical examination results were found. These data suggest a NOAEL of 14.1 ppm.

Three studies have evaluated the chronic toxicity of inhaled acrylonitrile in laboratory animals (Maltoni et al. 1977, 1988; Quast et al. 1980a). The Maltoni et al. (1977, 1988) studies primarily focused on the carcinogenic potential of acrylonitrile. Quast et al. (1980a) reported death and glial cell tumors at the lowest concentration tested (20 ppm) and decreased body weight, nasal mucosal irritation, and focal gliosis at 80 ppm. Because death was observed at the lowest concentration, this study was not considered suitable for derivation of an MRL.

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MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Acrylonitrile
CAS Numbers: 107-13-1
Date: April 2025
Profile Status: Final
Route: Oral
Duration: Acute
MRL: 0.09 mg/kg/day
Critical Effect: Total fetal malformations
Reference: Murray et al. 1978
Point of Departure: $BMDL_{05\text{-model average}}$ of 9.27 mg/kg/day
Uncertainty Factor: 100
LSE Graph Key: 3
Species: Rat

MRL Summary: An acute-duration oral MRL of 0.09 mg/kg/day was derived for acrylonitrile based on an increased incidence litters with malformations in rats administered acrylonitrile via gavage on GDs 6–15 (Murray et al. 1978). The MRL is based on a $BMDL_{05\text{-model average}}$ of 9.27 mg/kg/day and divided by a total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Selection of the Critical Effect: Several adverse effects have been reported in rats and mice following acute-duration oral exposure. The most sensitive effects appear to be neurological, specifically cholinomimetic effects and those characteristic of cyanide poisoning, forestomach thickening, and developmental toxicity. Other affected targets include body weight and hematological system. A summary of the endpoints and NOAEL/LOAEL values are presented in Table A-8.

Table A-8. Summary of Adverse Health Effects Following Acute-duration Oral Exposure to Acrylonitrile

Species, duration	Effect	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Reference
Rat, GDs 6–15 (gavage)	Hyperexcitability and excessive salivation in dams	25	65	Murray et al. 1978
Rat, GDs 6–15 (gavage)	Decreased maternal body weight gain	25	65	Murray et al. 1978
Rat, GDs 6–15 (gavage)	Thickening of the non-glandular stomach	25	65	Murray et al. 1978
Rat, GDs 6–15 (gavage)	Decreased fetal body weight and increased incidence of short tail, short trunk, and missing vertebrae, and total malformations	25	65	Murray et al. 1978
Rat, once (gavage)	Decreased hematocrit, mean cell hemoglobin, and platelet counts		80	Farooqui and Ahmed 1983

Table A-8. Summary of Adverse Health Effects Following Acute-duration Oral Exposure to Acrylonitrile

Species, duration	Effect	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Reference
Rat, GD 10 (gavage)	Maternal weight loss		100 (serious LOAEL)	Saillenfait and Sabate 2000
Rat, GD 10 (gavage)	Abnormal or poor development and allantois, trunk and caudal extremity misdirected		100	Saillenfait and Sabate 2000

CNS = central nervous system; GD = gestation day; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level

The lowest LOAEL is 65 mg/kg for increased incidences of malformations, decreased fetal body weight, decreased maternal body weight, forestomach thickening, and hyperexcitability; the NOAEL for these effects is 25 mg/kg (Murray et al. 1978).

Selection of the Principal Study: The Murray et al. (1978) study was selected as the principal study because it identified the lowest LOAEL for several sensitive targets.

Summary of the Principal Study:

Murray FJ, Schwetz BA, Nitschke KD, et al. 1978. Teratogenicity of acrylonitrile given to rats by gavage or by inhalation. Food Cosmet Toxicol 16(6):547-551. http://doi.org/10.1016/s0015-6264(78)80222-3.

Groups of 20–38 pregnant Sprague Dawley rats were administered 0, 10, 25, or 65 mg/kg/day acrylonitrile (>99% purity) via gavage in an aqueous solution on GDs 6–15; animals were sacrificed on GD 21. The following parameters were used to assess toxicity: daily observations, body weight, food and water consumption, number of live, dead, and resorbed fetuses, fetal body weight, fetal crown rump length, and examination for external, soft tissue, and skeletal abnormalities.

Hyperexcitability and excessive salivation were observed in rats administered 65 mg/kg/day. Significant decreases in maternal body weight gain (88% on GDs 6–9 and 28% on GDs 10–15) were observed at 65 mg/kg/day. Significant decreases in food consumption were observed at 25 and 65 mg/kg/day. Thickening of the non-glandular portion of the stomach was observed in the majority of rats at the high dose and in three rats at 25 mg/kg/day. A significant increase in absolute liver weight (no effect on relative liver weight) was observed at 65 mg/kg/day. A significant decrease in the incidence of pregnancy was observed at 65 mg/kg/day. No alterations in numbers of live fetus/litter or resorptions/litter were observed. Significant decreases in fetal body weight (7%) and fetal crown-rump length (1.8%) were observed at 65 mg/kg/day. Increases in the incidences of short tails, short trunk, and missing vertebrae and total malformations were observed at 65 mg/kg/day. Some increases in malformations (short tail and missing vertebrae) were also observed at 25 mg/kg/day, but the incidence was not significantly different than controls. Sialodacryadenitis was observed in most animals in all groups, including the controls; the investigators noted that it was unlikely that this infection significantly affected the outcome since it occurred in all groups and the findings in the control group were similar to past control groups.

Selection of the Point of Departure for the MRL: The $BMDL_{05}$ of 8.89 mg/kg/day for increased incidence of litter with malformations was selected as the POD for the MRL.

A BMD approach was used to identify a potential POD for derivation of the acute-duration oral MRL for acrylonitrile. The incidence data for litters with short tail, short trunk, and missing vertebrae and for total malformations were amenable to BMD modeling. The incidence data for malformations (Table A-9) were fit to all available dichotomous models in EPA's BMDS (version 3.2) with extra risk. Adequate model fit was judged by four criteria: goodness-of-fit statistics (p-value >0.1), scaled residual at the data point (except the control) closest to the predefined BMR, BMDL that is not 10 times lower than the lowest non-zero dose, and visual inspection of the dose-response curve. A BMR of 5% extra risk was used. Fetal body weight data were not amenable to BMD modeling because the number of fetuses per group was not reported. Maternal body weight data were modeled using all available continuous models in EPA's BMDS (version 3.2) using the data summarized in Table A-9. Adequate model fit criteria were the same as used for the fetal malformation modeling and a BMR of 1 standard deviation (SD) was used. BMD modeling could not be conducted for forestomach lesions because incidence data were not reported for the high-dose group. It could also not be conducted for the neurological effects because incidence data were not reported.

Table A-9. Incidence Data of Fetal Malformations and Alterations in Maternal Body Weights in Rats Administered Acrylonitrile on GDs 6–15

	Dose (mg/kg/day)			
Effect	0	10	25	65
Litters with short tail	1/38	0/35	2/29	6/17
Litters with missing vertebrae	1/38	0/35	2/29	6/17
Litters with short trunk	0/38	0/35	0/29	3/17
Litters with malformations	2/38	0/35	4/29	6/17
Maternal body weight gain (GDs 6–9)[a]	18±8	17±7	16±10	2±9
Maternal body weight gain (GDs 10–15)[a]	43±11	42±11	39±12	31±12

[a]Mean (g)±standard deviation; number of dams: 43, 39, 33, and 29 for the 0, 10, 25, and 65 mg/kg/day groups, respectively.

Source: Murray et al. 1978

The modeling results for litters with fetus with short tails and litters with fetuses with missing vertebrae were the same since missing vertebrae were only observed in fetuses with short tails. The results of the BMD modeling are presented in Table A-10. All models, with the exception of the Dichotomous Hill model, provided adequate fit to the incidence data. The BMDLs were within a factor of 3; thus, the Multistage 2 Degree model was selected since it had the lowest AIC; this model estimated a BMD_{05} of 23.42 mg/kg/day and a $BMDL_{05}$ of 13.11 mg/kg/day.

Table A-10. Results from BMD Analysis of Incidence of Litters with Short Tails and Missing Vertebrae in Rats Administered Acrylonitrile on GDs 6–15 (Murray et al. 1978)

Model	BMD_{05}[a] (mg/kg/day)	$BMDL_{05}$[a] (mg/kg/day)	p-value[b]	AIC	Scaled residuals[c]	
					Dose below BMD[d]	Dose above BMD[d]
Dichotomous Hill			NA	55.20	0.00	0.67
Gamma[d]	26.59	14.09	0.302	53.51	0.28	0.58
Log-Logistic[e]	26.76	14.01	0.295	53.57	0.29	0.58
Multistage Degree 3[f]	27.58	13.41	0.282	53.68	0.34	0.56
Multistage Degree 2[f,g]	**23.42**	**13.11**	**0.526**	**51.87**	**-0.02**	**0.66**
Multistage Degree 1[f]	13.46	7.64	0.126	55.59	-1.36	0.68
Weibull[d]	27.26	13.81	0.289	53.62	0.33	0.56
Logistic	27.74	19.59	0.496	52.04	0.34	0.65
Log-Probit	53.94	11.22	0.103	55.14	0.00	-0.11
Probit	24.92	17.51	0.455	52.13	0.17	0.82

[a]BMD and BMDL values for models that do not provide adequate fit are not included in this table.
[b]Values <0.1 fail to meet conventional χ^2 goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the BMD.
[d]Power restricted to ≥1.
[e]Slope restricted to ≥1.
[f]Betas restricted to ≥0.
[g]Recommended model. BMDLs for models providing adequate fit differed by <3-fold; therefore, the model with the lowest AIC (Multistage 2 Degree model) was selected.

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure dose associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{05}$ = exposure dose associated with a 5% extra risk)

The BMD modeling results for number of litters with fetus having short trunks are presented in Table A-11. The Multistage 1 Degree and Multistage 2 Degree models provided adequate fit to the incidence data. The other models appeared to overfit the incidence data as evidenced by p-values of >0.95. The Multistage 2 Degree model had the lowest AIC for the models with adequate fit and was selected; BMD and BMDL values of 38.56 and 23.88 mg/kg/day, respectively, were estimated with this model.

Table A-11. Results from BMD Analysis of Incidence of Litters with Short Trunks in Rats Administered Acrylonitrile on GDs 6–15 (Murray et al. 1978)

Model	BMD_{05}[a] (mg/kg/day)	$BMDL_{05}$[a] (mg/kg/day)	p-value[b]	AIC	Scaled residuals[c]	
					Dose below BMD[d]	Dose above BMD[d]
Dichotomous Hill			1.000	19.84	0.00	0.00
Gamma[d]			1.000	17.84	0.00	0.00
Log-Logistic[e]			1.000	17.84	0.00	0.00
Multistage Degree 3[f]			0.987	16.50	-0.54	0.00

Table A-11. Results from BMD Analysis of Incidence of Litters with Short Trunks in Rats Administered Acrylonitrile on GDs 6–15 (Murray et al. 1978)

Model	BMD_{05}[a] (mg/kg/day)	$BMDL_{05}$[a] (mg/kg/day)	p-value[b]	AIC	Scaled residuals[c]	
					Dose below BMD[d]	Dose above BMD[d]
Multistage Degree 2[f,g]	**38.56**	**23.88**	**0.802**	**19.56**	**-0.80**	**0.00**
Multistage Degree 1[f]	35.58	15.66	0.369	22.21	-1.03	0.00
Weibull[d]			1.000	19.84	0.00	0.00
Logistic			1.000	17.84	0.00	0.00
Log-Probit			1.000	19.84	0.00	0.00
Probit			1.000	19.84	0.00	0.00

[a]BMD and BMDL values for models that do not provide adequate fit are not included in this table.
[b]Values <0.1 fail to meet conventional χ^2 goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the BMD.
[d]Power restricted to ≥1.
[e]Slope restricted to ≥1.
[f]Betas restricted to ≥0.
[g]Recommended model. BMDLs for models providing adequate fit differed by <3-fold; therefore, the model with the lowest AIC (Multistage 2 Degree model) was selected.

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure dose associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{05}$ = exposure dose associated with a 5% extra risk)

The BMD modeling results for number of litters with malformations are presented in Table A-12. All models, with the exception of the Dichotomous Hill model, provided adequate fit to the incidence data. The Multistage 2 Degree model had the lowest AIC for the models with adequate fit. Rather than using the results of one of these models, ATSDR opted to model average the results for all models using EPA's BMDS Bayesian Model Average feature and using equal prior weights as recommended by EPA (2020b). Using model averaging, the posterior probabilities were 0.15, 0.09, 0.11, 0.13,0.07,0.08, 0.28, and 0.077 for the Dichotomous Hill, Gamma, Logistic, Log-Logistic, Log-Probit, Multistage, Probit, and Weibull models, respectively. The $BMD_{05\text{-model average}}$ was 19.77 mg/kg/day and the $BMDL_{05\text{-model average}}$ was 9.27 mg/kg/day.

Table A-12. Results from BMD Analysis of Incidence of Litters Malformations in Rats Administered Acrylonitrile on GDs 6–15 (Murray et al. 1978)

Model	BMD_{05}[a] (mg/kg/day)	$BMDL_{05}$[a] (mg/kg/day)	p-value[b]	AIC	Scaled residuals[c]	
					Dose below BMD[d]	Dose above BMD[d]
Dichotomous Hill	23.55	12.25	0.169	69.68	0.00	0.95
Gamma[d]	21.24	9.33	0.107	70.93	0.70	0.73
Log-Logistic[e]	20.91	9.35	0.107	70.97	0.68	0.74
Multistage Degree 3[f]	22.13	8.89	0.255	69.11	0.81	0.68
Multistage Degree 2[f,g]	**22.13**	**8.92**	**0.255**	**69.11**	**0.81**	**0.68**
Multistage Degree 1[f]	11.51	6.62	0.139	71.33	-1.65	0.82
Weibull[d]	21.23	8.97	0.102	71.10	0.73	0.71

Table A-12. Results from BMD Analysis of Incidence of Litters Malformations in Rats Administered Acrylonitrile on GDs 6–15 (Murray et al. 1978)

Model	BMD_{05}[a] (mg/kg/day)	$BMDL_{05}$[a] (mg/kg/day)	p-value[b]	AIC	Scaled residuals[c]	
					Dose below BMD[d]	Dose above BMD[d]
Logistic	21.77	15.54	0.224	69.66	0.83	0.64
Log-Probit	20.49	10.34	0.124	70.56	0.57	0.79
Probit	19.68	13.99	0.226	69.62	0.70	0.78
Bayesian model average	19.77	9.27				

[a]BMD and BMDL values for models that do not provide adequate fit are not included in this table.
[b]Values <0.1 fail to meet conventional χ^2 goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the BMD.
[d]Power restricted to ≥1.
[e]Slope restricted to ≥1.
[f]Betas restricted to ≥0.
[g]Recommended model. BMDLs for models providing adequate fit differed by <3-fold; therefore, the model with the lowest AIC (Multistage 3 Degree model) was selected.

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure dose associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{05}$ = exposure dose associated with a 5% extra risk)

The BMD modeling results for maternal body weight gain on GDs 6–9 are presented in Table A-13. The Exponential 3, Exponential 5, Polynomial 3 Degree, Polynomial 2 Degree, and Power models, all with constant variance, provided adequate fit. The Power model was selected since it had the lowest AIC; the model estimated a BMD_{1SD} of 49.15 mg/kg/day and a $BMDL_{1SD}$ of 36.45 mg/kg/day.

Table A-13. Results from BMD Analysis of Maternal Body Weight Gain on GDs 6–9 in Rats Administered Acrylonitrile on GDs 6–15 (Murray et al. 1978)

Model	BMD_{05}[a] (mg/kg/day)	$BMDL_{05}$[a] (mg/kg/day)	p-value[b]	AIC	Scaled residuals[c]	
					Dose below BMD[d]	Dose above BMD[d]
Constant Variance						
Exponential 2[d]			0.001	1,039.38	2.43	-1.18
Exponential 3[d]	44.62	34.08	0.620	1,027.80	0.05	0.32
Exponential 4[d]			0.001	1,039.38	2.43	-1.18
Exponential 5[d]	44.64	34.08	0.620	1,027.80	0.04	0.32
Hill[d]			NA	1,029.84	0.00	0.37
Polynomial Degree 3[d]	50.18	37.04	0.789	1,027.62	-0.01	0.12
Polynomial Degree 2[d]	47.24	36.61	0.881	1,025.80	-0.04	0.10

Table A-13. Results from BMD Analysis of Maternal Body Weight Gain on GDs 6–9 in Rats Administered Acrylonitrile on GDs 6–15 (Murray et al. 1978)

Model	BMD_{05}[a] (mg/kg/day)	$BMDL_{05}$[a] (mg/kg/day)	p-value[b]	AIC	Scaled residuals[c]	
					Dose below BMD[d]	Dose above BMD[d]
Power[d,e]	**49.15**	**36.45**	**0.667**	**1,027.73**	**-0.01**	**0.25**
Linear			0.064	1,031.06	1.90	-1.08

[a]Values <0.1 fail to meet adequate fit.
[b]Values <0.1 fail to meet conventional χ^2 goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the BMD.
[d]Restricted model.
[e]Recommended model. BMDLs for models providing adequate fit differed by <3-fold; therefore, the model with the lowest AIC (Power 2 Degree model) was selected.

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure dose associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{05}$ = exposure dose associated with a 5% extra risk)

The BMD modeling results for maternal body weight gain on GDs 10–15 are presented in Table A-14. All of the constant variance models except the Exponential 5 and Hill models provided adequate fit. The range of BMDLs were <3; thus, the model with the lowest AIC, the Linear model, was selected. The Linear model estimated a BMD_{1SD} and a $BMDL_{1SD}$ of 59.88 and 44.00 mg/kg/day, respectively.

Table A-14. Results from BMD Analysis of Maternal Body Weight Gain on GDs 10–15 in Rats Administered Acrylonitrile on GDs 6–15 (Murray et al. 1978)

Model	BMD_{05}[a] (mg/kg/day)	$BMDL_{05}$[a] (mg/kg/day)	p-value[b]	AIC	Scaled residuals[c]	
					Dose below BMD[d]	Dose above BMD[d]
Constant Variance						
Exponential 2[d]	59.49	40.94	0.846	1,112.80	-0.21	-0.36
Exponential 3[d]	60.96	41.77	0.900	1,114.48	0.01	-0.04
Exponential 4[d]	59.49	40.94	0.846	1,112.80	-0.21	-0.36
Exponential 5[d]			NA	1,116.47	0.00	0.00
Hill[d]			NA	1,116.47	0.00	0.00
Polynomial Degree 3[d]	61.17	44.23	0.824	1,114.52	0.01	-0.09
Polynomial Degree 2[d]	61.17	44.23	0.824	1,114.52	0.01	-0.09

Table A-14. Results from BMD Analysis of Maternal Body Weight Gain on GDs 10–15 in Rats Administered Acrylonitrile on GDs 6–15 (Murray et al. 1978)

Model	BMD_{05}[a] (mg/kg/day)	$BMDL_{05}$[a] (mg/kg/day)	p-value[b]	AIC	Scaled residuals[c]	
					Dose below BMD[d]	Dose above BMD[d]
Power[d]	61.16	44.27	0.868	1,114.50	0.02	-0.05
Linear[e]	**59.88**	**44.00**	**0.926**	**1,112.62**	**-0.10**	**-0.26**

[a]Values <0.1 fail to meet adequate fit.
[b]Values <0.1 fail to meet conventional χ^2 goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the BMD.
[d]Restricted model.
[e]Recommended model. BMDLs for models providing adequate fit differed by <3-fold; therefore, the model with the lowest AIC (Linear model) was selected.

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure dose associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{05}$ = exposure dose associated with a 5% extra risk)

The potential PODs for the maternal and fetal effects are presented in Table A-15.

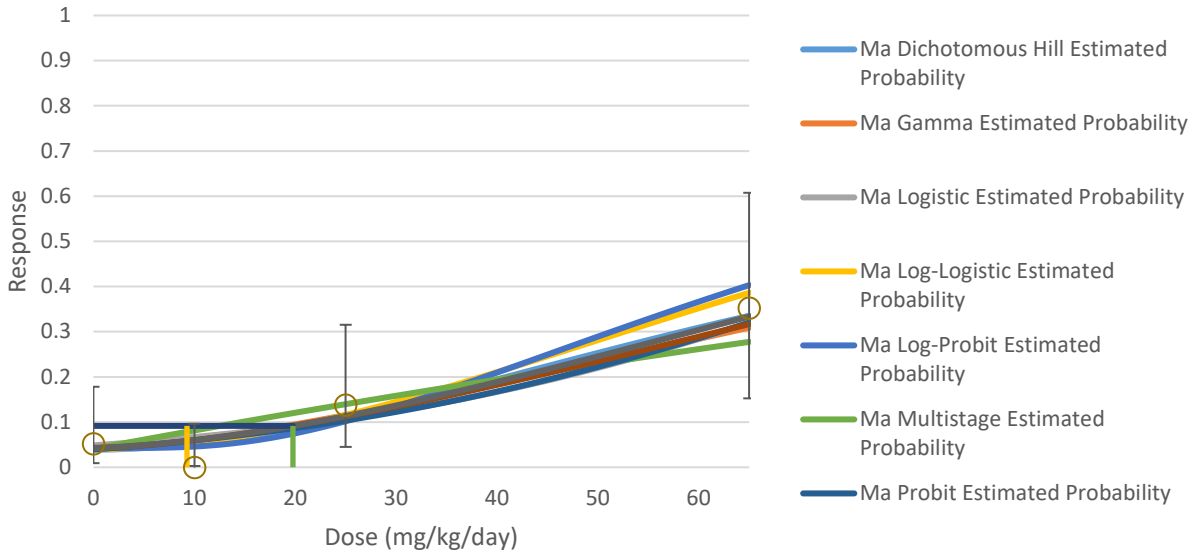
Table A-15. Potential Points of Departure for the Acute-duration Oral MRL for Acrylonitrile

Endpoint	BMD (mg/kg/day)	BMDL (mg/kg/day)
Increased incidence of litters with fetuses with short tails and litters with missing vertebrae	23.42	13.11
Increased incidence of litters with fetuses with short trunks	38.56	23.88
Increased incidence of litters with malformations	19.77	9.27
Decreased maternal weight gain on GDs 6–9	49.15	36.45
Decreased maternal weight gain on GDs 10–15	59.88	44.00

BMD = maximum likelihood estimate of the exposure dose associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD; GD = gestation day

The lowest BMDL is 9.27 mg/kg/day for increased incidence of litters with malformations estimated using Bayesian Model Averaging was selected as the POD for the acute-duration oral MRL. The model average probabilities are illustrated in Figure A-2. The $BMDL_{05\text{-model average}}$ of 9.27 mg/kg/day is lower than the NOAEL of 25 mg/kg/day for decreased fetal body weight and forestomach lesions.

Figure A-2. Model Averaging Estimated Probabilities for Incidence of Litters with Fetal Malformations in Rats Administered Acrylonitrile on GDs 6–15



Uncertainty Factors: The $BMDL_{05\text{-model average}}$ is divided by a total uncertainty factor (UF) of 100:

- 10 UF for extrapolation from animals to humans
- 10 UF for human variability

$$MRL = BMDL_{05\text{-model average}} \div UFs$$
$$9.27 \text{ mg/kg/day} \div (10x10) = 0.0927 \text{ mg/kg/day} \approx 0.09 \text{ mg/kg/day}$$

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Developmental toxicity has also been observed in a study conducted by Saillenfait and Sabate (2000), which found abnormal or poor development and allantois, and misdirected trunk and caudal extremities in the embryos of rats administered acrylonitrile via gavage on GD 10. An inhalation study also conducted by Murray et al. (1978) reported an increase in the total number of malformations in fetuses of rats exposed to 80 ppm acrylonitrile 6 hours/day on GDs 6–15.

Agency Contacts (Chemical Managers): Mohammad Shoeb

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Acrylonitrile
CAS Numbers: 107-13-1
Date: April 2025
Profile Status: Final
Route: Oral
Duration: Intermediate
MRL: 0.02 mg/kg/day
Critical Effect: Forestomach hyperplasia
Reference: Quast 2002
Point of Departure: $BMDL_{10}$ of 2.48 mg/kg/day
Uncertainty Factor: 100
LSE Graph Key: 12
Species: Rat

MRL Summary: An intermediate-duration oral MRL of 0.02 mg/kg/day was derived for acrylonitrile based on an increased incidence of forestomach hyperplasia in male rats exposed to 8.5 mg/kg/day acrylonitrile in drinking water for 1 year (Quast 2002). The MRL is based on a $BMDL_{10}$ of 2.48 mg/kg/day and divided by a total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Selection of the Critical Effect: Several effects have been observed in laboratory animals orally exposed to acrylonitrile for an intermediate duration; these are listed in Table A-16 in order of ascending LOAEL values.

Table A-16. Summary of Health Effects Following Intermediate-Duration Oral Exposure to Acrylonitrile

Species, duration	Effect	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Reference
Mouse, 14 weeks, 5 days/week (gavage)	4.2% decreased hemoglobin level in females		5	NTP 2001
Mouse, 28 days (gavage)	Impaired development of ovarian follicles		5	Luo et al. 2022
	Decreased number of pups		5 (SLOAEL)	
Rat, 1 year (water)	Squamous cell hyperplasia of the forestomach in males	3.4	8.5	Quast 2002
Mouse, 60 days (gavage)	Decreased sperm count, degeneration of seminiferous tubules	1	10	Tandon et al. 1988
Dog, 6 months (water)	Depression, lethargy, death, weight loss, esophageal ulcerations	10	16 (SLOAEL)	Quast et al. 1975
Rat ,48 weeks (water)	Decreased pup viability in F1b generation		20	Friedman and Beliles 2002
Rat, 12 weeks (gavage)	Decreased sperm motility and concentration		20	Dang et al. 2017

Table A-16. Summary of Health Effects Following Intermediate-Duration Oral Exposure to Acrylonitrile

Species, duration	Effect	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Reference
Rat, 28 days (gavage)	Increased sperm head and tail alterations		46	Shi et al. 2021
Rat, 12 weeks, 5 days/week (gavage)	Decreased sensory motor conduction velocity, weakness in hindlimbs, inability to rear	25	50	Gagnaire et al. 1998

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

The lowest LOAEL is 5 mg/kg/day for hematological, reproductive, and developmental effects. A small decrease in hemoglobin levels was observed in female mice (NTP 2001); a small decrease (4.3%) in hemoglobin levels was also observed in female rats exposed to 10.9 mg/kg/day (NOAEL of 3.7 mg/kg/day) (Johannsen and Levinskas 2002a). The biological relevance of this small magnitude change in hemoglobin levels is uncertain. A 28-day exposure study found alterations in the development of ovarian follicles and decreased number of live pups were observed in mice (Luo et al. 2022). At a slightly higher dose (8.5 mg/kg/day), forestomach lesions were observed in male rats (Quast 2002). Two other studies also reported forestomach lesions (Ghanayem et al. 1997; NTP 2001). Given the uncertainty regarding the relevance of the small change in hemoglobin levels and the lack of supporting data for the reproductive and developmental effects, the forestomach hyperplasia was selected as the critical effect; the NOAEL for this effect was lower than the LOAELs for the hematological, reproductive, and developmental effects.

Selection of the Principal Study: As noted, forestomach lesions have also been observed in two other intermediate-duration studies. Squamous metaplasia of the forestomach was reported by Ghanayem et al. (1997) in rats administered 23 mg/kg/day for 6 weeks; the NOAEL was 12 mg/kg/day. Forestomach inflammation and hyperplasia were observed in female mice administered 40 mg/kg 5 days/week for 14 weeks (NTP 2001). The Quast (2002) study was selected as the principal study because it identified the lowest LOAEL for forestomach lesions.

Summary of the Principal Study:

Quast JF. 2002. Two-year toxicity and oncogenicity study with acrylonitrile incorporated in the drinking water of rats. Toxicol Lett 132:153-196.

Groups of 10 male and 10 female Sprague Dawley rats were exposed to 0, 35, 100, or 300 ppm acrylonitrile in drinking water for 1 year; this is an interim sacrifice in a 2-year study. Using drinking consumption and body weight data, the investigators estimated doses of 0. 3.5, 8.5, and 21.3 mg/kg/day for males and 0. 4.4, 10.8, and 25.0 mg/kg/day for females. The following parameters were used to assess toxicity: daily clinical observations, water and food consumption, monthly body weight measurements, hematology (conducted on 10 rats/sex/group after 45, 87, 180, and 365 days in the controls and 300 ppm groups), urinalysis (in same rats as hematology), clinical chemistry (measured in 10 rats/sex/group in the controls and 300 ppm group after 46 and 365 days and in 10 rats/sex/group in all groups after 88 and 18 days), and ophthalmologic examination, organ weight (brain, heart, liver, kidneys, and testes), and gross necropsy and histopathology of major tissues and organs at 365 days.

A significant increase in mortality was observed in the 25.0 mg/kg/day females after 301 days of exposure; at 360 days, the mortality rate was 29.2% compared to 1.3% in controls. No increases in mortality were observed in males. Decreased weight gain was related to decreased food and water consumption. After 1 year of exposure, the body weight gain decrease was >10% in males at 8.5 (11%) and 21.3 (22%) mg/kg/day and in females at 25 mg/kg/day (18%). Decreased weight gain was related to decreased food and water consumption at all doses. No hematological alterations attributed to acrylonitrile exposure were found. Significant increases in urine specific gravity were observed in male and female rats exposed to 21.3/25.0 mg/kg/day; this correlated with the decreased water intake. Increases in BUN were observed at some time points; the investigators noted the change was not dose related and was within normal range and suggested that it may be secondary to the decreased water intake. No other exposure-related alterations in serum chemistry were found. Squamous cell hyperplasia was observed in males and females in the mid- and high-dose groups. The incidences were 4/10 and 10/10 in the 8.5 and 21.3 mg/kg/day males and 7/10 and 9/10 in the 10.8 and 25.0 mg/kg/day females; the incidence in controls was not reported. Benign forestomach papillomas were observed in 7/10 males and 5/10 females at 21.3/25.0 mg/kg/day. Increases in the incidence of central nervous system tumors, Zymbal gland carcinoma, mammary gland adenocarcinoma, and fibroadenoma were also observed.

Selection of the Point of Departure for the MRL: A $BMDL_{10}$ of 2.48 mg/kg/day for forestomach hyperplasia in male rats was selected as the POD for the MRL.

A BMD approach was used to identify a potential POD for derivation of the intermediate-duration oral MRL for acrylonitrile. The incidence data for forestomach squamous cell hyperplasia in the male rats were amenable to BMD modeling. The incidence data (0/10, 0/10, 4/10, 10/10 for the 0, 3.5, 8.5, and 21.3 mg/kg/day groups, respectively) were fit to all available dichotomous models in EPA's BMDS, (version 3.2) with extra risk. Adequate model fit was judged by four criteria: goodness-of-fit statistics (p-value >0.1), scaled residual at the data point (except the control) closest to the predefined BMR, BMDL that is not 10 times lower than the lowest non-zero dose, and visual inspection of the dose-response curve. A BMR of 10% extra risk was used.

The results of the BMD modeling are presented in Table A-17. All models except the Weibull model, provided adequate fit to the data. However, the p-values of approximately 1 and scaled residuals of 0.0 suggest that the Dichotomous Hill, Gamma, Log-Logistic, Logistic, Log-Probit, and Probit models are overfit and their BMDLs were not considered for MRL derivation. Of the remaining models, the BMDS recommended the Multistage Degree 1 model because it had the lowest BMDL (BMDLs for models providing adequate fit differed by >3-fold). Although this model met the first three criteria, the visual fit of the dose-response curve was not considered adequate. When the Multistage Degree 1 model was removed from consideration, the BMDLs for the remaining two models with adequate fit differed by <3-fold; thus, the model with the lowest AIC, the Multistage Degree 3 model, was selected; this model met all four fit criteria. The Multistage Degree 3 model estimated a BMD_{10} of 5.15 mg/kg/day and a $BMDL_{10}$ of 2.48 mg/kg/day. The fit of the model to the incidence data is presented in Figure A-3.

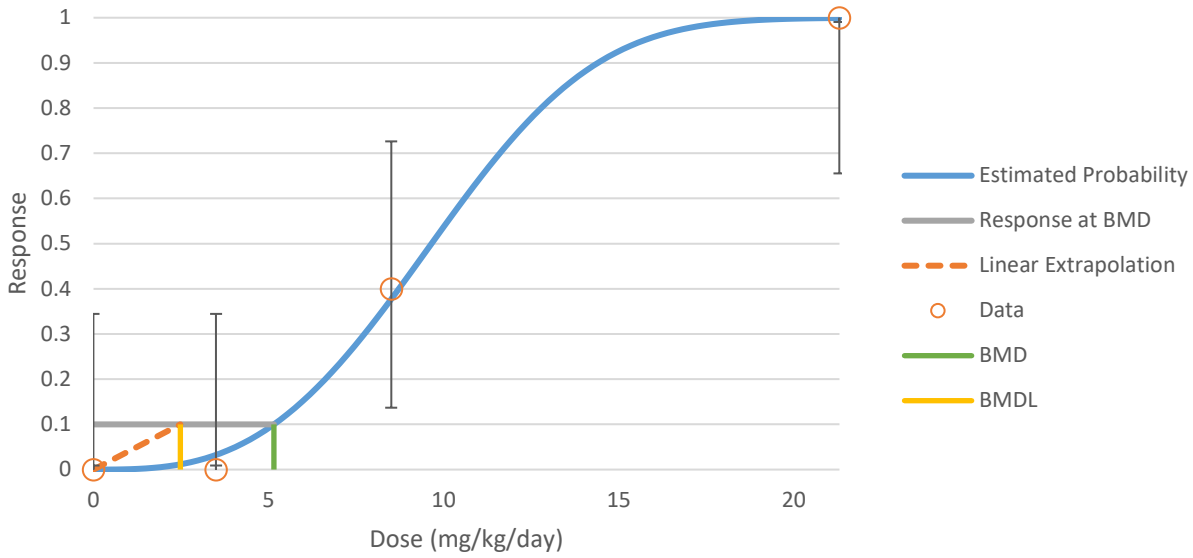
Table A-17. Results from BMD Analysis of Incidence of Squamous Cell Hyperplasia in Male Rats Exposed to Acrylonitrile in Drinking Water for 1 Year (Quast 2002)

Model	BMD_{10}[a] (mg/kg/day)	$BMDL_{10}$[a] (mg/kg/day)	p-Value[b]	AIC	Scaled residuals[c]	
					Dose below BMD[d]	Dose above BMD[d]
Dichotomous Hill	7.68	4.20	1.000	17.46	0.00	0.00
Gamma[d]	6.56	3.76	0.999	17.47	0.00	0.00
Log-Logistic[e]	7.69	4.20	1.000	17.46	0.00	0.00
Multistage Degree 3[f,g]	**5.15**	**2.48**	**0.948**	**16.16**	**-0.58**	**0.00**
Multistage Degree 2[f]	3.74	2.14	0.724	17.99	-0.98	0.00
Multistage Degree 1[f]	1.35	0.86	0.123	25.42	0.00	0.00
Weibull[d]	6.48	3.43	0.999	15.52	0.03	0.00
Logistic	7.63	4.14	1.000	15.46	0.00	0.00
Log-Probit	7.44	4.06	1.000	17.46	0.00	0.00
Probit	7.28	3.82	1.000	15.46	0.00	0.00

[a]BMD and BMDL values for models that provide adequate fit.
[b]Values <0.1 fail to meet conventional χ^2 goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the BMD.
[d]Power restricted to ≥1.
[e]Slope restricted to ≥1.
[f]Betas restricted to ≥0.
[g]Recommended model. BMDLs for models providing adequate fit differed by <3-fold; therefore, the model with the lowest AIC and adequate visual fit was selected (Multistage Degree 3).

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure dose associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{10}$ = exposure dose associated with a 10% extra risk)

Figure A-3. Predicted (Multistage Degree 3 Model) and Observed Forestomach Hyperplasia in Male Rats Exposed to Acrylonitrile via Drinking Water



Uncertainty Factors: The $BMDL_{10}$ is divided by a total uncertainty factor (UF) of 100:

- 10 UF for extrapolation from animals to humans
- 10 UF for human variability

$$MRL = BMDL_{10} \div UFs$$
$$2.48 \text{ mg/kg/day} \div (10x10) = 0.0248 \text{ mg/kg/day} \approx 0.02 \text{ mg/kg/day}$$

Other Additional Studies or Pertinent Information that Lend Support to this MRL: None

Agency Contacts (Chemical Managers): Mohammad Shoeb

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Acrylonitrile
CAS Numbers: 107-13-1
Date: April 2025
Profile Status: Final
Route: Oral
Duration: Chronic
MRL: 0.00009 mg/kg/day ($9x10^{-5}$ mg/kg/day)
Critical Effect: Increased severity of forestomach hyperplasia
Reference: Johannsen and Levinskas 2002b
Point of Departure: LOAEL of 0.09 mg/kg/day
Uncertainty Factor: 1,000
LSE Graph Key: 21
Species: Rat

MRL Summary: A chronic-duration oral MRL of 0.00009 mg/kg/day ($9x10^{-5}$ mg/kg/day) was derived for acrylonitrile based on an increased severity of forestomach hyperplasia in male rats exposed to 0.09 mg/kg/day acrylonitrile in drinking water for 22 months (Johannsen and Levinskas 2002b). The MRL is based on a LOAEL of 0.09 mg/kg/day and divided by a total uncertainty factor of 1,000 (10 for the use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

Selection of the Critical Effect: Six chronic-duration studies have evaluated the noncancer toxicity of acrylonitrile in laboratory animals. A summary of the lowest LOAELs for observed effects are listed in Table A-18 in order of ascending LOAEL values. The lowest LOAEL was 0.09 mg/kg/day for an increase in the severity of squamous cell hyperplasia in the forestomach identified in the Johannsen and Levinskas (2002b) 22-month study. Forestomach lesions were selected as the critical effect.

Table A-18. Summary of Health Effects Following Chronic-duration Oral Exposure to Acrylonitrile

Species, duration	Effect	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Reference
Rat, 22 months (water)	Increased severity of squamous cell hyperplasia in forestomach in males		0.09	Johannsen and Levinskas 2002b
Mouse, 2 years (gavage)	Increase in ovarian cysts		2.5	NTP 2001
Rat, 2 years (water)	Gliosis and perivascular cuffing in the brain		4.4[a]	Quast 2002
Rat, 26 months (water)	Epidermal inclusion cysts in males	2.5	8.4	Johannsen and Levinskas 2002a
Rat, 22 months (water)	Decreased hemoglobin and increased reticulocytes	0.09	8[a]	Johannsen and Levinskas 2002b
Rat, 20 months (gavage)	Renal transitional cell hyperplasia	0.1	10[a]	Johannsen and Levinskas 2002b

[a]Decreased survival reported at this dose.

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

Selection of the Principal Study: Five studies have reported forestomach lesions in rats and mice. A summary of the results of these studies is presented in Table A-19. The Johannsen and Levinskas (2002b) drinking water study identified the lowest LOAEL for forestomach lesions and was selected as the principal study.

Table A-19. Summary of Forestomach Lesions Following Chronic-Duration Oral Exposure to Acrylonitrile

Species, duration	Effect	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Reference
Rat, 22 months (water)	Increased severity of squamous cell hyperplasia in forestomach		0.09	Johannsen and Levinskas 2002b
Rat, 23-26 months (water)	Hyperplasia and/or hyperkeratosis in forestomach	0.1 M 0.1 F	0.3 M 0.4 F	Johannsen and Levinskas 2002a
Rat, 2 years (water)	Hyperplasia/hyperkeratosis of forestomach		4.4[a]	Quast 2002
Rat, 20 months (gavage)	Increased severity of squamous cell hyperplasia in forestomach	0.1	10[a]	Johannsen and Levinskas 2002b
Mouse, 2 years (gavage)	Focal epithelial hyperplasia in the forestomach	2.5	10	NTP 2001

[a]Decreased survival reported at this dose.

F = females; LOAEL = lowest-observed-adverse-effect level; M = males; NOAEL = no-observed-adverse-effect level

Summary of the Principal Study:

Johannsen FR and Levinskas GJ. 2002b. Comparative chronic toxicity and carcinogenicity of acrylonitrile by drinking water and oral intubation to Spartan Sprague Dawley rats. Toxicol Lett 132:197-219.

Groups of 100 male and 100 female Spartan Sprague-Dawley rats were administered 0, 1, or 100 ppm acrylonitrile in drinking water for their lifetime. Interim sacrifices of 10 rats/sex/group were done at 6, 12, and 18 months. The investigators reported that the average doses for the 1 and 100 ppm groups were 0.09 and 8.0 mg/kg/day in males, respectively, and 0.15 and 10.7 mg/kg/day for females, respectively. The following parameters were used to assess toxicity: cage-side physical observations, feed and water consumption, body weights (weekly through week 14, biweekly from weeks 16 to 26, and monthly thereafter), hematology (hemoglobin, hematocrit, red blood cell count, reticulocytes, prothrombin time, total and differential white blood cell counts), serum clinical chemistry (ALT, alkaline phosphatase, BUN, fasting glucose), urinalysis (pH, protein specific gravity, glucose, ketones, bilirubin, occult blood), organ weights (brain, pituitary, adrenal, gonads, heart, kidney, liver), and histopathological examination (approximately 40 tissues and organs examined) performed at the interim and terminal sacrifices.

Significant increases in deaths were observed at 8.0/10.7 mg/kg/day after 10 months of exposure. The study was terminated early due to high mortality during month 22 in males and month 19 in females. Slight decreases in body weight were observed in males (10%) and females (8%) in the 8.0/10.7 mg/kg/day group throughout the study. Decreases in hemoglobin levels were observed in males at 8.0 mg/kg/day at all time periods; an increase in reticulocytes and decrease in leucocyte counts were observed at termination. Consistent decreases in hematocrit and erythrocytes were also observed, although they were infrequently statistically significant. No alterations in clinical chemistry or urinalysis

parameters were found. Significant alterations in organ weight were limited to decreases in absolute and relative pituitary weights at 8.0/10.7 mg/kg/day at 12 months in males and at termination in females. Non-neoplastic histological alterations were limited to the forestomach, kidney, and uterus. Although no significant increase in the incidence of squamous cell hyperplasia of the forestomach was observed due to the high incidence in controls, significant increases in the incidences of moderate or severe lesions were observed in male rats exposed to 0.09 or 8.0 mg/kg/day and in males and females in the 8.0 and 10.7 mg/kg/day groups that died early or were killed due to morbidity. An increased incidence of transitional cell hyperplasia was observed at 10.7 mg/kg/day in the kidneys of female at termination. After 12 months of exposure, an increase in the incidence of squamous metaplasia was observed in the uterus of rats in the 10.7 mg/kg/day; this was not observed at later time periods. A high incidence of primary tumors was observed in males and females at 8.0/10.7 mg/kg/day. At 8.0/10.7 mg/kg/day, significant increases in the incidence of brain glial cell tumors (females only), spinal cord glial cell tumors (not examined in males), Zymbal's gland carcinoma, and forestomach squamous cell papilloma/papilloma (females only) were observed.

Selection of the Point of Departure for the MRL: A LOAEL of 0.09 mg/kg/day for increased severity of forestomach hyperplasia in male rats was selected as the POD for the MRL.

A BMD approach was not used to identify a potential POD for derivation of the chronic-duration oral MRL for acrylonitrile because only two non-control groups were used. Thus, a NOAEL/LOAEL approach was used.

Uncertainty Factors: The LOAEL is divided by a total uncertainty factor (UF) of 1,000:

- 10 for the use of a LOAEL
- 10 UF for extrapolation from animals to humans
- 10 UF for human variability

MRL = LOAEL ÷ UFs
0.09 mg/kg/day ÷ (10x10x10) = 0.00009 mg/kg/day ($9x10^{-5}$ mg/kg/day)

Other Additional Studies or Pertinent Information that Lend Support to this MRL: None

Agency Contacts (Chemical Managers): Mohammad Shoeb

APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR ACRYLONITRILE

The objective of the toxicological profile is to evaluate the potential for human exposure and the potential health hazards associated with inhalation, oral, or dermal/ocular exposure to acrylonitrile.

B.1 LITERATURE SEARCH AND SCREEN

A literature search and screen were conducted to identify studies examining health effects, toxicokinetics, mechanisms of action, susceptible populations, biomarkers, chemical interactions, physical and chemical properties, production, use, environmental fate, environmental releases, and environmental and biological monitoring data for acrylonitrile. ATSDR primarily focused on peer-reviewed articles without language restrictions. Foreign language studies are reviewed based on available English-language abstracts and/or tables (or summaries in regulatory assessments, such as International Agency for Research on Cancer [IARC] documents). If the study appears critical for hazard identification or MRL derivation, translation into English is requested. Non-peer-reviewed studies that were considered relevant to the assessment of the health effects of acrylonitrile have undergone peer review by at least three ATSDR-selected experts who have been screened for conflict of interest. The inclusion criteria used to identify relevant studies examining the health effects of acrylonitrile are presented in Table B-1.

Table B-1. Inclusion Criteria for the Literature Search and Screen[a]

Health Effects
Species
Human
Laboratory mammals
Route of exposure
Inhalation
Oral
Dermal (or ocular)
Parenteral (these studies will be considered supporting data)
Health outcome
Death
Systemic effects
Body weight effects
Respiratory effects
Cardiovascular effects
Gastrointestinal effects
Hematological effects
Musculoskeletal effects
Hepatic effects
Renal effects
Dermal effects
Ocular effects
Endocrine effects
Immunological effects
Neurological effects
Reproductive effects

Table B-1. Inclusion Criteria for the Literature Search and Screen[a]

Developmental effects
Other noncancer effects
Cancer
Toxicokinetics
Absorption
Distribution
Metabolism
Excretion
PBPK models
Biomarkers
Biomarkers of exposure
Biomarkers of effect
Interactions with other chemicals
Potential for human exposure
Releases to the environment
Air
Water
Soil
Environmental fate
Transport and partitioning
Transformation and degradation
Environmental monitoring
Air
Water
Sediment and soil
Other media
Biomonitoring
General populations
Occupation populations

[a]Physical-chemical properties are not generally obtained from literature searches, but rather from curated governmental databases such as PubChem.

B.1.1 Literature Search

The literature search was conducted to update the Toxicological Profile for Acrylonitrile released in 1990. All literature cited in the previous (1990) toxicological profile were considered for inclusion in the updated profile. The initial literature search, which was performed in October 2021, was restricted to studies added to databases since January 1988. An updated literature search was performed after the Toxicological Profile for Acrylonitrile Draft for Public Comment was released in August 2023 to identify any additional studies added to databases between September 2021 and December 2023.

APPENDIX B

The following main databases were searched in April 2017, October 2021, and/or December 2023:

- PubMed
- National Technical Reports Library (NTRL)
- Scientific and Technical Information Network's TOXCENTER
- National Library of Medicine's TOXLINE (April 2017 only)

The search strategy used the chemical names, Chemical Abstracts Service (CAS) numbers, synonyms, Medical Subject Headings (MeSH) headings, and keywords for acrylonitrile. The query strings used for the literature search are presented in Table B-2.

The search was augmented by searching the Toxic Substances Control Act Test Submissions (TSCATS), NTP website, and National Institute of Health Research Portfolio Online Reporting Tools Expenditures and Results (NIH RePORTER) databases using the queries presented in Table B-3. Additional databases were searched in the creation of various tables and figures, such as the TRI Explorer, the Substance Priority List (SPL) resource page, and other items as needed. Regulations applicable to acrylonitrile were identified by searching international and U.S. agency websites and documents.

Review articles were identified and used for the purpose of providing background information and identifying additional references. ATSDR also identified reports from the grey literature, which included unpublished research reports, technical reports from government agencies, conference proceedings and abstracts, and theses and dissertations.

Table B-2. Database Query Strings

Database search date	Query string
PubMed	
12/2023	("Acrylonitrile"[mh] AND 2021/09/01:3000[mhda]) OR (("2-Propenenitrile"[tw] OR "Acritet"[tw] OR "Acrylon"[tw] OR "Acrylonitrile"[tw] OR "Carbacryl"[tw] OR "Cyanoethylene"[tw] OR "ENT 54"[tw] OR "Fumigrain"[tw] OR "Miller's fumigrain"[tw] OR "NCI-C50215"[tw] OR "NSC 6362"[tw] OR "Propenenitrile"[tw] OR "TL 314"[tw] OR "Ventox"[tw] OR "Vinyl cyanide"[tw]) AND (2021/09/01:3000[edat] OR 2021/09/01:3000[crdat]))
10/2021	(("Acrylonitrile"[mh] AND (2015/01/01 : 3000[dp] OR 2015/01/01 : 3000[mhda])) OR ((("2-Propenenitrile"[tw] OR "Acritet"[tw] OR "Acrylon"[tw] OR "Acrylonitrile"[tw] OR "Carbacryl"[tw] OR "Cyanoethylene"[tw] OR "ENT 54"[tw] OR "Fumigrain"[tw] OR "Miller's fumigrain"[tw] OR "NCI-C50215"[tw] OR "NSC 6362"[tw] OR "Propenenitrile"[tw] OR "TL 314"[tw] OR "Ventox"[tw] OR "Vinyl cyanide"[tw]) NOT medline[sb]) AND (2015/01/01 : 3000[dp] OR 2015/01/01 : 3000[crdat] OR 2015/01/01 : 3000[edat])))
04/2017	(("Acrylonitrile"[mh] AND (1988/01/01 : 3000[dp] OR 1988/01/01 : 3000[mhda])) OR ((("2-Propenenitrile"[tw] OR "Acritet"[tw] OR "Acrylon"[tw] OR "Acrylonitrile"[tw] OR "Carbacryl"[tw] OR "Cyanoethylene"[tw] OR "ENT 54"[tw] OR "Fumigrain"[tw] OR "Miller's fumigrain"[tw] OR "NCI-C50215"[tw] OR "NSC 6362"[tw] OR "Propenenitrile"[tw] OR "TL 314"[tw] OR "Ventox"[tw] OR "Vinyl cyanide"[tw]) NOT medline[sb]) AND (1988/01/01 : 3000[dp] OR 1988/01/01 : 3000[crdat] OR 1988/01/01 : 3000[edat]))) OR ((("Nitriles/toxicity"[mh] OR "Nitriles/adverse effects"[mh] OR "Nitriles/poisoning"[mh] OR "Nitriles/pharmacokinetics"[mh]) OR ("Nitriles"[mh] AND ("environmental exposure"[mh] OR ci[sh])) OR ("Nitriles"[mh] AND toxicokinetics[mh:noexp]) OR ("Nitriles/blood"[mh] OR "Nitriles/cerebrospinal fluid"[mh] OR "Nitriles/urine"[mh]) OR ("Nitriles"[mh] AND ("endocrine system"[mh] OR "hormones, hormone substitutes, and hormone

Table B-2. Database Query Strings

Database search date	Query string
	antagonists"[mh] OR "endocrine disruptors"[mh])) OR ("Nitriles"[mh] AND ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("Nitriles/antagonists and inhibitors"[mh]) OR ("Nitriles/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("Nitriles"[majr] AND cancer[sb]) OR ("Nitriles/pharmacology"[majr])) AND ("2-Propenenitrile"[tw] OR "Acritet"[tw] OR "Acrylon"[tw] OR "Acrylonitrile"[tw] OR "Carbacryl"[tw] OR "Cyanoethylene"[tw] OR "ENT 54"[tw] OR "Fumigrain"[tw] OR "Miller's fumigrain"[tw] OR "NCI-C50215"[tw] OR "NSC 6362"[tw] OR "Propenenitrile"[tw] OR "TL 314"[tw] OR "Ventox"[tw] OR "Vinyl cyanide"[tw]) AND (1988/01/01 : 1990[dp] OR 1988/01/01 : 1990[mhda]))
Toxline	
04/2017	("2-propenenitrile" OR "acritet" OR "acrylon" OR "acrylonitrile" OR "carbacryl" OR "cyanoethylene" OR "ent 54" OR "fumigrain" OR "miller's fumigrain" OR "nci-c50215" OR "nsc 6362" OR "propenenitrile" OR "tl 314" OR "ventox" OR "vinyl cyanide" OR 107-13-1 [rn]) AND 1988:2017 [yr] AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR FEDRIP [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org]
NTRL	
12/2023	Date limited 2020-present "2-Propenenitrile" OR "Acritet" OR "Acrylon" OR "Acrylonitrile" OR "Carbacryl" OR "Cyanoethylene" OR "ENT 54" OR "Fumigrain" OR "Miller's fumigrain" OR "NCI-C50215" OR "NSC 6362" OR "Propenenitrile" OR "TL 314" OR "Ventox" OR "Vinyl cyanide"
10/2021	"Acrylonitrile" OR "Propenenitrile" OR "Cyanoethylene" OR "Ventox" OR "vinyl cyanide" OR "Acritet" OR "Acrylon" OR "Carbacryl" OR "Fumigrain"
Toxcenter	
12/2023	FILE 'TOXCENTER' ENTERED AT 10:33:17 ON 14 DEC 2023 CHARGED TO COST=ET027.02.02.LB.01 L1 10875 SEA FILE=TOXCENTER 107-13-1 L2 7572 SEA FILE=TOXCENTER L1 NOT PATENT/DT L3 512 SEA FILE=TOXCENTER L2 AND ED>=20210901 ACT TOXQUERY/Q --------- L4 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) L5 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT) L6 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50) L7 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT

Table B-2. Database Query Strings

Database search date	Query string
	L8 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?)
	L9 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?)
	L10 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?)
	L11 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE))
	L12 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?)
	L13 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?)
	L14 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?)
	L15 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?)
	L16 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?)
	L17 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?)
	L18 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?)
	L19 QUE (ENDOCRIN? AND DISRUPT?)
	L20 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?)
	L21 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)
	L22 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)
	L23 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?)
	L24 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)
	L25 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?)
	L26 QUE (NEPHROTOX? OR HEPATOTOX?)
	L27 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?)
	L28 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?)
	L29 QUE L4 OR L5 OR L6 OR L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR L28
	L30 QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE OR PORCINE OR MONKEY? OR MACAQUE?)
	L31 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE)
	L32 QUE L29 OR L30 OR L31
	L33 QUE (NONHUMAN MAMMALS)/ORGN

Table B-2. Database Query Strings

Database search date	Query string
	L34 QUE L32 OR L33 L35 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?) L36 QUE L34 OR L35 --------- L37 256 SEA FILE=TOXCENTER L3 AND L36 L38 51 SEA FILE=TOXCENTER L37 AND MEDLINE/FS L41 205 SEA FILE=TOXCENTER L37 NOT MEDLINE/FS L42 229 DUP REM L38 L41 (27 DUPLICATES REMOVED) L*** DEL 51 S L37 AND MEDLINE/FS L*** DEL 51 S L37 AND MEDLINE/FS L43 51 SEA FILE=TOXCENTER L42 L*** DEL 205 S L37 NOT MEDLINE/FS L*** DEL 205 S L37 NOT MEDLINE/FS L44 178 SEA FILE=TOXCENTER L42 L45 178 SEA FILE=TOXCENTER (L43 OR L44) NOT MEDLINE/FS D SCAN L45
10/2021	FILE 'TOXCENTER' ENTERED AT 14:07:09 ON 04 OCT 2021 CHARGED TO COST=EH011.13.01.01 L1 10026 SEA FILE=TOXCENTER 107-13-1 L2 9894 SEA FILE=TOXCENTER L1 NOT TSCATS/FS L3 6886 SEA FILE=TOXCENTER L2 NOT PATENT/DT L4 865 SEA FILE=TOXCENTER L3 AND ED>=20170401 ACT TOXQUERY/Q --------- L5 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) L6 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT) L7 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50) L8 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT L9 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?) L10 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?) L11 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?) L12 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE)) L13 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?) L14 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?) L15 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?) L16 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?)

Table B-2. Database Query Strings

Database search date	Query string
	L17 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?)
	L18 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?)
	L19 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?)
	L20 QUE (ENDOCRIN? AND DISRUPT?)
	L21 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?)
	L22 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)
	L23 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)
	L24 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?)
	L25 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)
	L26 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?)
	L27 QUE (NEPHROTOX? OR HEPATOTOX?)
	L28 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?)
	L29 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?)
	L30 QUE L5 OR L6 OR L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR L28 OR L29
	L31 QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE OR PORCINE OR MONKEY? OR MACAQUE?)
	L32 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE)
	L33 QUE L30 OR L31 OR L32
	L34 QUE (NONHUMAN MAMMALS)/ORGN
	L35 QUE L33 OR L34
	L36 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?)
	L37 QUE L35 OR L36

	L38 455 SEA FILE=TOXCENTER L4 AND L37
	L39 114 SEA FILE=TOXCENTER L38 AND MEDLINE/FS
	L40 52 SEA FILE=TOXCENTER L38 AND BIOSIS/FS
	L41 286 SEA FILE=TOXCENTER L38 AND CAPLUS/FS
	L42 3 SEA FILE=TOXCENTER L38 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS)
	L43 411 DUP REM L39 L40 L41 L42 (44 DUPLICATES REMOVED)
	L*** DEL 114 S L38 AND MEDLINE/FS

Table B-2. Database Query Strings

Database search date	Query string
	L*** DEL 114 S L38 AND MEDLINE/FS L44 114 SEA FILE=TOXCENTER L43 L*** DEL 52 S L38 AND BIOSIS/FS L*** DEL 52 S L38 AND BIOSIS/FS L45 38 SEA FILE=TOXCENTER L43 L*** DEL 286 S L38 AND CAPLUS/FS L*** DEL 286 S L38 AND CAPLUS/FS L46 256 SEA FILE=TOXCENTER L43 L*** DEL 3 S L38 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS) L*** DEL 3 S L38 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS) L47 3 SEA FILE=TOXCENTER L43 L48 297 SEA FILE=TOXCENTER (L44 OR L45 OR L46 OR L47) NOT MEDLINE/FS D SCAN L48
04/2017	(FILE 'HOME' ENTERED AT 11:25:12 ON 07 APR 2017) FILE 'TOXCENTER' ENTERED AT 11:25:35 ON 07 APR 2017 CHARGED TO COST=EH011.13.01.01 L1 8065 SEA FILE=TOXCENTER 107-13-1 L2 5660 SEA FILE=TOXCENTER L1 AND PY>1987 L3 5660 SEA FILE=TOXCENTER L2 NOT TSCATS/FS L4 3863 SEA FILE=TOXCENTER L3 NOT PATENT/DT ACT TOXQUERY/Q --------- L5 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) L6 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT) L7 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50) L8 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT L9 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?) L10 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?) L11 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?) L12 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE)) L13 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?) L14 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?) L15 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?) L16 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?) L17 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?) L18 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR

Table B-2. Database Query Strings

Database search date	Query string
	SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?)
	L19 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?)
	L20 QUE (ENDOCRIN? AND DISRUPT?)
	L21 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?)
	L22 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)
	L23 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)
	L24 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR
	NEOPLAS?)
	L25 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)
	L26 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?)
	L27 QUE (NEPHROTOX? OR HEPATOTOX?)
	L28 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?)
	L29 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?)
	L30 QUE L5 OR L6 OR L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR L28 OR L29
	L31 QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE
	OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE
	OR PORCINE OR MONKEY? OR MACAQUE?)
	L32 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA
	OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE)
	L33 QUE L30 OR L31 OR L32
	L34 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR
	PRIMATES OR PRIMATE?)
	L35 QUE L33 OR L34

	L36 2390 SEA FILE=TOXCENTER L4 AND L35
	L37 577 SEA FILE=TOXCENTER L36 AND MEDLINE/FS
	L38 412 SEA FILE=TOXCENTER L36 AND BIOSIS/FS
	L39 1328 SEA FILE=TOXCENTER L36 AND CAPLUS/FS
	L40 73 SEA FILE=TOXCENTER L36 NOT (L37 OR L38 OR L39)
	L41 1838 DUP REM L37 L38 L40 L39 (552 DUPLICATES REMOVED)
	ANSWERS '1-1838' FROM FILE TOXCENTER
	L*** DEL 577 S L36 AND MEDLINE/FS
	L*** DEL 577 S L36 AND MEDLINE/FS
	L42 577 SEA FILE=TOXCENTER L41
	L*** DEL 412 S L36 AND BIOSIS/FS
	L*** DEL 412 S L36 AND BIOSIS/FS
	L43 207 SEA FILE=TOXCENTER L41
	L*** DEL 1328 S L36 AND CAPLUS/FS
	L*** DEL 1328 S L36 AND CAPLUS/FS

Table B-2. Database Query Strings

Database search date	Query string
	L44 1004 SEA FILE=TOXCENTER L41 L*** DEL 73 S L36 NOT (L37 OR L38 OR L39) L*** DEL 73 S L36 NOT (L37 OR L38 OR L39) L45 50 SEA FILE=TOXCENTER L41 L46 1261 SEA FILE=TOXCENTER (L42 OR L43 OR L44 OR L45) NOT MEDLINE/FSD SCAN L46

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS via ChemView	
12/2023; 10/2021	Compounds searched: 107-13-1
NTP	
12/2023	Date limited 2020-present "107-13-1" "Acrylonitrile" "Propenenitrile" "vinyl cyanide" "Cyanoethylene" "Ventox" "Acritet" "Acrylon" "Carbacryl" "Fumigrain"
10/2021	Limited 2010-present "107-13-1" "Acrylonitrile" "Propenenitrile" "Cyanoethylene" "Ventox" "vinyl cyanide" "Acritet" "Acrylon" "Carbacryl" "Fumigrain"
04/2017	107-13-1 OR Acritet OR Acrylon OR Acrylonitrile OR Carbacryl OR Cyanoethylene OR Fumigrain OR Propenenitrile OR Ventox "Vinyl cyanide"
Regulations.gov	
12/2023	Documents limited to notices, EPA or FDA "107-13-1" "Acrylonitrile" "Propenenitrile" "vinyl cyanide"
NIH RePORTER	
09/2024	Search Criteria: Fiscal Year: Active Projects Text Search: "2-Propenenitrile" OR "Acritet" OR "Acrylon" OR "Acrylonitrile" OR "Carbacryl" OR "Cyanoethylene" OR "ENT 54" OR "Fumigrain" OR "Miller's fumigrain" OR "NCI-C50215" OR "NSC 6362" OR "Propenenitrile" OR "TL 314" OR "Ventox" OR "Vinyl cyanide" (advanced) Limit to: Project Title, Project Terms, Project Abstracts
06/2022	Text Search: "2-Propenenitrile" OR "Acritet" OR "Acrylon" OR "Acrylonitrile" OR "Carbacryl" OR "Cyanoethylene" OR "ENT 54" OR "Fumigrain" OR "Miller's fumigrain" OR "NCI-C50215" OR "NSC 6362" OR "Propenenitrile" OR "TL 314" OR "Ventox" OR "Vinyl cyanide" (advanced search) Limit to: Project Title, Project Terms, Project Abstracts Fiscal Year: Active Projects

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
Other	Includes additional reference identified throughout the assessment process, which may include studies found by tree searching; recommended by intraagency, interagency, peer, or public reviewers; or published more recently than the date of literature search(es). Additional references include those for specific regulations or guidelines and publications found by targeted searches for specific information (e.g., searches for reviews of general [not chemical-specific] mechanisms of toxicity).

The 2021 pre-public comment search results were:

- Number of records identified from PubMed, Toxline, NTRL, and TOXCENTER (after duplicate removal): 3,933
- Number of records identified from other strategies: 75
- Total number of records to undergo literature screening: 4,008

The 2023 post-public comment search results were:

- Number of records identified from PubMed, NTRL, and TOXCENTER (after duplicate removal): 806
- Number of records identified from other strategies: 47
- Total number of records to undergo literature screening: 853

B.1.2 Literature Screening

A two-step process was used to screen the literature search to identify relevant studies on acrylonitrile during the pre- and post-public comment drafts:

- Title and abstract screen
- Full text screen

Pre-Public Comment Title and Abstract Screen. Within the reference library, titles and abstracts were screened manually for relevance. Studies that were considered (see Table B-1 for inclusion criteria) were moved to the second step of the literature screening process. Studies were excluded when the title and abstract clearly indicated that the study was not relevant to the toxicological profile.

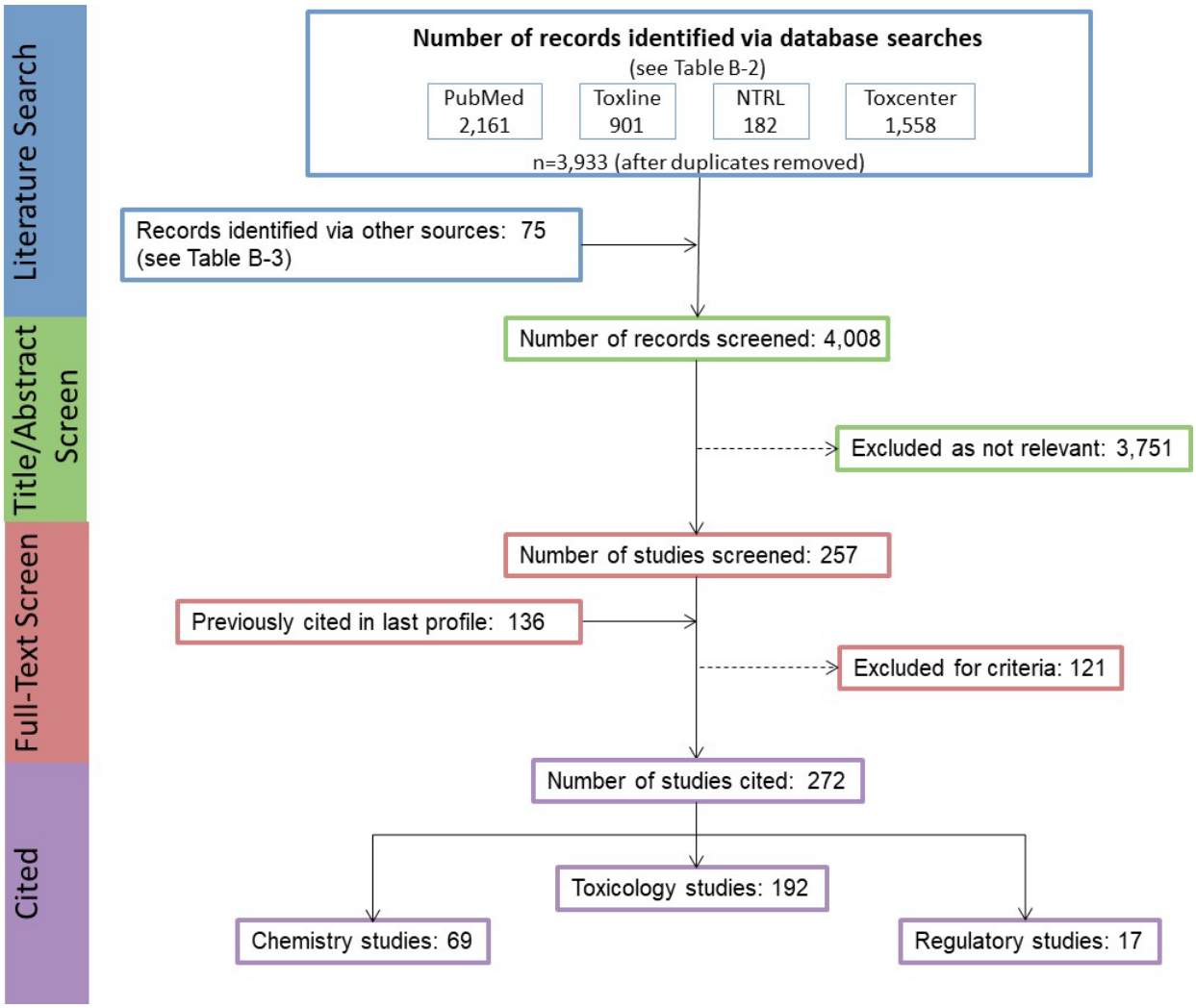
- Number of titles and abstracts screened: 4,008
- Number of studies considered relevant and moved to the next step: 257

Pre-Public Comment Full Text Screen. The second step in the literature screening process was a full text review of individual studies considered relevant in the title and abstract screen step. Each study was reviewed to determine whether it was relevant for inclusion in the toxicological profile.

- Number of studies undergoing full text review: 257
- Number of studies cited in the previous toxicological profile: 136
- Total number of studies cited in the profile: 272

A summary of the results of the pre-public literature search and screening is presented in Figure B-1.

Figure B-1. October 2021 Pre-Public Comment Literature Search Results and Screen for Acrylonitrile*



*The chemistry studies category includes studies pertaining to the potential for human exposure (Table B-1). The toxicology studies category includes human and animal studies of health effects as well as studies of toxicokinetics, biomarkers, and interactions with other chemicals (Table B-1). The regulatory studies category includes those studies cited in Chapter 7.

Post-Public Comment Title and Abstract Screen. Within the reference library, titles and abstracts were screened manually for relevance. Studies that were considered relevant (see Table B-1 for inclusion criteria) were moved to the second step of the literature screening process. Studies were excluded when the title and abstract clearly indicated that the study was not relevant to the toxicological profile.

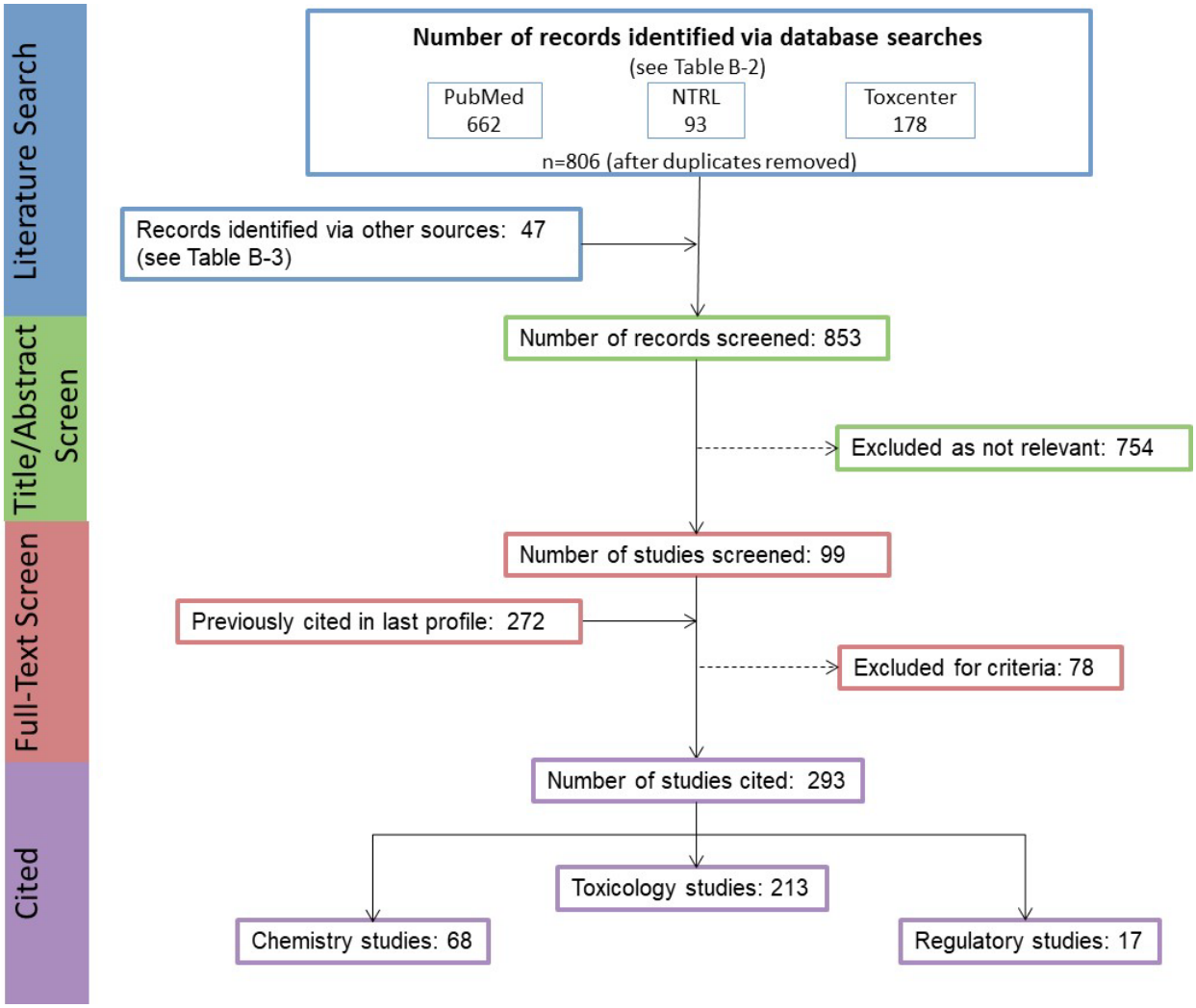
- Number of titles and abstracts screened: 853
- Number of studies considered relevant and moved to the next step: 99

Post-Public Comment Full Text Screen. The second step in the literature screening process was a full text review of individual studies considered relevant in the title and abstract screen step. Each study was reviewed to determine whether it was relevant for inclusion in the toxicological profile.

- Number of studies undergoing full text review: 99
- Number of studies cited in the pre-public draft of the toxicological profile: 272
- Total number of studies cited in the profile: 293

A summary of the results of the post-public comment literature search and screening is presented in Figure B-2.

Figure B-2. December 2023 Post-Public Comment Literature Search Results and Screen for Acrylonitrile*



*The chemistry studies category includes studies pertaining to the potential for human exposure (Table B-1). The toxicology studies category includes human and animal studies of health effects as well as studies of toxicokinetics, biomarkers, and interactions with other chemicals (Table B-1). The regulatory studies category includes those studies cited in Chapter 7.

APPENDIX C FRAMEWORK FOR ATSDR'S SYSTEMATIC REVIEW OF HEALTH EFFECTS DATA FOR ACRYLONITRILE

To increase the transparency of ATSDR's process of identifying, evaluating, synthesizing, and interpreting the scientific evidence on the health effects associated with exposure to acrylonitrile, ATSDR utilized a slight modification of NTP's Office of Health Assessment and Translation (OHAT) systematic review methodology (NTP 2013, 2015; Rooney et al. 2014). ATSDR's framework is an eight-step process for systematic review with the goal of identifying the potential health hazards of exposure to acrylonitrile:

- Step 1. Problem Formulation
- Step 2. Literature Search and Screen for Health Effects Studies
- Step 3. Extract Data from Health Effects Studies
- Step 4. Identify Potential Health Effect Outcomes of Concern
- Step 5. Assess the Risk of Bias for Individual Studies
- Step 6. Rate the Confidence in the Body of Evidence for Each Relevant Outcome
- Step 7. Translate Confidence Rating into Level of Evidence of Health Effects
- Step 8. Integrate Evidence to Develop Hazard Identification Conclusions

C.1 PROBLEM FORMULATION

The objective of the toxicological profile and this systematic review was to identify the potential health hazards associated with inhalation, oral, or dermal/ocular exposure to acrylonitrile. The inclusion criteria used to identify relevant studies examining the health effects of acrylonitrile are presented in Table C-1.

Data from human and laboratory animal studies were considered relevant for addressing this objective. Human studies were divided into two broad categories: observational epidemiology studies and controlled exposure studies. The observational epidemiology studies were further divided: cohort studies (retrospective and prospective studies), population studies (with individual data or aggregate data), and case-control studies.

Table C-1. Inclusion Criteria for Identifying Health Effects Studies

Species
Human
Laboratory mammals
Route of exposure
Inhalation
Oral
Dermal (or ocular)
Parenteral (these studies will be considered supporting data)
Health outcome
Death
Systemic effects
Body weight effects
Respiratory effects
Cardiovascular effects

Table C-1. Inclusion Criteria for Identifying Health Effects Studies

Gastrointestinal effects
Hematological effects
Musculoskeletal effects
Hepatic effects
Renal effects
Dermal effects
Ocular effects
Endocrine effects
Immunological effects
Neurological effects
Reproductive effects
Developmental effects
Other noncancer effects
Cancer

C.2 LITERATURE SEARCH AND SCREEN FOR HEALTH EFFECTS STUDIES

A literature search and screen were conducted to identify studies examining the health effects of acrylonitrile. The literature search framework for the toxicological profile is discussed in detail in Appendix B.

C.2.1 Literature Search

As noted in Appendix B, the literature searches were intended to update the Toxicological Profile for Acrylonitrile. See Appendix B for the databases searched and the search strategy.

A total of 4,008 and 853 records relevant to all sections of the toxicological profile were identified in the initial and update literature search, respectively.

C.2.2 Literature Screening

As described in Appendix B, a two-step process was used to screen the literature search to identify relevant studies examining the health effects of acrylonitrile.

Title and Abstract Screen. In the Title and Abstract Screen step, 53 documents (inclusive of both literature searches) were considered to meet the health effects inclusion criteria in Table C-1 and were moved to the next step in the process.

Full Text Screen. In the second step in the literature screening process for the systematic review, a full text review of 53 health effect documents (documents identified in the update literature search and documents cited in older versions of the profile) was performed. From those 53 documents (71 studies), 27 documents (36 studies) were included in the qualitative review.

C.3 EXTRACT DATA FROM HEALTH EFFECTS STUDIES

Relevant data extracted from the individual studies selected for inclusion in the systematic review were collected in customized data forms. A summary of the type of data extracted from each study is presented in Table C-2. For references that included more than one experiment or species, data extraction records were created for each experiment or species.

Table C-2. Data Extracted from Individual Studies

Citation
Chemical form
Route of exposure (e.g., inhalation, oral, dermal)
Specific route (e.g., gavage in oil, drinking water)
Species
Strain
Exposure duration category (e.g., acute, intermediate, chronic)
Exposure duration
Frequency of exposure (e.g., 6 hours/day, 5 days/week)
Exposure length
Number of animals or subjects per sex per group
Dose/exposure levels
Parameters monitored
Description of the study design and method
Summary of calculations used to estimate doses (if applicable)
Summary of the study results
Reviewer's comments on the study
Outcome summary (one entry for each examined outcome)
No-observed-adverse-effect level (NOAEL) value
Lowest-observed-adverse-effect level (LOAEL) value
Effect observed at the LOAEL value

A summary of the extracted data for each study is presented in the Supplemental Document for acrylonitrile and overviews of the results of the inhalation, oral, and dermal exposure studies are presented in Sections 2.2–2.18 of the profile and in the Levels Significant Exposures table in Section 2.1 of the profile (Tables 2-1, 2-2, and 2-3).

C.4 IDENTIFY POTENTIAL HEALTH EFFECT OUTCOMES OF CONCERN

Overviews of the potential health effect outcomes for acrylonitrile identified in human and animal studies are presented in Tables C-3 and C-4, respectively. The available human studies examined a range of effects; these studies and case reports have reported respiratory, cardiovascular, gastrointestinal, hematological, hepatic, dermal, and neurological effects. Animal studies examined a number of endpoints following inhalation, oral, or dermal exposure; the dermal studies were limited to an examination of lethality. The inhalation oral exposure studies examined most endpoints and reported body weight, respiratory, gastrointestinal, hematological, renal, endocrine, reproductive, and developmental effects. Of the consistently observed effects, respiratory effects following inhalation

Table C-3. Overview of the Health Outcomes for Acrylonitrile Evaluated in Human Studies

	Body weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological	Neurological	Reproductive	Developmental	Other Noncancer	Caner
Inhalation studies																	
Cross sectional		3		2	3	1	4	1	1	2			7				5
		3		2	2	1	2	0	1	0			3				1
Case report			1														
			1														
Experimental													1				
													0				
Oral studies																	
Cross sectional																	
Dermal studies																	
Cross sectional																	
Case Report													1				
													1				
Experimental									1								
									0								

Number of studies examining endpoint	0	1	2	3	4	5–9	≥10
Number of studies reporting outcome	0	1	2	3	4	5–9	≥10

Table C-4. Overview of the Health Outcomes for Acrylonitrile Evaluated in Experimental Animal Studies

	Body weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological[a]	Neurological[a]	Reproductive[a]	Developmental	Other Noncancer	Caner
Inhalation studies																	
Acute-duration	0	3	0	0	0	0	1	2	0	1	0	0	4	1	1	0	0
	0	3	0	0	0	0	0	1	0	1	0	0	4	1	1	0	0
Intermediate-duration	4	3	2	2	2	0	2	2	0	2	2	2	1	4	1	0	0
	2	3	0	1	0	0	0	0	0	0	0	0	1	1	1	0	0
Chronic-duration	1	1	1	1	1	0	1	1	0	0	0	0	1	0	0	0	2
	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2
Oral studies																	
Acute-duration	2	1	0	2	1	0	0	0	0	0	0	0	4	0	2	0	0
	2	1	0	2	1	0	0	0	0	0	0	0	4	0	2	0	0
Intermediate-duration	9	2	3	5	5	1	4	4	0	0	2	2	4	7	2	0	1
	5	0	0	4	3	0	0	0	0	0	1	0	2	4	2	0	1
Chronic-duration	6	5	5	5	5	2	5	5	3	5	4	4	6	4	0	3	7
	5	0	0	3	3	0	0	2	1	0	0	0	2	1	0	0	7
Dermal studies																	
Acute-duration	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Intermediate-duration	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Chronic-duration	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Number of studies examining endpoint	0	1	2	3	4	5–9	≥10
Number of studies reporting outcome	0	1	2	3	4	5–9	≥10

[a]Number of studies examining endpoint includes study evaluating histopathology, but not evaluating function.

exposure, neurotoxicity, and gastrointestinal effects following oral exposure, and developmental effects following inhalation or oral exposure were considered sensitive outcomes (i.e., effects were observed at low concentrations or doses). Studies examining these potential outcomes were carried through to Steps 4–8 of the systematic review. There were 36 studies (published in 27 documents) examining these potential outcomes carried through to Steps 4–8 of the systematic review.

C.5 ASSESS THE RISK OF BIAS FOR INDIVIDUAL STUDIES

C.5.1 Risk of Bias Assessment

The risk of bias of individual studies was assessed using OHAT's Risk of Bias Tool (NTP 2015). The risk of bias questions for observational epidemiology studies, human-controlled exposure studies, and animal experimental studies are presented in Tables C-5, C-6, and C-7, respectively. Each risk of bias question was answered on a four-point scale:

- **Definitely low risk of bias (++)**
- **Probably low risk of bias (+)**
- **Probably high risk of bias (-)**
- **Definitely high risk of bias (– –)**

In general, "definitely low risk of bias" or "definitely high risk of bias" were used if the question could be answered with information explicitly stated in the study report. If the response to the question could be inferred, then "probably low risk of bias" or "probably high risk of bias" responses were typically used.

Table C-5. Risk of Bias Questionnaire for Observational Epidemiology Studies

Selection bias
Were the comparison groups appropriate?
Confounding bias
Did the study design or analysis account for important confounding and modifying variables?
Attrition/exclusion bias
Were outcome data complete without attrition or exclusion from analysis?
Detection bias
Is there confidence in the exposure characterization?
Is there confidence in outcome assessment?
Selective reporting bias
Were all measured outcomes reported?

Table C-6. Risk of Bias Questionnaire for Human-Controlled Exposure Studies

Selection bias
Was administered dose or exposure level adequately randomized?
Was the allocation to study groups adequately concealed?
Performance bias
Were the research personnel and human subjects blinded to the study group during the study?
Attrition/exclusion bias
Were outcome data complete without attrition or exclusion from analysis?
Detection bias
Is there confidence in the exposure characterization?
Is there confidence in outcome assessment?
Selective reporting bias
Were all measured outcomes reported?

Table C-7. Risk of Bias Questionnaire for Experimental Animal Studies

Selection bias
Was administered dose or exposure level adequately randomized?
Was the allocation to study groups adequately concealed?
Performance bias
Were experimental conditions identical across study groups?
Were the research personnel blinded to the study group during the study?
Attrition/exclusion bias
Were outcome data complete without attrition or exclusion from analysis?
Detection bias
Is there confidence in the exposure characterization?
Is there confidence in outcome assessment?
Selective reporting bias
Were all measured outcomes reported?

After the risk of bias questionnaires were completed for the health effects studies, the studies were assigned to one of three risk of bias tiers based on the responses to the key questions listed below and the responses to the remaining questions.

- Is there confidence in the exposure characterization? (only relevant for observational studies)
- Is there confidence in the outcome assessment?
- Does the study design or analysis account for important confounding and modifying variables? (only relevant for observational studies)

First Tier. Studies placed in the first tier received ratings of "definitely low" or "probably low" risk of bias on the key questions **AND** received a rating of "definitely low" or "probably low" risk of bias on the responses to at least 50% of the other applicable questions.

Second Tier. A study was placed in the second tier if it did not meet the criteria for the first or third tiers.

Third Tier. Studies placed in the third tier received ratings of "definitely high" or "probably high" risk of bias for the key questions **AND** received a rating of "definitely high" or "probably high" risk of bias on the response to at least 50% of the other applicable questions.

The results of the risk of bias assessment for the different types of acrylonitrile health effects studies (observational epidemiology and animal experimental studies) are presented in Tables C-8 and C-9, respectively.

Table C-8. Summary of Risk of Bias Assessment for Acrylonitrile—Observational Epidemiology Studies

Reference	Risk of bias criteria and ratings						Risk of bias tier
	Selection bias	Confounding bias	Attrition / exclusion bias	Detection bias		Selective reporting bias	
	Were the comparison groups appropriate?	Did the study design or analysis account for important confounding and modifying variables?*	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?*	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	
Outcome: Respiratory effects (following inhalation exposure)							
Cross sectional							
Simons et al. 2016		+	+	+	+	+	First
Case series							
Wilson 1944		–			–	+	Third
Wilson et al. 1948		–	+	–	–	+	Third
Outcome: Neurological effects							
Cross sectional							
Vogel and Kirkendall 1984							
Case series/case report							
Grunske 1949							
Wilson 1944		–			–	+	Third
Wilson et al. 1948		–	+	–	–	+	Third

Table C-8. Summary of Risk of Bias Assessment for Acrylonitrile—Observational Epidemiology Studies

Reference	Risk of bias criteria and ratings						Risk of bias tier
	Selection bias	Confounding bias	Attrition / exclusion bias	Detection bias		Selective reporting bias	
	Were the comparison groups appropriate?	Did the study design or analysis account for important confounding and modifying variables?*	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?*	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	
Experimental							
Jakubowski et al. 1987		+	+	+	+	-	First

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias; na = not applicable

*Key question used to assign risk of bias tier.

Table C-9. Summary of Risk of Bias Assessment for Acrylonitrile—Experimental Animal Studies

Reference	Risk of bias criteria and ratings								Risk of bias tier
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	
Outcome: Respiratory effects (following inhalation exposure)									
Inhalation acute exposure									
Gut et al. 1984	–	+	+	+	+	+	–	+	Second
Inhalation intermediate exposure									
Nemec et al. 2008	++	+	++	+	++	+	+	+	First
Quast et al. 1983 (6 months)	+	+	++	+	++	+	+	+	First
Quast et al. 1983 (12 months)	+	+	++	+	++	+	+	+	First
Inhalation chronic exposure									
Quast et al. 1980a	+	+	++	+	++	+	+	+	First
Outcome: Gastrointestinal effects (following oral exposure)									
Oral acute exposure									
Murray et al. 1978	–	+	+	+	+	+	+	+	First

Table C-9. Summary of Risk of Bias Assessment for Acrylonitrile—Experimental Animal Studies

Reference	Risk of bias criteria and ratings								Risk of bias tier
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	
Oral intermediate exposure									
Ghanayem et al. 1997	–	+	+	+	+	+	+	+	Second
Humiston et al. 1975									
NTP 2001	–	+	++	+	++	++	+	++	First
Quast et al. 1975									
Quast 2002	+	+	++	+	++	++	+	+	First
Oral chronic exposure									
Johannsen and Levinskas 2002a	++	+	++	+	+	+	+	+	First
Johannsen and Levinskas 2002b (gavage)	++	+	++	+	+	+	+	+	First
Johannsen and Levinskas 2002b (drinking water)	++	+	++	+	+	+	+	+	First
NTP 2001	–	+	++	+	++	++	+	++	First
Quast 2002	+	+	++	+	++	++	++	+	First

Table C-9. Summary of Risk of Bias Assessment for Acrylonitrile—Experimental Animal Studies

Reference	Risk of bias criteria and ratings								Risk of bias tier
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	
Outcome: Neurological effects									
Inhalation acute exposure									
Dudley and Neal 1942 (monkey)	–	+	–	–	+	–	+	+	Second
Dudley and Neal 1942 (dog)	–	+	–	–	+	–	+	+	Second
Dudley and Neal 1942 (cat)	–	+	–	–	+	–	+	+	Second
Gut et al. 1985	–	+	+	+	+	+	–	+	Second
Inhalation intermediate exposure									
Gagnaire et al. 1998	–	+	+	+	+	+	+	+	First
Inhalation chronic exposure									
Quast et al. 1980a	+	+	++	+	++	+	+	+	First
Oral acute exposure									
Ahmed and Patel 1981 (rat)	–	+	+	+	+	++	+	+	First

Table C-9. Summary of Risk of Bias Assessment for Acrylonitrile—Experimental Animal Studies

Reference	Risk of bias criteria and ratings								Risk of bias tier
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	
Ahmed and Patel 1981 (mouse)	–	+	+	+	+	++	+	+	First
Ghanayem et al. 1991	–	+	+	+	+	+	+	+	First
Murray et al. 1978	–	+	+	+	+	+	+	+	First
Oral intermediate exposure									
Friedman and Beliles 2002	++	+	++	+	+	+	+	+	First
Gagnaire et al. 1998	–	+	+	+	+	+	+	+	First
Humiston et al. 1975									
Quast et al. 1975									
Oral chronic exposure									
Bigner et al. 1986	+	+	+	+	+	--	+	+	First
Johannsen and Levinskas 2002a	++	+	++	+	+	+	+	+	First
Johannsen and Levinskas 2002b (gavage)	++	+	++	+	+	+	+	+	First

Table C-9. Summary of Risk of Bias Assessment for Acrylonitrile—Experimental Animal Studies

Reference	Risk of bias criteria and ratings								Risk of bias tier
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	
Johannsen and Levinskas 2002b (drinking water)	++	+	++	+	+	+	+	+	First
NTP 2001	–	+	++	+	++	++	+	++	First
Quast 2002	+	+	++	+	++	++	++	+	First
Outcome: Developmental effects									
Inhalation acute exposure									
Murray et al. 1978	+	+	++	+	+	+	+	++	First
Inhalation intermediate exposure									
Nemec et al. 2008	++	+	++	+	+	++	+	++	First
Oral acute exposure									
Murray et al. 1978	+	+	++	+	+	+	+	++	First
Saillenfait and Sabate 2000	+	+	+	+	+	+	++	++	First
Oral intermediate exposure									
Friedman and Beliles 2002	++	+	+	+	+	+	+	+	First

Table C-9. Summary of Risk of Bias Assessment for Acrylonitrile—Experimental Animal Studies

Reference	Risk of bias criteria and ratings								Risk of bias tier
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	
Luo et al. 2022	+	+	+	+	+	+	+		

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias; na = not applicable
*Key question used to assign risk of bias tier

C.6 RATE THE CONFIDENCE IN THE BODY OF EVIDENCE FOR EACH RELEVANT OUTCOME

Confidences in the bodies of human and animal evidence were evaluated independently for each potential outcome. ATSDR did not evaluate the confidence in the body of evidence for carcinogenicity; rather, the Agency defaulted to the cancer weight-of-evidence assessment of other agencies including DHHS, EPA, and IARC. The confidence in the body of evidence for an association or no association between exposure to acrylonitrile and a particular outcome was based on the strengths and weaknesses of individual studies. Four descriptors were used to describe the confidence in the body of evidence for effects or when no effect was found:

- **High confidence:** the true effect is highly likely to be reflected in the apparent relationship
- **Moderate confidence:** the true effect may be reflected in the apparent relationship
- **Low confidence:** the true effect may be different from the apparent relationship
- **Very low confidence:** the true effect is highly likely to be different from the apparent relationship

Confidence in the body of evidence for a particular outcome was rated for each type of study: case-control, case series, cohort, population, human-controlled exposure, and experimental animal. In the absence of data to the contrary, data for a particular outcome were collapsed across animal species, routes of exposure, and exposure durations. If species (or strain), route, or exposure duration differences were noted, then the data were treated as separate outcomes.

C.6.1 Initial Confidence Rating

In ATSDR's modification to the OHAT approach, the body of evidence for an association (or no association) between exposure to acrylonitrile and a particular outcome was given an initial confidence rating based on the key features of the individual studies examining that outcome. The presence of these key features of study design was determined for individual studies using four "yes or no" questions in Distiller, which were customized for epidemiology, human controlled exposure, or experimental animal study designs. Separate questionnaires were completed for each outcome assessed in a study. The key features for observational epidemiology (cohort, population, and case-control) studies, human controlled exposure, and experimental animal studies are presented in Tables C-10, C-11, and C-12, respectively. The initial confidence in the study was determined based on the number of key features present in the study design:

- **High Initial Confidence:** Studies in which the responses to the four questions were "yes".
- **Moderate Initial Confidence:** Studies in which the responses to only three of the questions were "yes".
- **Low Initial Confidence:** Studies in which the responses to only two of the questions were "yes".
- **Very Low Initial Confidence:** Studies in which the response to one or none of the questions was "yes".

Table C-10. Key Features of Study Design for Observational Epidemiology Studies

Exposure was experimentally controlled
Exposure occurred prior to the outcome
Outcome was assessed on individual level rather than at the population level
A comparison group was used

Table C-11. Key Features of Study Design for Human-Controlled Exposure Studies

A comparison group was used or the subjects served as their own control
A sufficient number of subjects were tested
Appropriate methods were used to measure outcomes (i.e., clinically-confirmed outcome versus self-reported)
Appropriate statistical analyses were performed and reported or the data were reported in such a way to allow independent statistical analysis

Table C-12. Key Features of Study Design for Experimental Animal Studies

A concurrent control group was used
A sufficient number of animals per group were tested
Appropriate parameters were used to assess a potential adverse effect
Appropriate statistical analyses were performed and reported or the data were reported in such a way to allow independent statistical analysis

The presence or absence of the key features and the initial confidence levels for studies examining respiratory, gastrointestinal, or neurological effects observed in the observational epidemiology and animal experimental studies are presented in Tables C-13 and C-14, respectively.

Table C-13. Presence of Key Features of Study Design for Acrylonitrile—Observational Epidemiology Studies

Reference	Key features				Initial study confidence
	Controlled exposure	Exposure prior to outcome	Outcomes assessed on an individual level	Comparison group	
Outcome: Respiratory effects (following inhalation exposure)					
Cross sectional					
Simons et al. 2016	No	Yes	Yes	No	Low
Case Series					
Wilson 1944	No	Yes	No	No	Very low
Wilson et al. 1948	No	Yes	No	No	Very low
Outcome: Neurological effects					
Cross sectional					
Vogel and Kirkendall 1984					
Case Series/Case Report					
Grunske 1949					
Wilson 1944	No	Yes	No	No	Very low
Wilson et al. 1948	No	Yes	No	No	Very low
Experimental					
Jakubowski et al. 1987	Yes	Yes	Yes	No	Moderate

Table C-14. Presence of Key Features of Study Design for Acrylonitrile—Experimental Animal Studies

Reference	Key feature: Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	Initial study confidence
Outcome: Respiratory effects (following inhalation exposure)					
Inhalation acute exposure					
Gut et al. 1984	Yes	No	No	No	Low
Inhalation intermediate exposure					
Nemec et al. 2008	Yes	Yes	Yes	Yes	High
Quast et al. 1983 (6 months)	Yes	Yes	Yes	Yes	High
Quast et al. 1983 (12 months)	Yes	Yes	Yes	Yes	High
Inhalation chronic exposure					
Quast et al. 1980a	Yes	Yes	Yes	Yes	High
Outcome: Gastrointestinal effects (following oral exposure)					
Oral acute exposure					
Murray et al. 1978	Yes	Yes	Yes	Yes	High
Oral intermediate exposure					
Ghanayem et al. 1997	Yes	Yes	Yes	No	Moderate
Humiston et al. 1975					
NTP 2001	Yes	Yes	Yes	Yes	High
Quast et al. 1975					
Quast 2002	Yes	Yes	Yes	Yes	High
Oral chronic exposure					
Johannsen and Levinskas 2002a	Yes	Yes	Yes	Yes	High
Johannsen and Levinskas 2002b (gavage)	Yes	Yes	Yes	Yes	High
Johannsen and Levinskas 2002b (drinking water)	Yes	Yes	Yes	Yes	High
NTP 2001	Yes	Yes	Yes	Yes	High
Quast 2002	Yes	Yes	Yes	Yes	High
Outcome: Neurological effects					
Inhalation acute exposure					
Dudley and Neal 1942 (monkey)	No	No	Yes	Yes	Low
Dudley and Neal 1942 (dog)	No	No	Yes	Yes	Low
Dudley and Neal 1942 (cat)	No	No	Yes	Yes	Low
Gut et al. 1985	Yes	No	No	No	Low

Table C-14. Presence of Key Features of Study Design for Acrylonitrile—Experimental Animal Studies

Reference	Key feature: Concurrent control group	Key feature: Sufficient number of animals per group	Key feature: Appropriate parameters to assess potential effect	Key feature: Adequate data for statistical analysis	Initial study confidence
Inhalation intermediate exposure					
Gagnaire et al. 1998	Yes	Yes	Yes	Yes	High
Inhalation chronic exposure					
Quast et al. 1980a	Yes	Yes	Yes	Yes	High
Oral acute exposure					
Ahmed and Patel 1981(rat)	Yes	No	Yes	No	Low
Ahmed and Patel 1981 (mouse)	Yes	No	Yes	No	Low
Ghanayem et al. 1991	Yes	No	Yes	No	Low
Murray et al. 1978	Yes	Yes	Yes	Yes	High
Oral intermediate exposure					
Friedman and Beliles 2002	Yes	Yes	Yes	Yes	High
Gagnaire et al. 1998	Yes	Yes	Yes	Yes	High
Humiston et al. 1975					
Quast et al. 1975					
Oral chronic exposure					
Bigner et al. 1986	Yes	Yes	Yes	Yes	High
Johannsen and Levinskas 2002a	Yes	Yes	Yes	Yes	High
Johannsen and Levinskas 2002b (gavage)	Yes	Yes	Yes	Yes	High
Johannsen and Levinskas 2002b (drinking water)	Yes	Yes	Yes	Yes	High
NTP 2001	Yes	Yes	Yes	Yes	High
Quast 2002	Yes	Yes	Yes	Yes	High
Outcome: Developmental effects					
Inhalation acute exposure					
Murray et al. 1978	Yes	Yes	Yes	Yes	High
Inhalation intermediate exposure					
Nemec et al. 2008	Yes	Yes	Yes	Yes	High
Oral acute exposure					
Murray et al. 1978	Yes	Yes	Yes	Yes	High
Saillenfait and Sabate 2000	Yes	No	Yes	Yes	Moderate
Oral intermediate exposure					
Friedman and Beliles 2002	Yes	Yes	Yes	Yes	High
Luo et al. 2022	Yes	Yes	Yes	Yes	High

A summary of the initial confidence ratings for each outcome is presented in Table C-15. If individual studies for a particular outcome and study type had different study quality ratings, then the highest confidence rating for the group of studies was used to determine the initial confidence rating for the body of evidence; any exceptions were noted in Table C-15.

Table C-15. Initial Confidence Rating for Acrylonitrile Health Effects Studies

	Initial study confidence	Initial confidence rating
Outcome: Respiratory effects (following inhalation exposure)		
Inhalation acute exposure		
Human studies		
Simons et al. 2016	Low	Low
Wilson 1944	Very low	
Wilson et al. 1948	Very low	
Animal studies		
Gut et al. 1985	Low	Low
Inhalation intermediate exposure		
Animal studies		
Nemec et al. 2008	High	High
Quast et al. 1983 (6 months)	High	
Quast et al. 1983 (12 months)	High	
Inhalation chronic exposure		
Animal studies		
Quast et al. 1980a	High	High
Outcome: Gastrointestinal effects (following oral exposure)		
Oral acute exposure		
Animal studies		
Murray et al. 1978	High	High
Oral intermediate exposure		
Animal studies		
Ghanayem et al. 1997	Moderate	High
Humiston et al. 1975		
NTP 2001	High	
Quast et al. 1975		
Quast 2002	High	
Oral chronic exposure		
Animal studies		
Johannsen and Levinskas 2002a	High	High
Johannsen and Levinskas 2002b (gavage)	High	
Johannsen and Levinskas 2002b (drinking water)	High	
NTP 2001	High	
Quast 2002	High	

Table C-15. Initial Confidence Rating for Acrylonitrile Health Effects Studies

	Initial study confidence	Initial confidence rating
Outcome: Neurological effects		
Inhalation acute exposure		
Human studies		
Grunske 1949		Moderate
Jakubowski et al. 1987	Moderate	
Vogel and Kirkendall 1984		
Wilson 1944	Very low	
Wilson et al. 1948	Very low	
Animal studies		
Dudley and Neal 1942 (monkey)	Low	Low
Dudley and Neal 1942 (dog)	Low	
Dudley and Neal 1942 (cat)	Low	
Gut et al. 1985	Low	
Inhalation intermediate exposure		
Animal studies		
Gagnaire et al. 1998	High	High
Inhalation intermediate exposure		
Animal studies		
Quast et al. 1980a	High	High
Oral acute exposure		
Animal studies		
Ahmed and Patel 1981(rat)	Low	High
Ahmed and Patel 1981 (mouse)	Low	
Ghanayem et al. 1991	Low	
Murray et al. 1978	High	
Oral intermediate exposure		
Animal studies		
Friedman and Beliles 2002	High	High
Gagnaire et al. 1998	High	
Humiston et al. 1975		
Quast et al. 1975		
Oral chronic exposure		
Animal studies		
Bigner et al. 1986	High	High
Johannsen and Levinskas 2002a	High	
Johannsen and Levinskas 2002b (gavage)	High	
Johannsen and Levinskas 2002b (drinking water)	High	
NTP 2001	High	
Quast 2002	High	

Table C-15. Initial Confidence Rating for Acrylonitrile Health Effects Studies

	Initial study confidence	Initial confidence rating
Outcome: Developmental effects		
Inhalation acute exposure		
Animal studies		
Murray et al. 1978	High	High
Inhalation intermediate exposure		
Animal studies		
Nemec et al. 2008	High	High
Oral acute exposure		
Animal studies		
Murray et al. 1978	High	High
Saillenfait and Sabate 2000	Moderate	
Oral intermediate exposure		
Animal studies		
Friedman and Beliles 2002	High	High
Luo et al. 2022	High	

C.6.2 Adjustment of the Confidence Rating

The initial confidence rating was then downgraded or upgraded depending on whether there were substantial issues that would decrease or increase confidence in the body of evidence. The nine properties of the body of evidence that were considered are listed below. The summaries of the assessment of the confidence in the body of evidence for hepatic effects and developmental effects are presented in Table C-16. If the confidence ratings for a particular outcome were based on more than one type of human study, then the highest confidence rating was used for subsequent analyses. An overview of the confidence in the body of evidence for all health effects associated with acrylonitrile exposure is presented in Table C-17.

Table C-16. Adjustments to the Initial Confidence in the Body of Evidence

	Initial confidence	Adjustments to the initial confidence rating	Final confidence
Outcome: Respiratory effects (following inhalation exposure)			
Human studies	Low		Low
Animal studies	High	+1(dose response)	High
Outcome: Gastrointestinal effects (following oral exposure)			
Human studies			
Animal studies	High	+1 (magnitude), +1 (consistency)	High
Outcome: Neurological effects			
Human studies	Moderate		Moderate
Animal studies	High		High

Table C-16. Adjustments to the Initial Confidence in the Body of Evidence

	Initial confidence	Adjustments to the initial confidence rating	Final confidence
Outcome: Developmental effects			
Human studies			
Animal studies	High		High

Table C-17. Confidence in the Body of Evidence for Acrylonitrile

	Confidence in body of evidence	
Outcome	Human studies	Animal studies
Respiratory effects following inhalation exposure	Low	High
Gastrointestinal effects following oral exposure	–	High
Neurological effects	Moderate	High
Developmental effects	–	High

Five properties of the body of evidence were considered to determine whether the confidence rating should be downgraded:

- **Risk of bias.** Evaluation of whether there is substantial risk of bias across most of the studies examining the outcome. This evaluation used the risk of bias tier groupings for individual studies examining a particular outcome (Tables C-8 and C-9). Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for risk of bias:
  - No downgrade if most studies are in the risk of bias first tier
  - Downgrade one confidence level if most studies are in the risk of bias second tier
  - Downgrade two confidence levels if most studies are in the risk of bias third tier

- **Unexplained inconsistency.** Evaluation of whether there is inconsistency or large variability in the magnitude or direction of estimates of effect across studies that cannot be explained. Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for unexplained inconsistency:
  - No downgrade if there is little inconsistency across studies or if only one study evaluated the outcome
  - Downgrade one confidence level if there is variability across studies in the magnitude or direction of the effect
  - Downgrade two confidence levels if there is substantial variability across studies in the magnitude or direct of the effect

- **Indirectness.** Evaluation of four factors that can affect the applicability, generalizability, and relevance of the studies:
  - Relevance of the animal model to human health—unless otherwise indicated, studies in rats, mice, and other mammalian species are considered relevant to humans
  - Directness of the endpoints to the primary health outcome—examples of secondary outcomes or nonspecific outcomes include organ weight in the absence of histopathology or clinical chemistry findings in the absence of target tissue effects

- Nature of the exposure in human studies and route of administration in animal studies—inhalation, oral, and dermal exposure routes are considered relevant unless there are compelling data to the contrary
- Duration of treatment in animal studies and length of time between exposure and outcome assessment in animal and prospective human studies—this should be considered on an outcome-specific basis

Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for indirectness:

- No downgrade if none of the factors are considered indirect
- Downgrade one confidence level if one of the factors is considered indirect
- Downgrade two confidence levels if two or more of the factors are considered indirect

- **Imprecision.** Evaluation of the narrowness of the effect size estimates and whether the studies have adequate statistical power. Data are considered imprecise when the ratio of the upper to lower 95% CIs for most studies is ≥10 for tests of ratio measures (e.g., odds ratios) and ≥100 for absolute measures (e.g., percent control response). Adequate statistical power is determined if the study can detect a potentially biologically meaningful difference between groups (20% change from control response for categorical data or risk ratio of 1.5 for continuous data). Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for imprecision:
  - No downgrade if there are no serious imprecisions
  - Downgrade one confidence level for serious imprecisions
  - Downgrade two confidence levels for very serious imprecisions

- **Publication bias.** Evaluation of the concern that studies with statistically significant results are more likely to be published than studies without statistically significant results.
  - Downgrade one level of confidence for cases where there is serious concern with publication bias

Four properties of the body of evidence were considered to determine whether the confidence rating should be upgraded:

- **Large magnitude of effect.** Evaluation of whether the magnitude of effect is sufficiently large so that it is unlikely to have occurred as a result of bias from potential confounding factors.
  - Upgrade one confidence level if there is evidence of a large magnitude of effect in a few studies, provided that the studies have an overall low risk of bias and there is no serious unexplained inconsistency among the studies of similar dose or exposure levels; confidence can also be upgraded if there is one study examining the outcome, provided that the study has an overall low risk of bias

- **Dose response.** Evaluation of the dose-response relationships measured within a study and across studies. Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
  - Upgrade one confidence level for evidence of a monotonic dose-response gradient
  - Upgrade one confidence level for evidence of a non-monotonic dose-response gradient where there is prior knowledge that supports a non-monotonic dose-response and a non-monotonic dose-response gradient is observed across studies

- **Plausible confounding or other residual biases.** This factor primarily applies to human studies and is an evaluation of unmeasured determinants of an outcome such as residual bias towards the null (e.g., "healthy worker" effect) or residual bias suggesting a spurious effect (e.g., recall bias). Below is the criterion used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
  - Upgrade one confidence level for evidence that residual confounding or bias would underestimate an apparent association or treatment effect (i.e., bias toward the null) or suggest a spurious effect when results suggest no effect

- **Consistency in the body of evidence.** Evaluation of consistency across animal models and species, consistency across independent studies of different human populations and exposure scenarios, and consistency across human study types. Below is the criterion used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
  - Upgrade one confidence level if there is a high degree of consistency in the database

C.7 TRANSLATE CONFIDENCE RATING INTO LEVEL OF EVIDENCE OF HEALTH EFFECTS

In the seventh step of the systematic review of the health effects data for acrylonitrile, the confidence in the body of evidence for specific outcomes was translated to a level of evidence rating. The level of evidence rating reflected the confidence in the body of evidence and the direction of the effect (i.e., toxicity or no toxicity); route-specific differences were noted. The level of evidence for health effects was rated on a five-point scale:

- **High level of evidence:** High confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Moderate level of evidence:** Moderate confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Low level of evidence:** Low confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Evidence of no health effect:** High confidence in the body of evidence that exposure to the substance is not associated with the health outcome
- **Inadequate evidence:** Low or moderate confidence in the body of evidence that exposure to the substance is not associated with the health outcome OR very low confidence in the body of evidence for an association between exposure to the substance and the health outcome

A summary of the level of evidence of health effects for acrylonitrile is presented in Table C-18.

Table C-18. Level of Evidence of Health Effects for Acrylonitrile

Outcome	Confidence in body of evidence	Direction of health effect	Level of evidence for health effect
Human studies			
Respiratory effects	Low	Effect	Low
Gastrointestinal effects	–		
Neurological effects	Moderate	Effect	Moderate
Developmental effects	–		
Animal studies			
Respiratory effects	High	Effect	High
Gastrointestinal effects	High	Effect	High
Neurological effects	High	Effect	High
Developmental effects	High	Effect	High

C.8 INTEGRATE EVIDENCE TO DEVELOP HAZARD IDENTIFICATION CONCLUSIONS

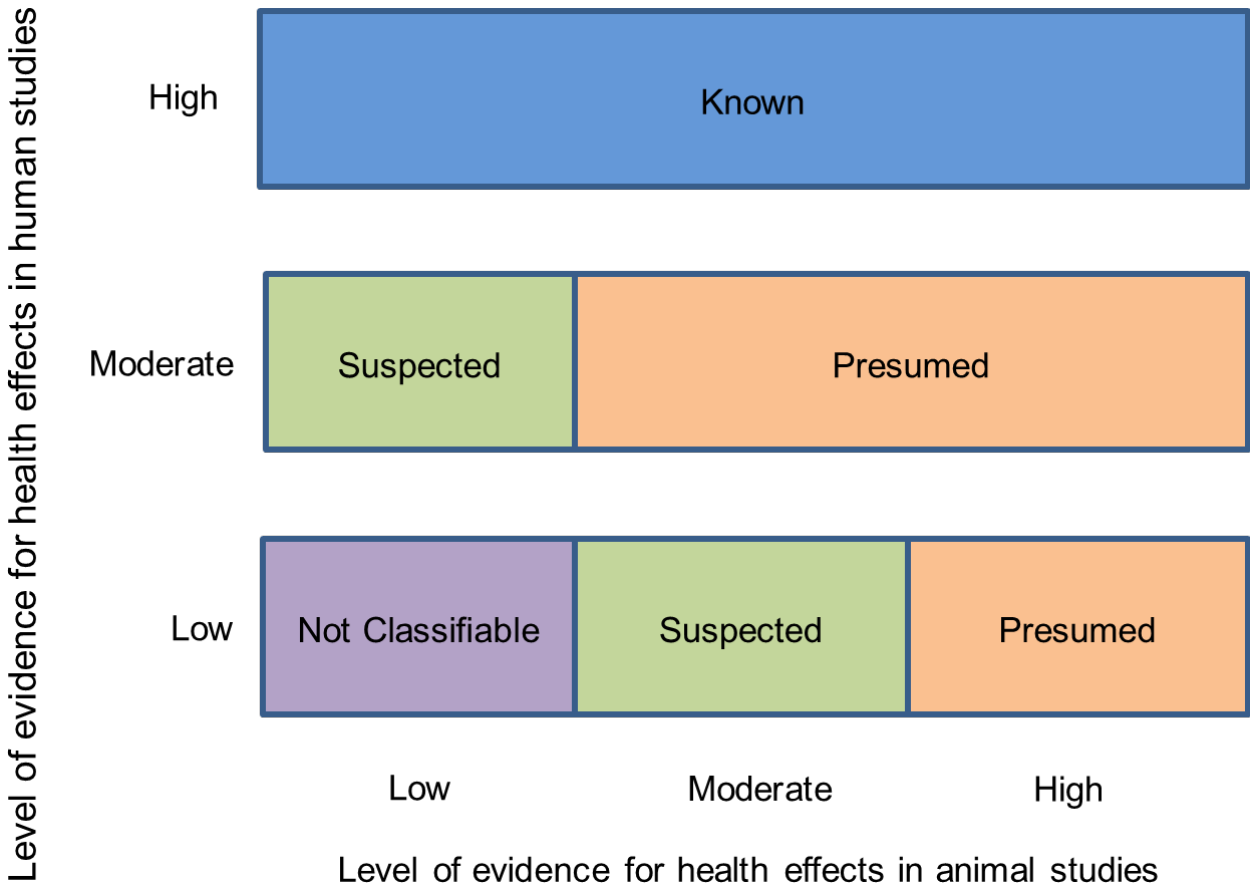
The final step involved the integration of the evidence streams for the human studies and animal studies to allow for a determination of hazard identification conclusions. For health effects, there were four hazard identification conclusion categories:

- **Known** to be a hazard to humans
- **Presumed** to be a hazard to humans
- **Suspected** to be a hazard to humans
- **Not classifiable** as to the hazard to humans

The initial hazard identification was based on the highest level of evidence in the human studies and the level of evidence in the animal studies; if there were no data for one evidence stream (human or animal), then the hazard identification was based on the one data stream (equivalent to treating the missing evidence stream as having low level of evidence). The hazard identification scheme is presented in Figure C-1 and described below:

- **Known:** A health effect in this category would have:
  - High level of evidence for health effects in human studies **AND** a high, moderate, or low level of evidence in animal studies.
- **Presumed:** A health effect in this category would have:
  - Moderate level of evidence in human studies **AND** high or moderate level of evidence in animal studies **OR**
  - Low level of evidence in human studies **AND** high level of evidence in animal studies
- **Suspected:** A health effect in this category would have:
  - Moderate level of evidence in human studies **AND** low level of evidence in animal studies **OR**
  - Low level of evidence in human studies **AND** moderate level of evidence in animal studies
- **Not classifiable:** A health effect in this category would have:
  - Low level of evidence in human studies **AND** low level of evidence in animal studies

Figure C-1. Hazard Identification Scheme



Other relevant data such as mechanistic or mode-of-action data were considered to raise or lower the level of the hazard identification conclusion by providing information that supported or opposed biological plausibility.

Two hazard identification conclusion categories were used when the data indicated that there may be no health effect in humans:

- **Not identified** to be a hazard in humans
- **Inadequate** to determine hazard to humans

If the human level of evidence conclusion of no health effect was supported by the animal evidence of no health effect, then the hazard identification conclusion category of "not identified" was used. If the human or animal level of evidence was considered inadequate, then a hazard identification conclusion category of "inadequate" was used. As with the hazard identification for health effects, the impact of other relevant data was also considered for no health effect data.

The hazard identification conclusions for acrylonitrile are listed below and summarized in Table C-19.

Presumed Health Effects

- Respiratory effects following inhalation exposure
  - Low level of evidence from acute exposure studies/case reports of irritation following acute exposure (Simons et al. 2016; Wilson 1944; Wilson et al. 1948)
  - High level of evidence of nasal irritation and hyperplasia in rats (Nemec et al. 2008; Quast et al. 1983)
- Gastrointestinal effects following oral exposure
  - None of the available human studies evaluated potential gastrointestinal effects.
  - High level of evidence of increased incidence or severity of forestomach squamous cell hyperplasia (Ghanayem et al. 1997; Johannsen and Levinskas 2002a, 2002b; NTP 2001; Quast 2002) or thickening of forestomach (Murray et al. 1978). One study reported esophageal ulcerations in dogs (Quast et al. 1975). One study did not find gastrointestinal effects (Humiston et al. 1975).
- Neurological effects
  - Moderate evidence in humans of overt signs of neurotoxicity similar to those associated with cyanide poisoning (Vogel and Kirkendall 1984; Wilson 1944; Wilson et al. 1948). A toxicokinetic study in humans reported that no adverse effects were found (Jakubowski et al. 1987).
  - High evidence in animals of overt signs of neurotoxicity in several species (Ahmed and Patel 1981; Bigner et al. 1986; Dudley and Neal 1942; Ghanayem et al. 1991; Gut et al. 1985; Murray et al. 1978; Quast et al. 1975).
  - High evidence of glial lesions in rats and mice (Quast et al. 1980a; Quast 2002) or decreased sensory nerve conduction velocity (Gagnaire et al. 1998). Several studies have not found histological alterations (Johannsen and Levinskas 2002a, 2002b).
- Developmental effects
  - None of the available human studies evaluated potential developmental effects.
  - High level of evidence of developmental effects, particularly decreased body weight (Friedman and Beliles 2002; Luo et al. 2022; Murray et al. 1978) and skeletal malformations (Murray et al. 1978; Saillenfait and Sabate 2000) observed following inhalation or oral exposure. Developmental effects were often reported at maternally toxic doses.

Table C-19. Hazard Identification Conclusions for Acrylonitrile

Outcome	Hazard identification
Respiratory effects following inhalation exposure	Presumed health effect
Gastrointestinal effects following oral exposure	Presumed health effect
Neurological effects	Presumed health effect
Developmental effects	Presumed health effect

APPENDIX D. USER'S GUIDE

Chapter 1. Relevance to Public Health

This chapter provides an overview of U.S. exposures, a summary of health effects based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information, and an overview of the minimal risk levels. This is designed to present interpretive, weight-of-evidence discussions for human health endpoints by addressing the following questions:

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

Minimal Risk Levels (MRLs)

Where sufficient toxicologic information is available, ATSDR derives MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a hazardous substance emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Section 1.2, Summary of Health Effects, contains basic information known about the substance. Other sections, such as Section 3.2 Children and Other Populations that are Unusually Susceptible and Section 3.4 Interactions with Other Substances, provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive endpoint which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a

substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables that are provided in Chapter 2. Detailed discussions of the MRLs are presented in Appendix A.

Chapter 2. Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species and MRLs to humans for noncancer endpoints. The LSE tables and figures can be used for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE tables and figures follow. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

TABLE LEGEND

See Sample LSE Table (page D-5)

(1) Route of exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically, when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure (i.e., inhalation, oral, and dermal). LSE figures are limited to the inhalation and oral routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures. Profiles with more than one chemical may have more LSE tables and figures.

(2) Exposure period. Three exposure periods—acute (<15 days), intermediate (15–364 days), and chronic (≥365 days)—are presented within each relevant route of exposure. In this example, two oral studies of chronic-duration exposure are reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Figure key. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 51 identified NOAELs and less serious LOAELs (also see the three "51R" data points in sample LSE Figure 2-X).

(4) Species (strain) No./group. The test species (and strain), whether animal or human, are identified in this column. The column also contains information on the number of subjects and sex per group. Chapter 1, Relevance to Public Health, covers the relevance of animal data to human toxicity and Section 3.1, Toxicokinetics, contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(5) Exposure parameters/doses. The duration of the study and exposure regimens are provided in these columns. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 51), rats were orally exposed to “Chemical X” via feed for 2 years. For a

more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Aida et al. 1992).

(6) Parameters monitored. This column lists the parameters used to assess health effects. Parameters monitored could include serum (blood) chemistry (BC), biochemical changes (BI), body weight (BW), clinical signs (CS), developmental toxicity (DX), food intake (FI), gross necropsy (GN), hematology (HE), histopathology (HP), immune function (IX), lethality (LE), neurological function (NX), organ function (OF), ophthalmology (OP), organ weight (OW), reproductive function (RX), urinalysis (UR), and water intake (WI).

(7) Endpoint. This column lists the endpoint examined. The major categories of health endpoints included in LSE tables and figures are death, body weight, respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, dermal, ocular, endocrine, immunological, neurological, reproductive, developmental, other noncancer, and cancer. "Other noncancer" refers to any effect (e.g., alterations in blood glucose levels) not covered in these systems. In the example of key number 51, three endpoints (body weight, hematological, and hepatic) were investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no adverse effects were seen in the organ system studied. The body weight effect reported in key number 51 is a NOAEL at 25.5 mg/kg/day. NOAELs are not reported for cancer and death; with the exception of these two endpoints, this field is left blank if no NOAEL was identified in the study.

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused an adverse health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific endpoint used to quantify the adverse effect accompanies the LOAEL. Key number 51 reports a less serious LOAEL of 6.1 mg/kg/day for the hepatic system, which was used to derive a chronic exposure, oral MRL of 0.008 mg/kg/day (see footnote "c"). MRLs are not derived from serious LOAELs. A cancer effect level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases. If no LOAEL/CEL values were identified in the study, this field is left blank.

(10) Reference. The complete reference citation is provided in Chapter 8 of the profile.

(11) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. For example, footnote "c" indicates that the LOAEL of 6.1 mg/kg/day in key number 51 was used to derive an oral MRL of 0.008 mg/kg/day.

FIGURE LEGEND

See Sample LSE Figure (page D-6)

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(12) Exposure period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the chronic exposure period are illustrated.

(13) Endpoint. These are the categories of health effects for which reliable quantitative data exist. The same health effect endpoints appear in the LSE table.

(14) Levels of exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(15) LOAEL. In this example, the half-shaded circle that is designated 51R identifies a LOAEL critical endpoint in the rat upon which a chronic oral exposure MRL is based. The key number 51 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 6.1 mg/kg/day (see entry 51 in the sample LSE table) to the MRL of 0.008 mg/kg/day (see footnote "c" in the sample LSE table).

(16) CEL. Key number 59R is one of studies for which CELs were derived. The diamond symbol refers to a CEL for the test species (rat). The number 59 corresponds to the entry in the LSE table.

(17) Key to LSE figure. The key provides the abbreviations and symbols used in the figure.

Table 2-X. Levels of Significant Exposure to [Chemical X] – Oral (1)

Figure key[a] (3)	Species (strain) No./group (4)	Exposure parameters (5)	Doses (mg/kg/day) (5)	Parameters monitored (6)	Endpoint (7)	NOAEL (mg/kg/day) (8)	Less serious LOAEL (mg/kg/day) (9)	Serious LOAEL (mg/kg/day) (9)	Effect
CHRONIC EXPOSURE (2)									
51	Rat (Wistar) 40 M, 40 F	2 years (F)	M: 0, 6.1, 25.5, 138.0 F: 0, 8.0, 31.7, 168.4	CS, WI, BW, OW, HE, BC, HP	Bd wt	25.5	138.0		Decreased body weight gain in males (23–25%) and females (31–39%)
					Hemato	138.0			
					Hepatic		6.1[c]		Increases in absolute and relative weights at ≥6.1/8.0 mg/kg/day after 12 months of exposure; fatty generation at ≥6.1 mg/kg/day in males and at ≥31.7 mg/kg/day in females, and granulomas in females at 31.7 and 168.4 mg/kg/day after 12, 18, or 24 months of exposure and in males at ≥6.1 mg/kg/day only after 24 months of exposure
Aida et al. 1992 (10)									
52	Rat (F344) 78 M	104 weeks (W)	0, 3.9, 20.6, 36.3	CS, BW, FI, BC, OW, HP	Hepatic	36.3			
					Renal	20.6	36.3		Increased incidence of renal tubular cell hyperplasia
					Endocr	36.3			
George et al. 2002									
59	Rat (Wistar) 58M, 58F	Lifetime (W)	M: 0, 90 F: 0, 190	BW, HP	Cancer		190 F		Increased incidence of hepatic neoplastic nodules in females only; no additional description of the tumors was provided
Tumasonis et al. 1985									

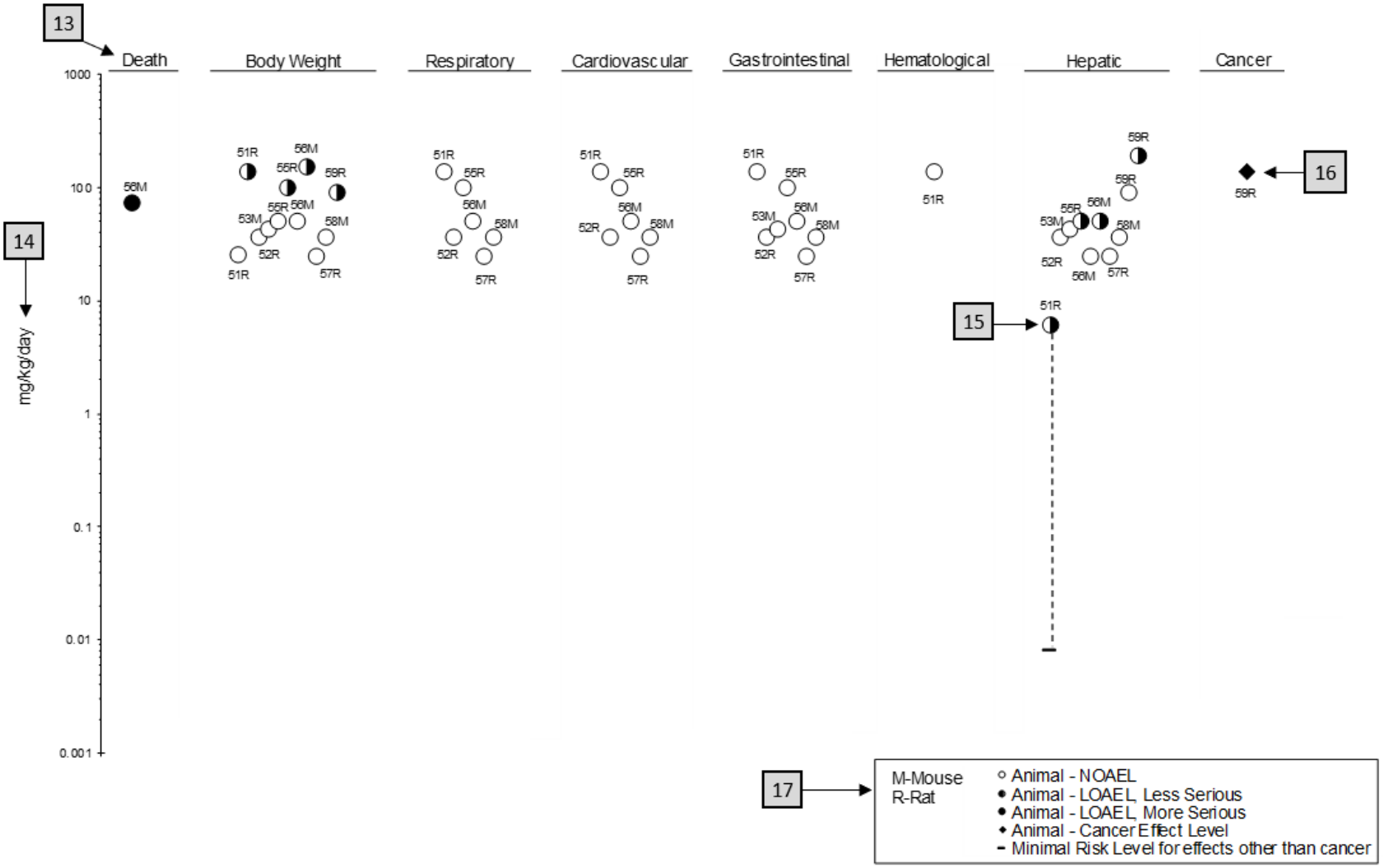
[a]The number corresponds to entries in Figure 2-x.

(11) [b]Used to derive an acute-duration oral minimal risk level (MRL) of 0.1 mg/kg/day based on the $BMDL_{05}$ of 10 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

[c]Used to derive a chronic-duration oral MRL of 0.008 mg/kg/day based on the $BMDL_{10}$ of 0.78 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

APPENDIX D

Figure 2-X. Levels of Significant Exposure to [Chemical X] - Oral



APPENDIX E. QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances may find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Relevance to Public Health: The Relevance to Public Health Section provides an overview of exposure and health effects and evaluates, interprets, and assesses the significance of toxicity data to human health. A table listing minimal risk levels (MRLs) is also included in this chapter.

Chapter 2: Health Effects: Specific health effects identified in both human and animal studies are reported by type of health effect (e.g., death, hepatic, renal, immune, reproductive), route of exposure (e.g., inhalation, oral, dermal), and length of exposure (e.g., acute, intermediate, and chronic).
NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting.

Pediatrics:

Section 3.2 Children and Other Populations that are Unusually Susceptible
Section 3.3 Biomarkers of Exposure and Effect

ATSDR Information Center

Phone: 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY)
Internet: http://www.atsdr.cdc.gov

ATSDR develops educational and informational materials for health care providers categorized by hazardous substance, clinical condition, and/or by susceptible population. The following additional materials are available online:

Clinician Briefs and Overviews discuss health effects and approaches to patient management in a brief/factsheet style. They are narrated PowerPoint presentations with Continuing Education credit available (see https://www.atsdr.cdc.gov/environmental-medicine/hcp/emhsis/index.html).

Managing Hazardous Materials Incidents is a set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident (see https://www.atsdr.cdc.gov/MHMI/index.html).

Fact Sheets (ToxFAQs™) provide answers to frequently asked questions about toxic substances (see https://wwwn.cdc.gov/TSP/ToxFAQs/ToxFAQsLanding.aspx).

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. Contact: NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015 • Web Page: https://www.cdc.gov/nceh/.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 400 7th Street, S.W., Suite 5W, Washington, DC 20024 • Phone: 202-245-0625 or 1-800-CDC-INFO (800-232-4636) • Web Page: https://www.cdc.gov/niosh/.

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. Contact: NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212 • Web Page: https://www.niehs.nih.gov/.

Clinical Resources (Publicly Available Information)

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: http://www.aoec.org/.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266 • Web Page: http://www.acoem.org/.

The American College of Medical Toxicology (ACMT) is a nonprofit association of physicians with recognized expertise in medical toxicology. Contact: ACMT, 10645 North Tatum Boulevard, Suite 200-111, Phoenix AZ 85028 • Phone: 844-226-8333 • FAX: 844-226-8333 • Web Page: http://www.acmt.net.

The Pediatric Environmental Health Specialty Units (PEHSUs) is an interconnected system of specialists who respond to questions from public health professionals, clinicians, policy makers, and the public about the impact of environmental factors on the health of children and reproductive-aged adults. Contact information for regional centers can be found at https://www.pehsu.net/.

The American Association of Poison Control Centers (AAPCC) provide support on the prevention and treatment of poison exposures. Contact: AAPCC, 515 King Street, Suite 510, Alexandria VA 22314 • Phone: 701-894-1858 • Poison Help Line: 1-800-222-1222 • Web Page: http://www.aapcc.org/.

APPENDIX F. GLOSSARY

Absorption—The process by which a substance crosses biological membranes and enters systemic circulation. Absorption can also refer to the taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure—Exposure to a chemical for a duration of ≤14 days, as specified in the Toxicological Profiles.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)—The amount of a chemical adsorbed by sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Benchmark Dose (BMD) or Benchmark Concentration (BMC)—is the dose/concentration corresponding to a specific response level estimate using a statistical dose-response model applied to either experimental toxicology or epidemiology data. For example, a BMD_{10} would be the dose corresponding to a 10% benchmark response (BMR). The BMD is determined by modeling the dose-response curve in the region of the dose-response relationship where biologically observable data are feasible. The BMDL or BMCL is the 95% lower confidence limit on the BMD or BMC.

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers—Indicators signaling events in biologic systems or samples, typically classified as markers of exposure, effect, and susceptibility.

Cancer Effect Level (CEL)—The lowest dose of a chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or malignant tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-control study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without the outcome.

Case Report—A report that describes a single individual with a particular disease or exposure. These reports may suggest some potential topics for scientific research, but are not actual research studies.

Case Series—Reports that describe the experience of a small number of individuals with the same disease or exposure. These reports may suggest potential topics for scientific research, but are not actual research studies.

Ceiling Value—A concentration that must not be exceeded.

Chronic Exposure—Exposure to a chemical for ≥365 days, as specified in the Toxicological Profiles.

Clastogen—A substance that causes breaks in chromosomes resulting in addition, deletion, or rearrangement of parts of the chromosome.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome, and who are disease-free at start of follow-up. Often, at least one exposed group is compared to one unexposed group, while in other cohorts, exposure is a continuous variable and analyses are directed towards analyzing an exposure-response coefficient.

Cross-sectional Study—A type of epidemiological study of a group or groups of people that examines the relationship between exposure and outcome to a chemical or to chemicals at a specific point in time.

Data Needs—Substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment.

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the response or amount of the response.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the effect occurs. Effects include malformations and variations, altered growth, and *in utero* death.

Epidemiology—The investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Excretion—The process by which metabolic waste products are removed from the body.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic, or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one-half of a quantity of a chemical from the body or environmental media.

Health Advisory—An estimate of acceptable drinking water levels for a chemical substance derived by EPA and based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Immediately Dangerous to Life or Health (IDLH)—A condition that poses a threat of life or health, or conditions that pose an immediate threat of severe exposure to contaminants that are likely to have adverse cumulative or delayed effects on health.

Immunotoxicity—Adverse effect on the functioning of the immune system that may result from exposure to chemical substances.

Incidence—The ratio of new cases of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure—Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

***In Vitro*—**Isolated from the living organism and artificially maintained, as in a test tube.

***In Vivo*—**Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO})—The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50})—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{Lo})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50})—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50})—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

Metabolism—Process in which chemical substances are biotransformed in the body that could result in less toxic and/or readily excreted compounds or produce a biologically active intermediate.

Minimal LOAEL—Indicates a minimal adverse effect or a reduced capacity of an organ or system to absorb additional toxic stress that does not necessarily lead to the inability of the organ or system to function normally.

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a Minimal Risk Level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity—The state of being diseased; the morbidity rate is the incidence or prevalence of a disease in a specific population.

Mortality—Death; the mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations, which are changes in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a hazardous substance.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Although effects may be produced at this dose, they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An odds ratio that is greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) regulatory limit on the amount or concentration of a substance not to be exceeded in workplace air averaged over any 8-hour work shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests (insects or other organisms harmful to cultivated plants or animals).

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments, which, in general, do not represent real, identifiable anatomic regions of the body, whereas the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic endpoints. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—A type of physiologically based dose-response model that is comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information, including tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as blood:air partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which a group is followed over time and the pertinent observations are made on events occurring after the start of the study.

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation RfC is expressed in units of mg/m^3 or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily oral exposure of the human population to a potential hazard that is likely to be without risk of deleterious noncancer health effects during a lifetime. The oral RfD is expressed in units of mg/kg/day.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). RQs are (1) ≥1 pound or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a hazardous substance. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a hazardous substance.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, existing health condition, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio/Relative Risk—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio that is greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed group.

Serious LOAEL—A dose that evokes failure in a biological system and can lead to morbidity or mortality.

Short-Term Exposure Limit (STEL)—A STEL is a 15-minute TWA exposure that should not be exceeded at any time during a workday.

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which it is believed that nearly all workers may be repeatedly exposed, day after day, for a working lifetime without adverse effect. The TLV may be expressed as a Time-Weighted Average (TLV-TWA), as a Short-Term Exposure Limit (TLV-STEL), or as a ceiling limit (TLV-C).

Time-Weighted Average (TWA)—An average exposure within a given time period.

Toxicokinetic—The absorption, distribution, metabolism, and elimination of toxic compounds in the living organism.

Toxics Release Inventory (TRI)—The TRI is an EPA program that tracks toxic chemical releases and pollution prevention activities reported by industrial and federal facilities.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL), Reference Dose (RfD), or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis (3 being the approximate logarithmic average of 10 and 1).

Xenobiotic—Any substance that is foreign to the biological system.

APPENDIX G. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

AAPCC	American Association of Poison Control Centers
ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ACMT	American College of Medical Toxicology
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AEGL	Acute Exposure Guideline Level
AIC	Akaike's information criterion
AIHA	American Industrial Hygiene Association
ALT	alanine aminotransferase
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BCF	bioconcentration factor
BMD/C	benchmark dose or benchmark concentration
BMD_X	dose that produces a X% change in response rate of an adverse effect
$BMDL_X$	95% lower confidence limit on the BMD_X
BMDS	Benchmark Dose Software
BMR	benchmark response
BUN	blood urea nitrogen
C	centigrade
CAA	Clean Air Act
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
cm	centimeter
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DWEL	drinking water exposure level
EAFUS	Everything Added to Food in the United States
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
ERPG	emergency response planning guidelines
F	Fahrenheit
F1	first-filial generation
FDA	Food and Drug Administration
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FR	Federal Register

FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GGT	γ-glutamyl transferase
GRAS	generally recognized as safe
HEC	human equivalent concentration
HED	human equivalent dose
HHS	Department of Health and Human Services
HPLC	high-performance liquid chromatography
HSDB	Hazardous Substances Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	kilokilogram; 1 kilokilogram is equivalent to 1,000 kilograms and 1 metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactate dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Level of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
MRL	Minimal Risk Level
MS	mass spectrometry
MSHA	Mine Safety and Health Administration
Mt	metric ton
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NCEH	National Center for Environmental Health
ND	not detected
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences

NIOSH	National Institute for Occupational Safety and Health
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NTP	National Toxicology Program
OR	odds ratio
OSHA	Occupational Safety and Health Administration
PAC	Protective Action Criteria
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PEHSU	Pediatric Environmental Health Specialty Unit
PEL	permissible exposure limit
PEL-C	permissible exposure limit-ceiling value
pg	picogram
PND	postnatal day
POD	point of departure
ppb	parts per billion
ppbv	parts per billion by volume
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure limit
REL-C	recommended exposure limit-ceiling value
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SD	standard deviation
SE	standard error
SGOT	serum glutamic oxaloacetic transaminase (same as aspartate aminotransferase or AST)
SGPT	serum glutamic pyruvic transaminase (same as alanine aminotransferase or ALT)
SIC	standard industrial classification
SLOAEL	serious lowest-observed-adverse-effect level
SMR	standardized mortality ratio
sRBC	sheep red blood cell
STEL	short term exposure limit
TLV	threshold limit value
TLV-C	threshold limit value-ceiling value
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey

USNRC	U.S. Nuclear Regulatory Commission
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result