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,

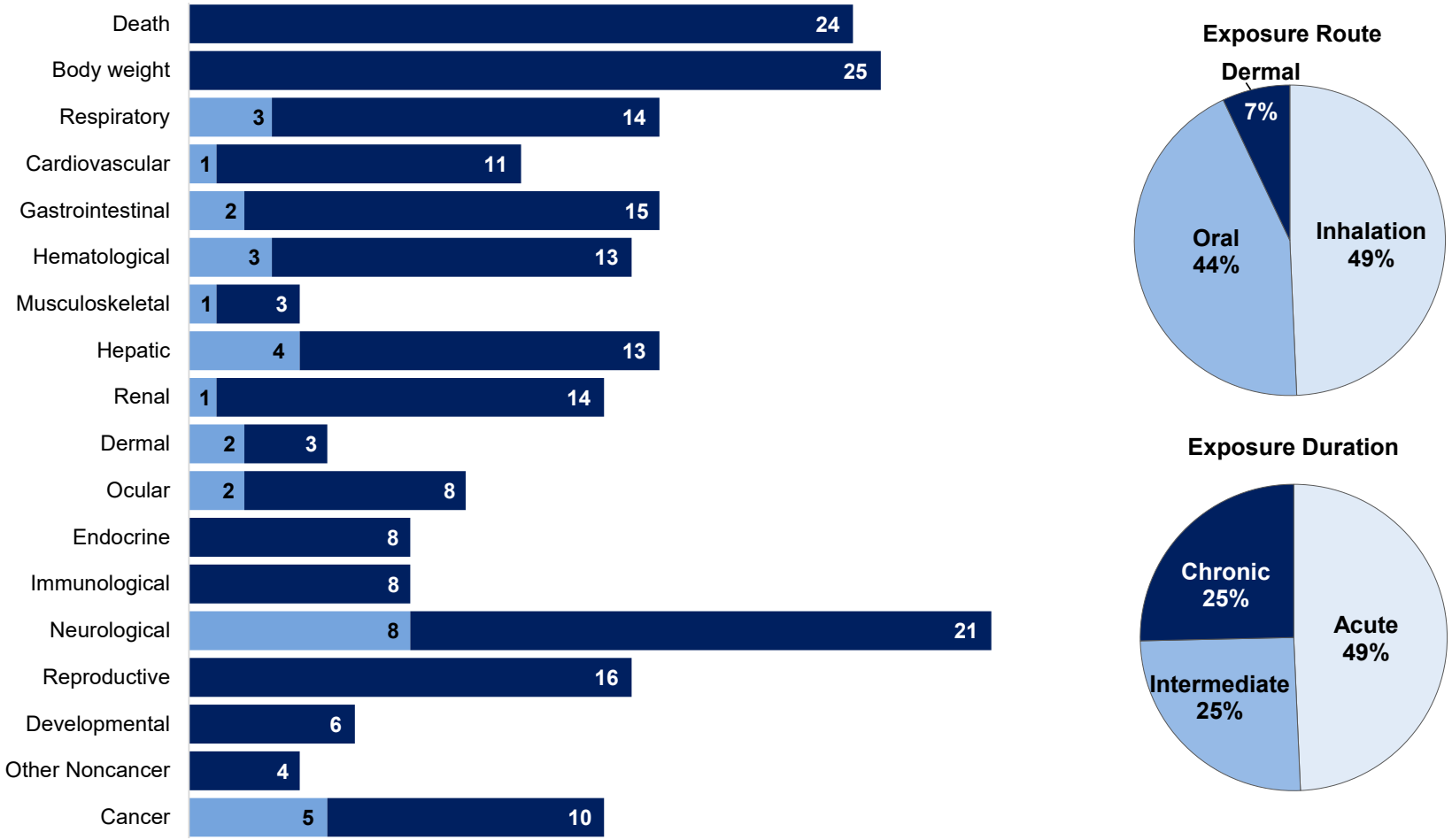
cholinergic symptoms, decreased activity, paralysis, and convulsions. Other neurological effects including decreased sensory nerve conduction velocity, and glial lesions.

- **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

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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	

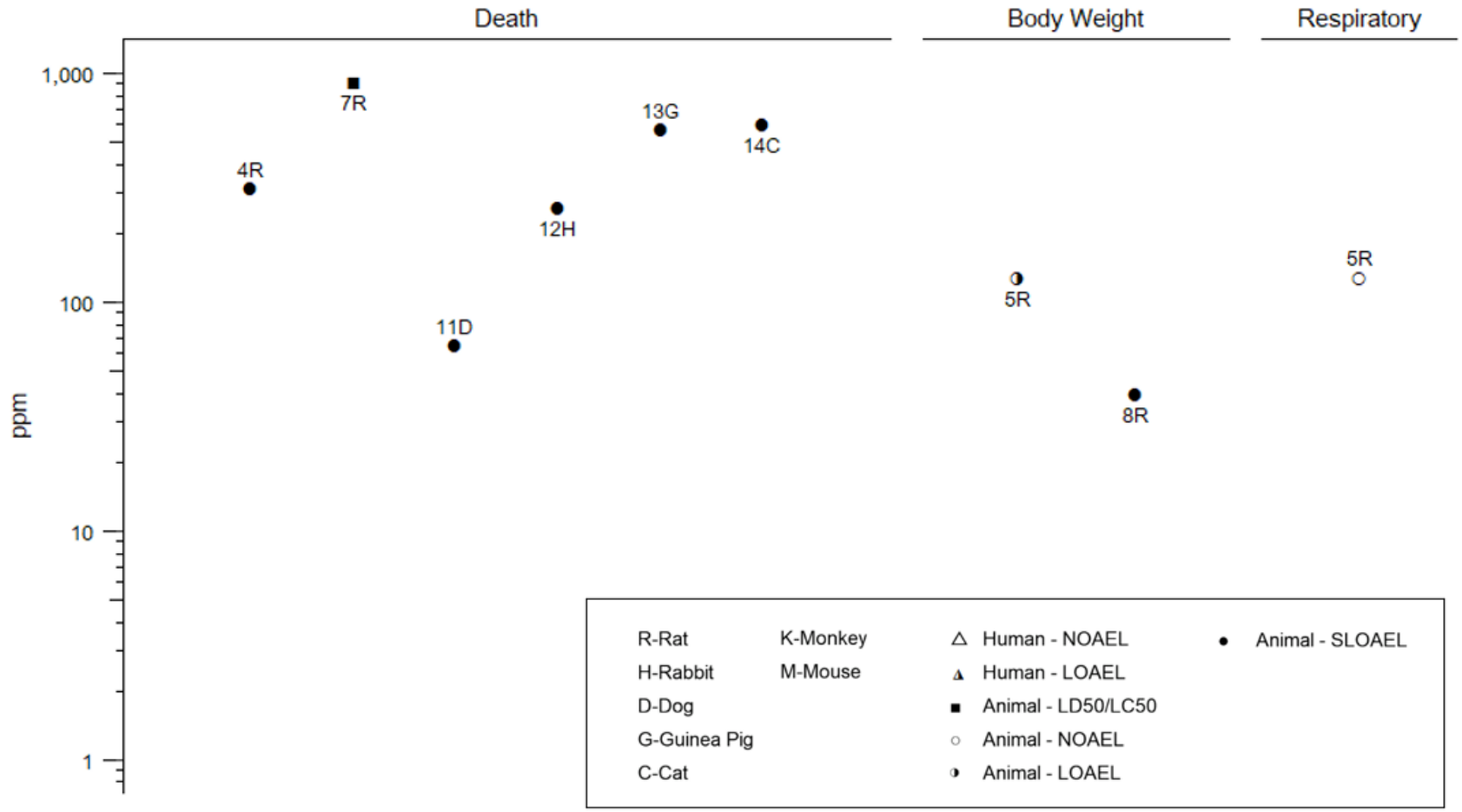
Table 2-1. Levels of Significant Exposure to Acrylonitrile – Inhalation (ppm)

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)



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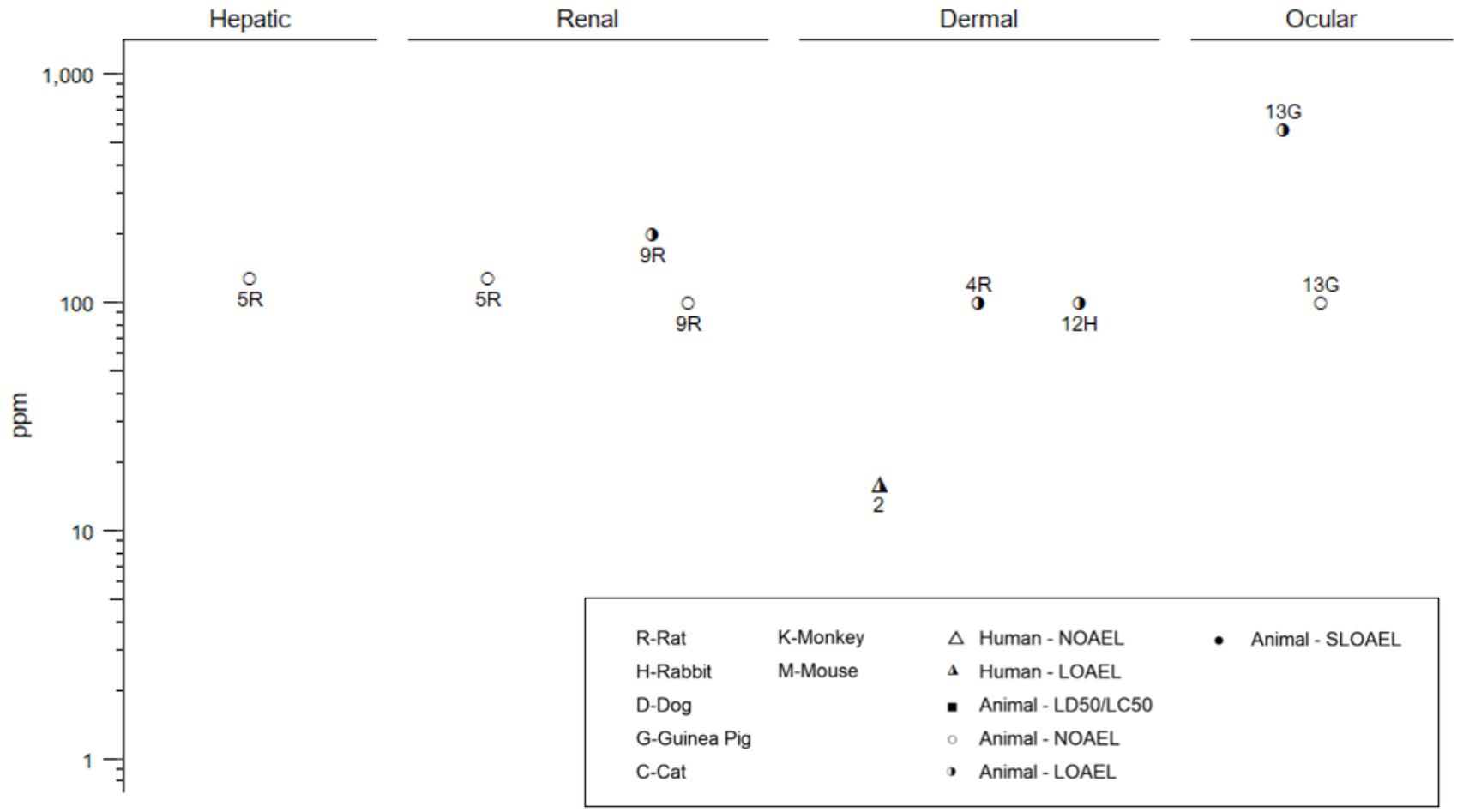

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Acute (≤14 days)

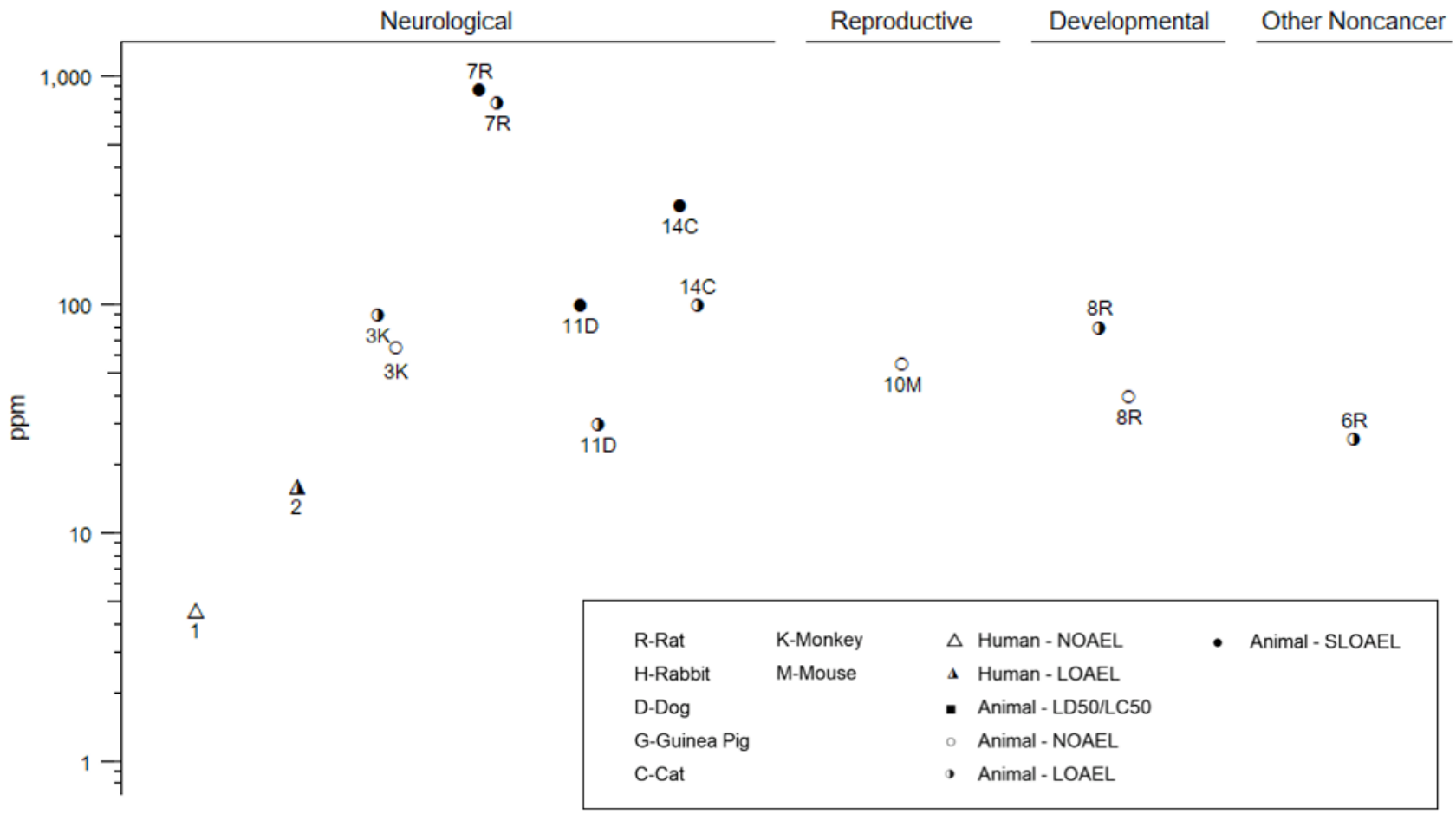
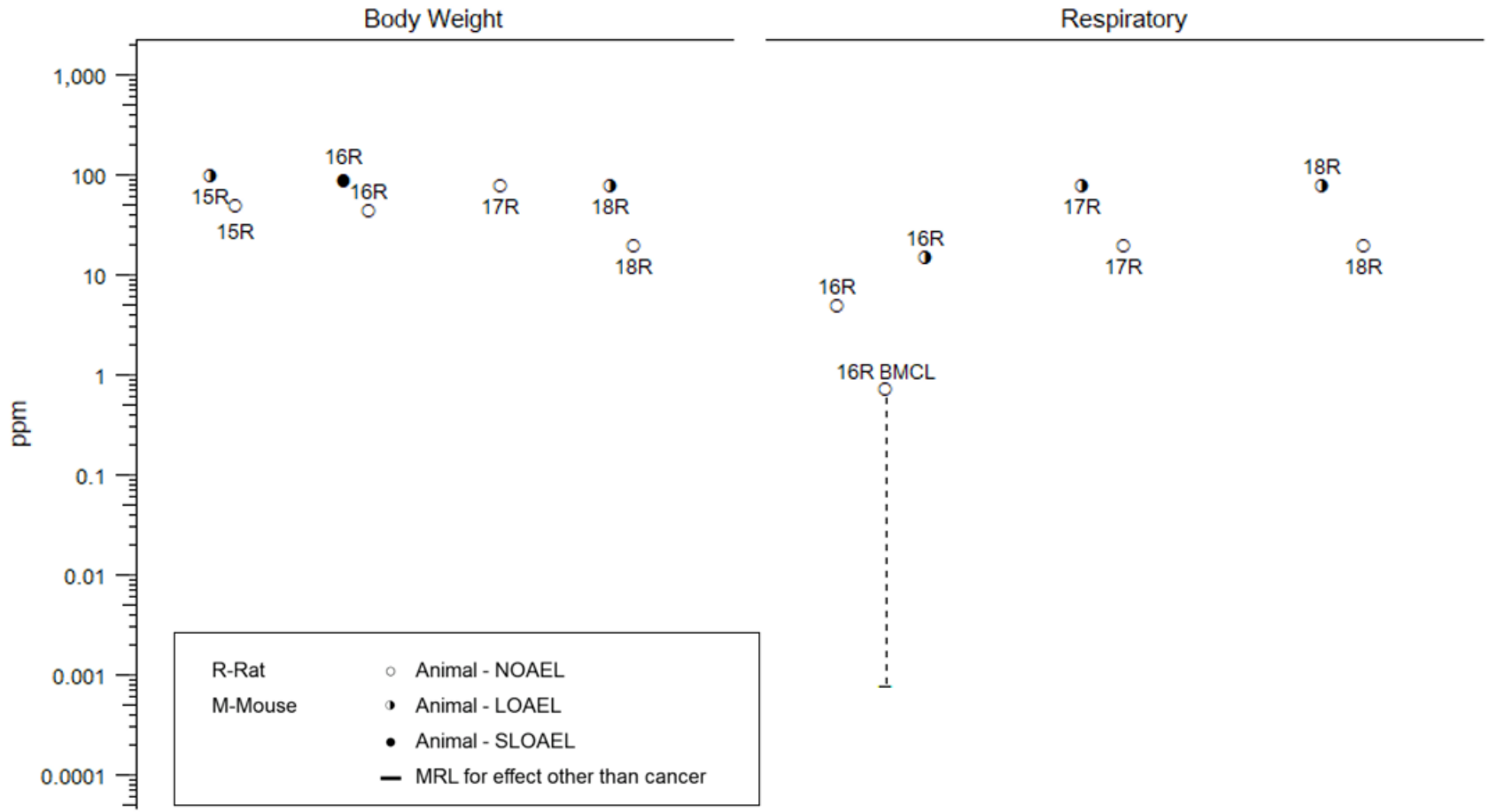


Figure 2-2. Levels of Significant Exposure to Acrylonitrile – Inhalation
Intermediate (15–364 days)



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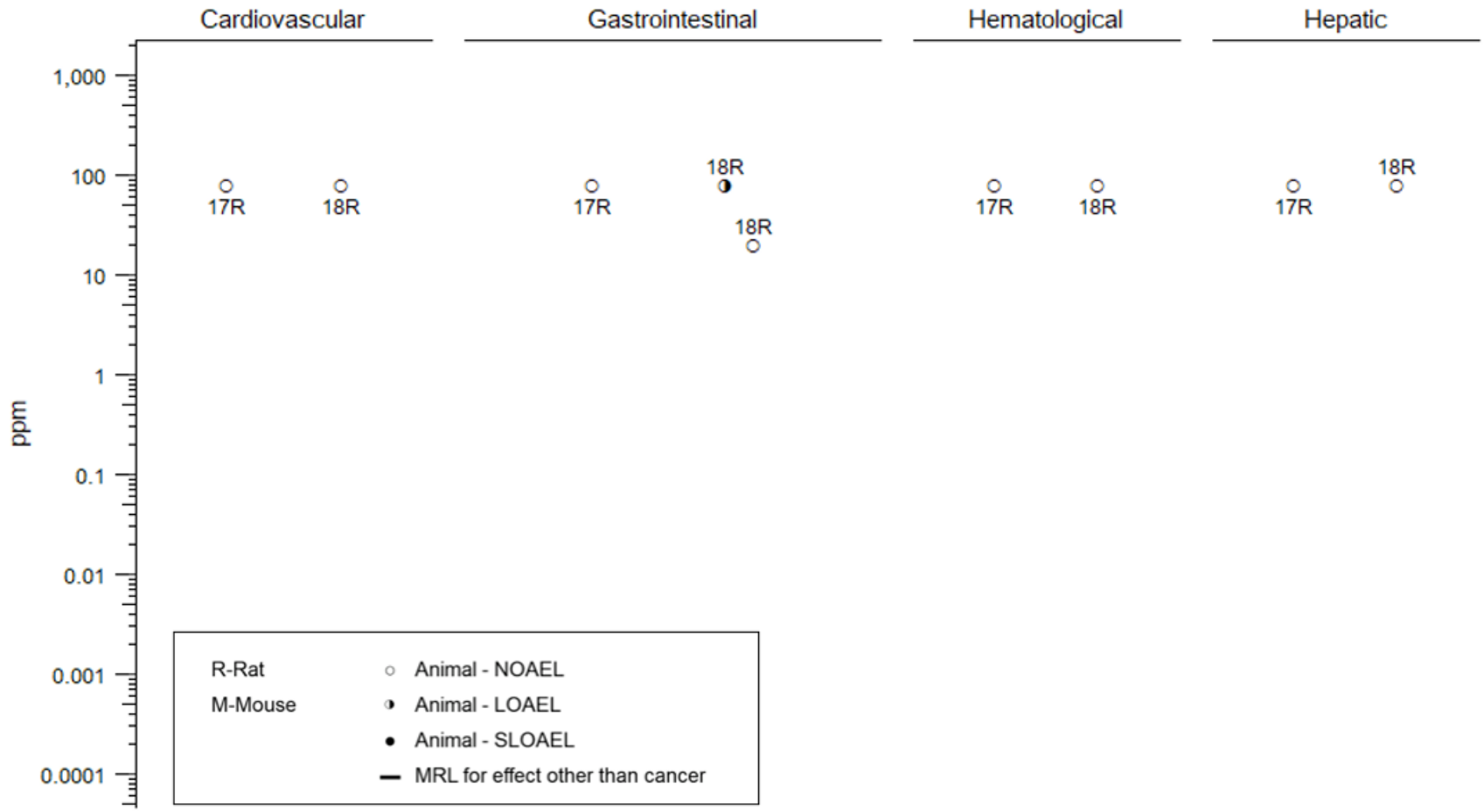
Intermediate (15–364 days)



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Intermediate (15–364 days)

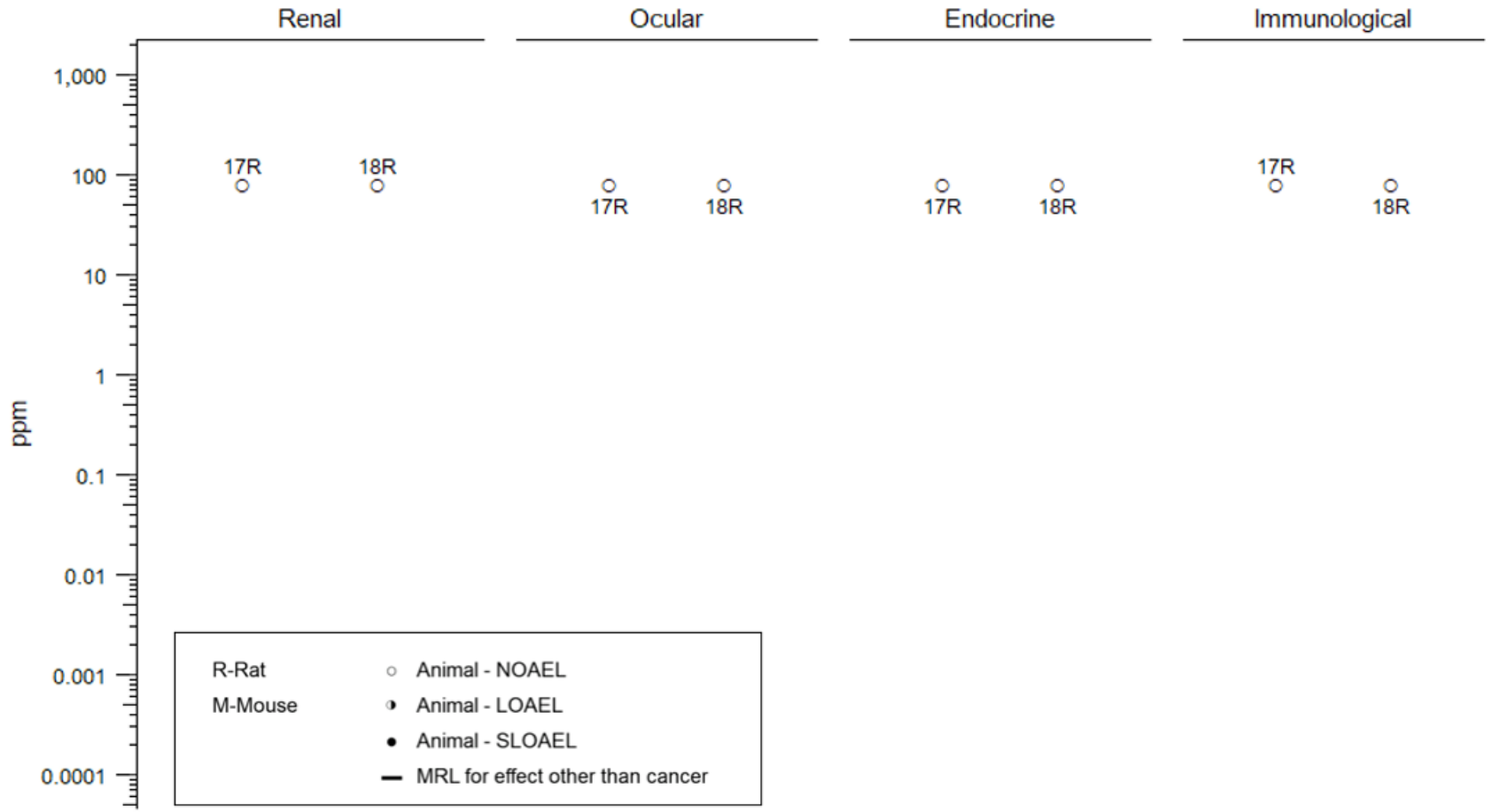


Figure 2-2. Levels of Significant Exposure to Acrylonitrile – Inhalation
Intermediate (15–364 days)

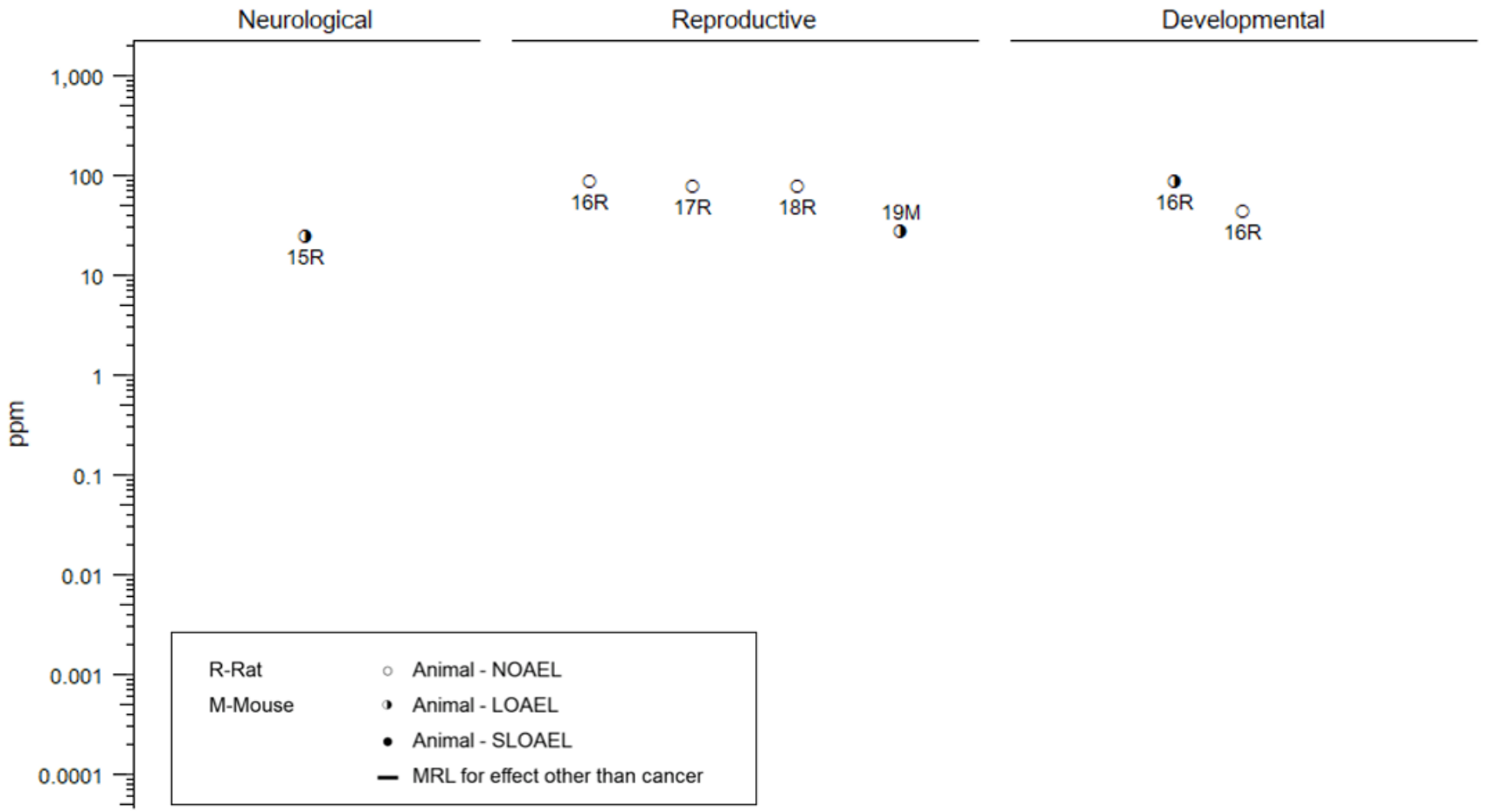
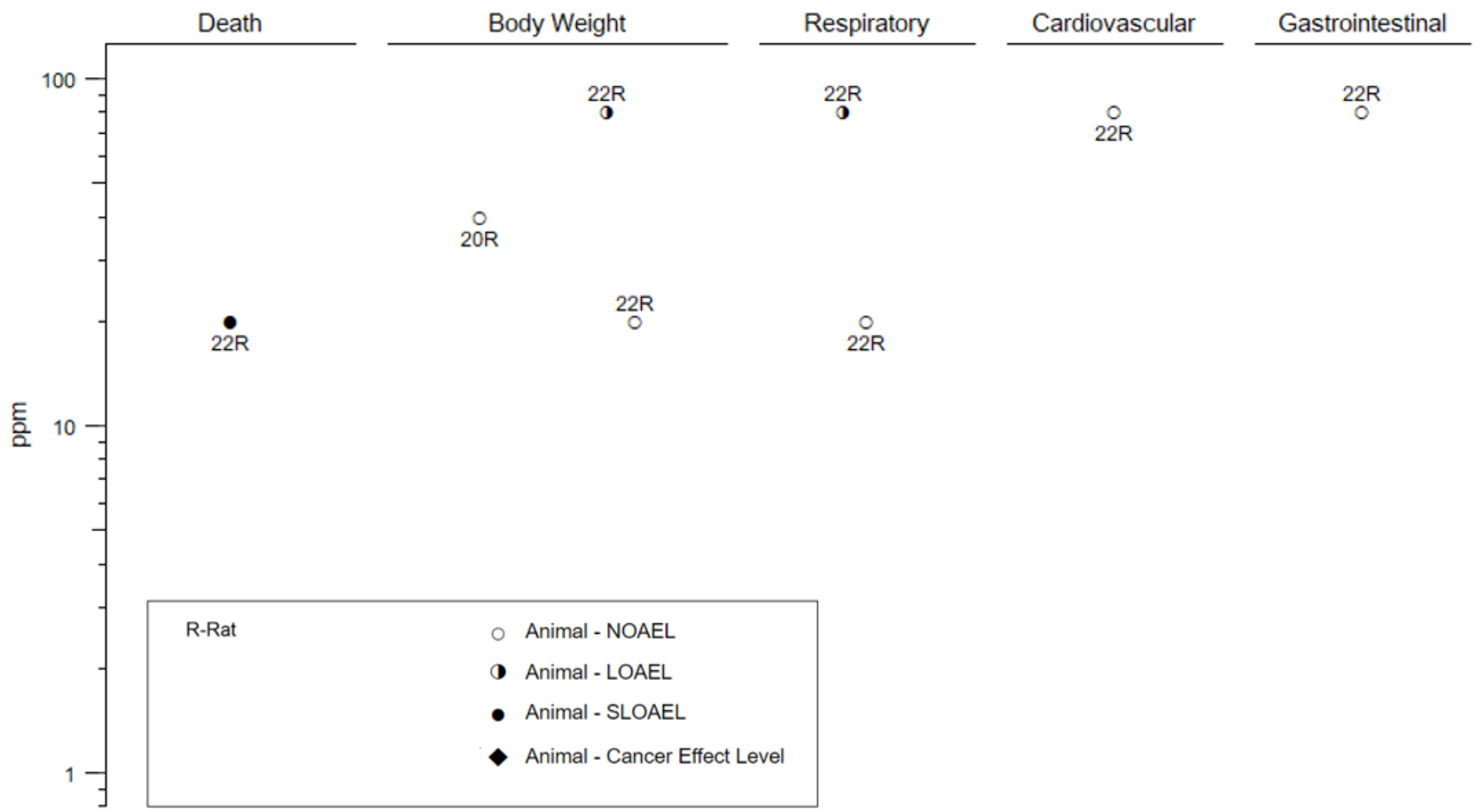


Figure 2-2. Levels of Significant Exposure to Acrylonitrile – Inhalation
Chronic (≥365 days)



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Chronic (≥365 days)

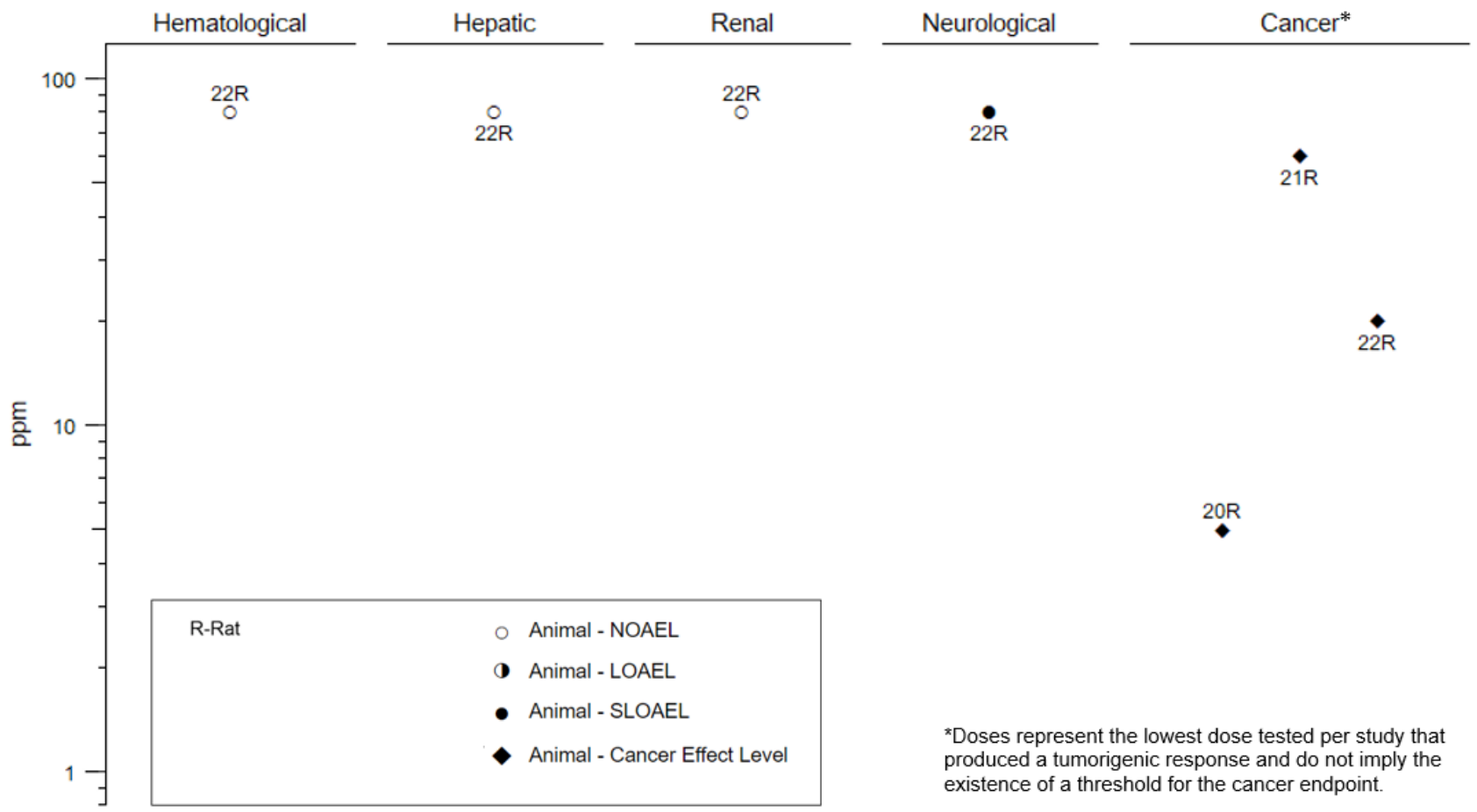

Table 2-2. Levels of Significant Exposure to Acrylonitrile – Oral (mg/kg/day)

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

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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)

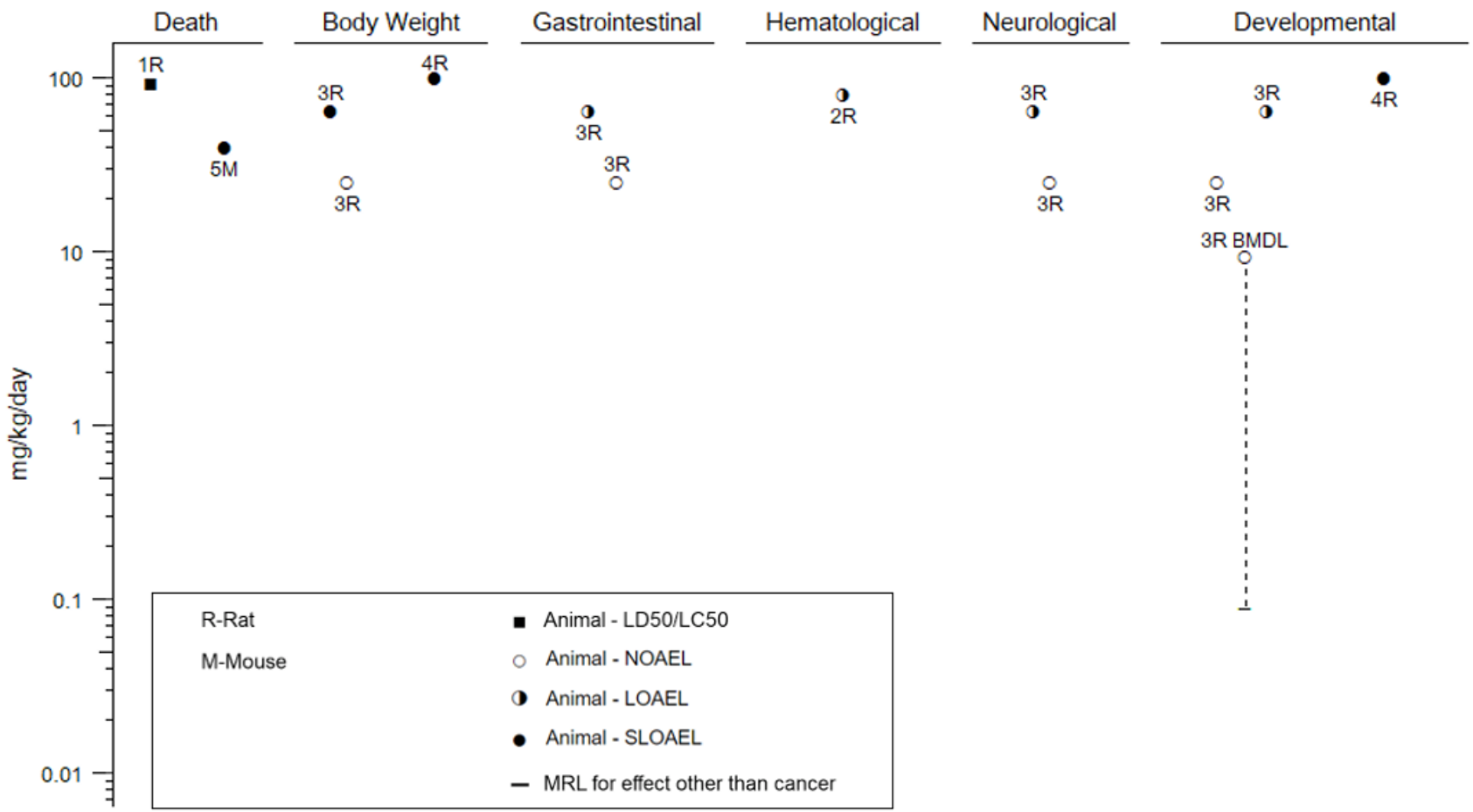

Figure 2-3. Levels of Significant Exposure to Acrylonitrile – Oral
Intermediate (15–364 days)

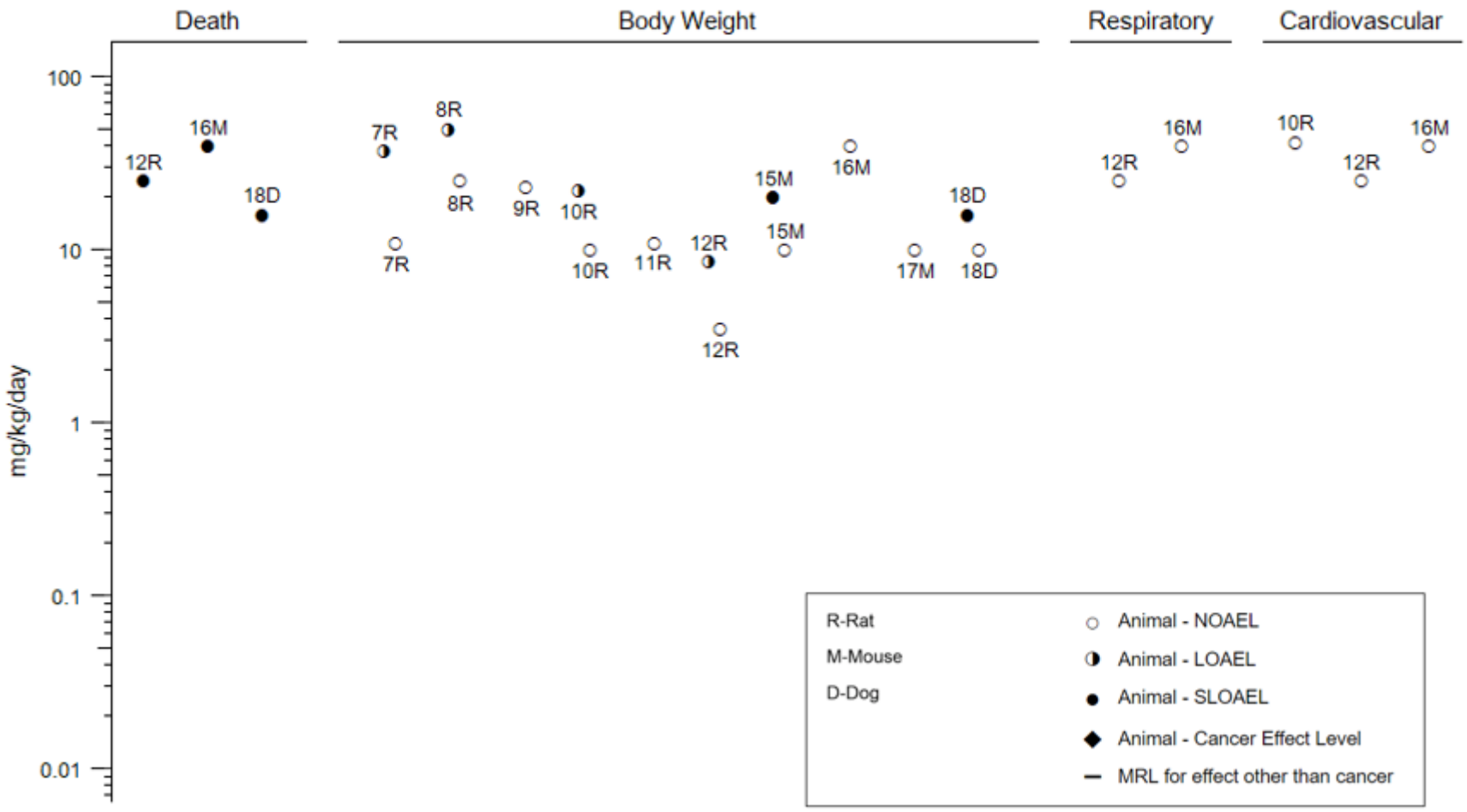

Figure 2-3. Levels of Significant Exposure to Acrylonitrile – Oral
Intermediate (15–364 days)

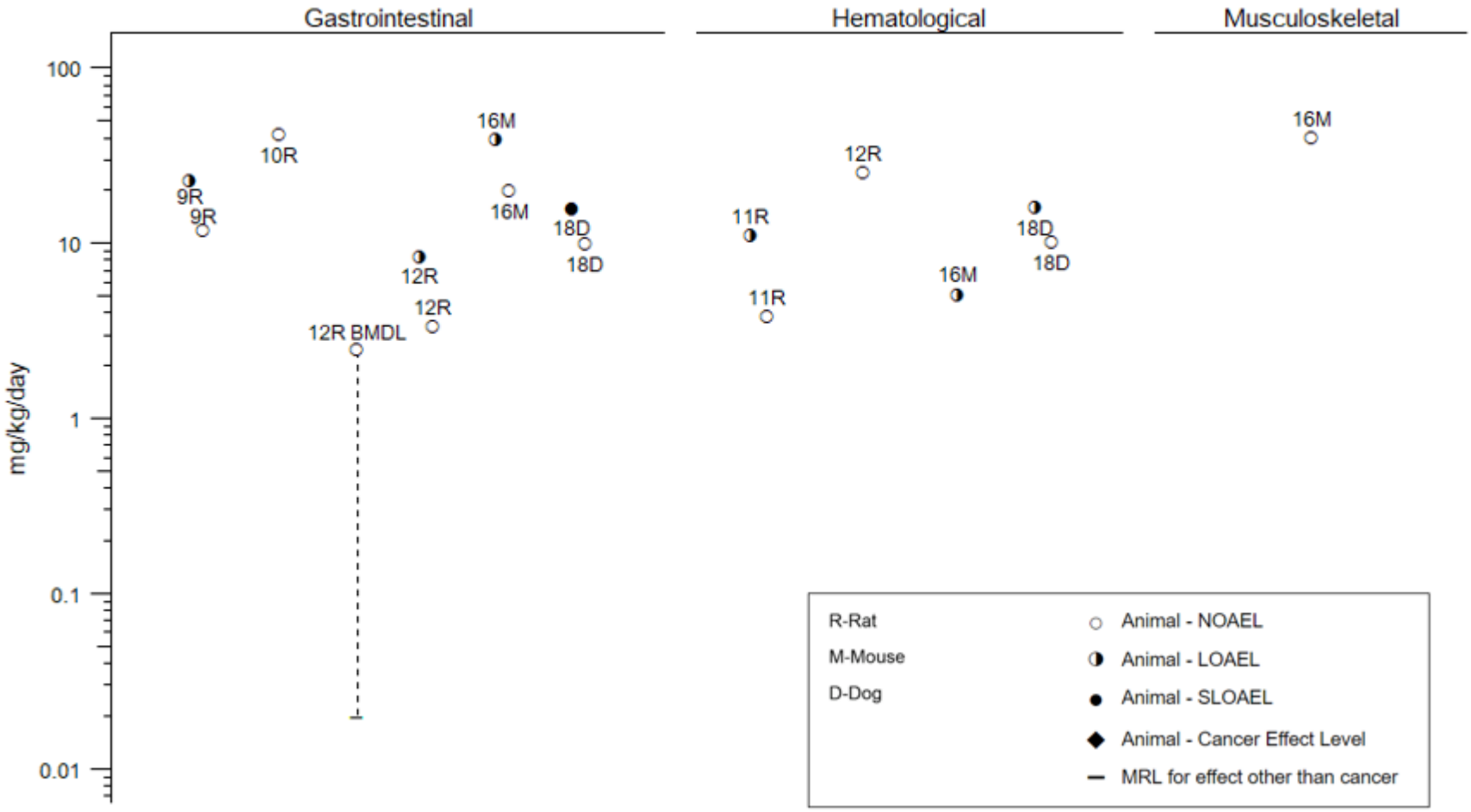

Figure 2-3. Levels of Significant Exposure to Acrylonitrile – Oral
Intermediate (15–364 days)

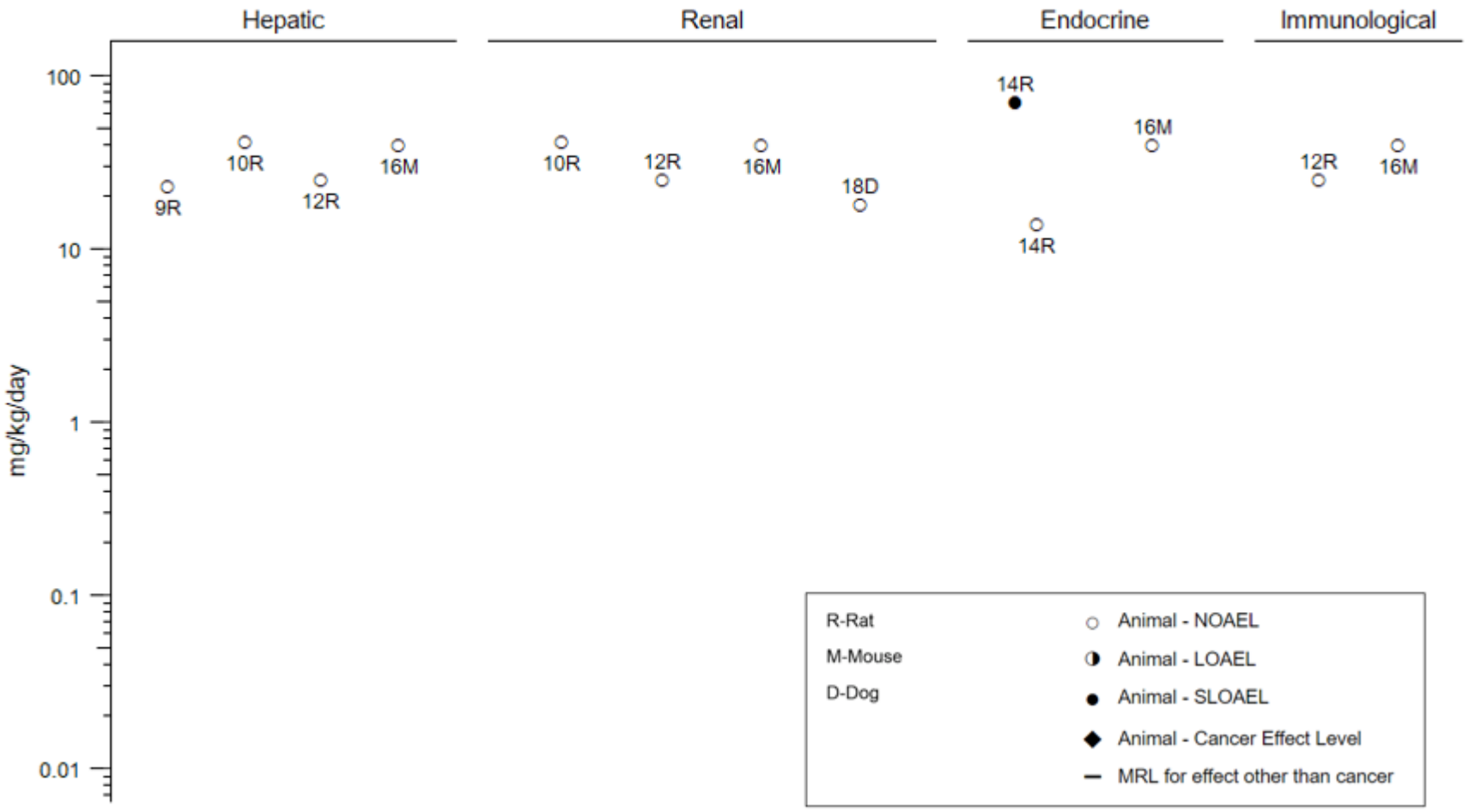

Figure 2-3. Levels of Significant Exposure to Acrylonitrile – Oral
Intermediate (15–364 days)

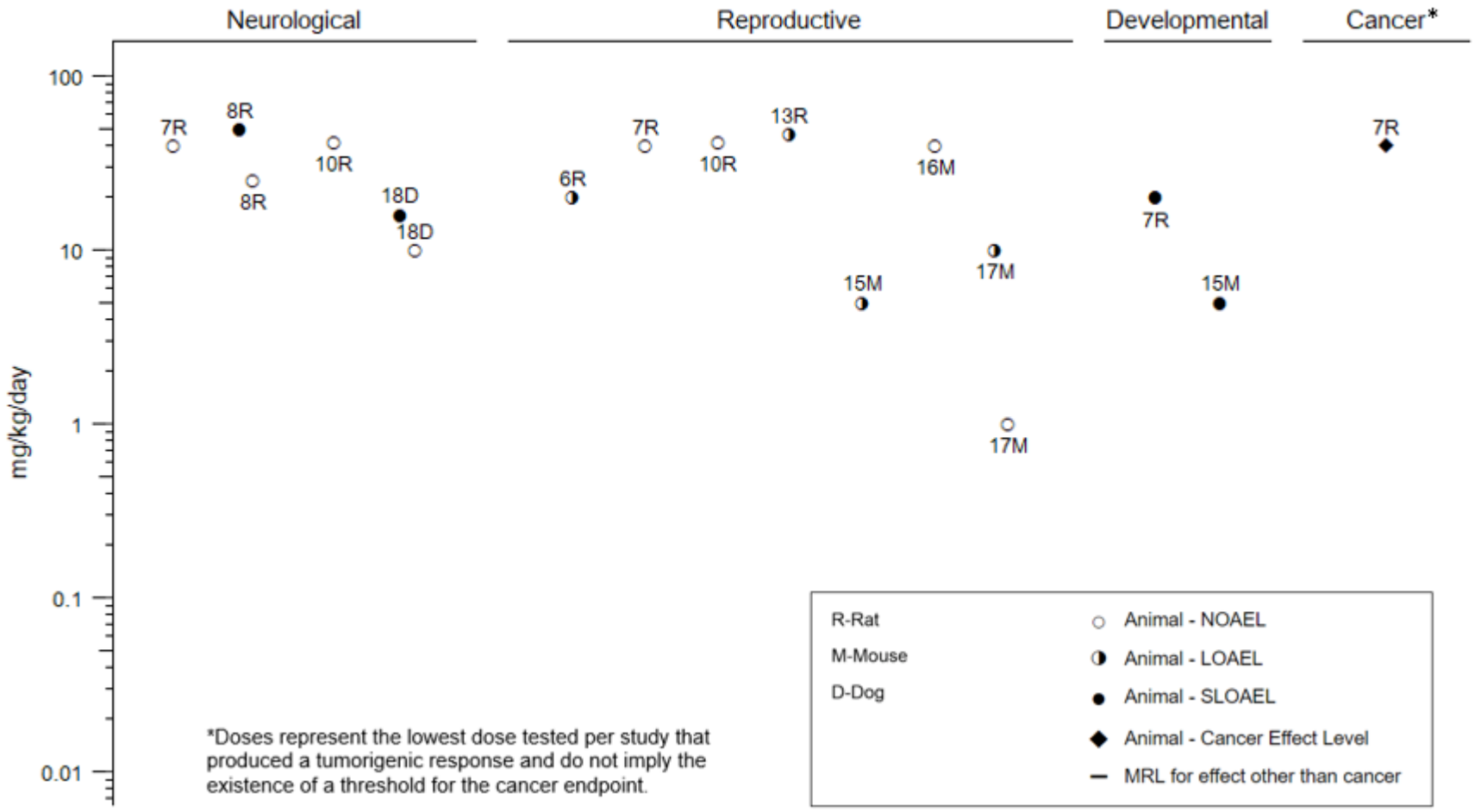

Figure 2-3. Levels of Significant Exposure to Acrylonitrile – Oral
Chronic (≥365 days)

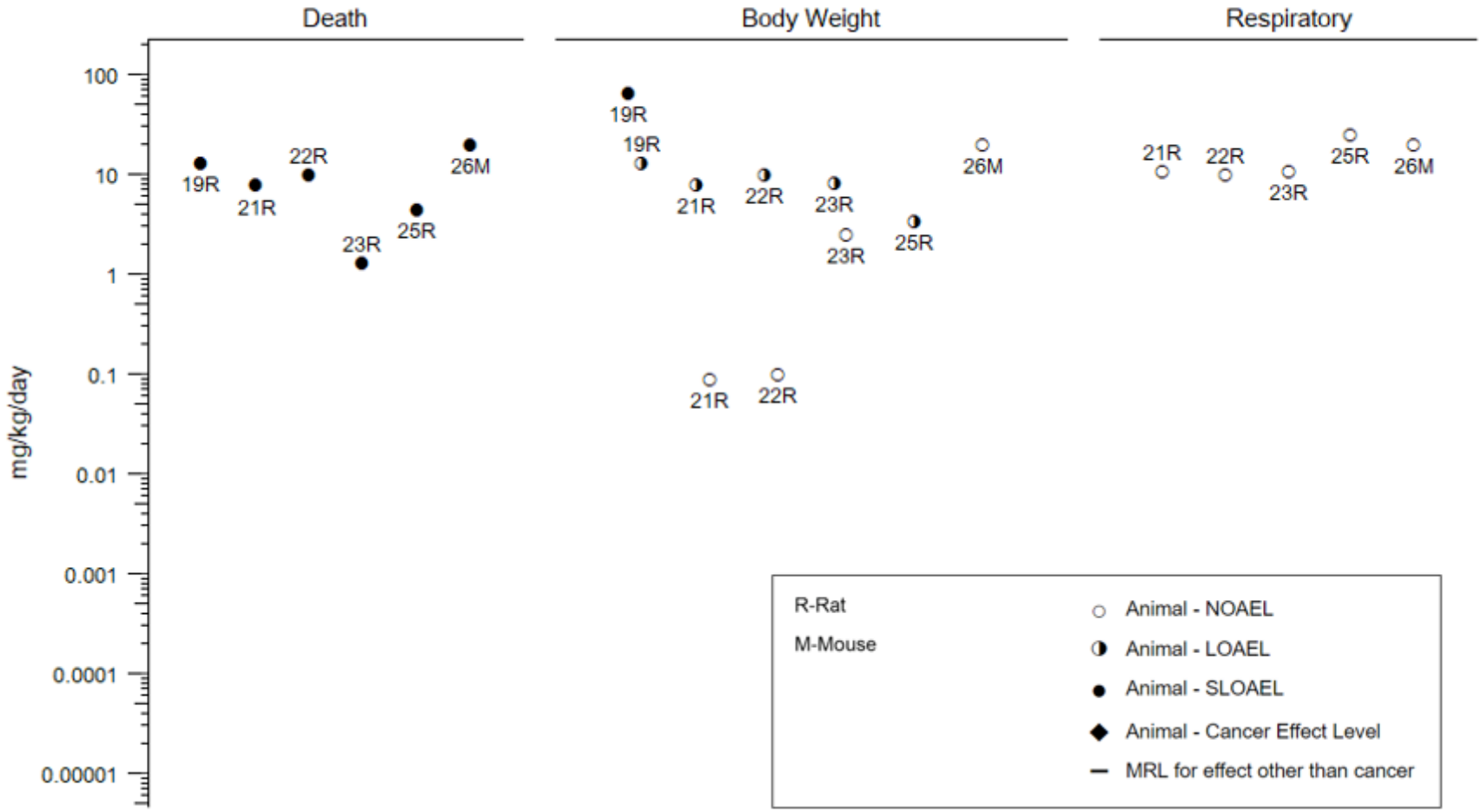

Figure 2-3. Levels of Significant Exposure to Acrylonitrile – Oral
Chronic (≥365 days)

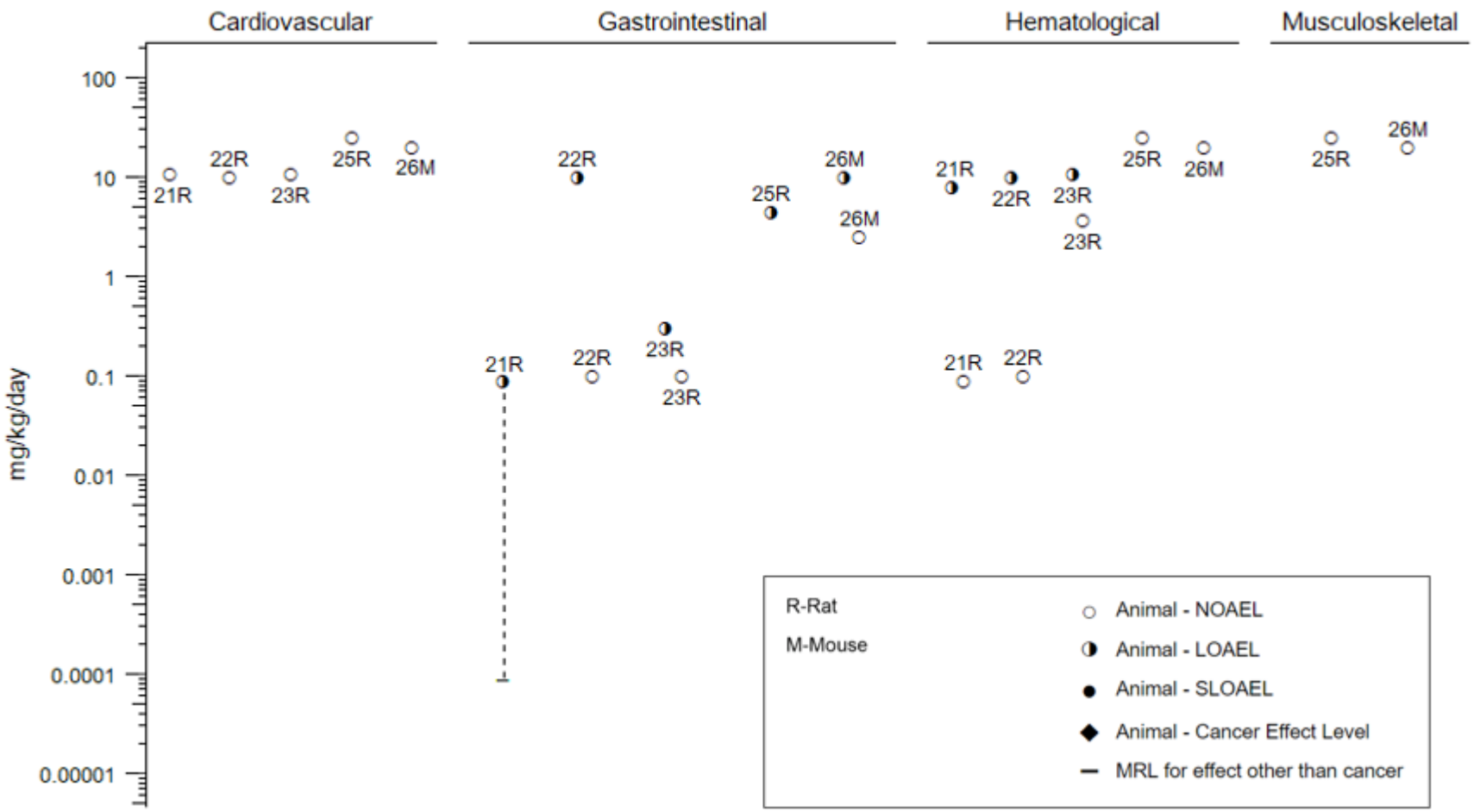

Figure 2-3. Levels of Significant Exposure to Acrylonitrile – Oral
Chronic (≥365 days)

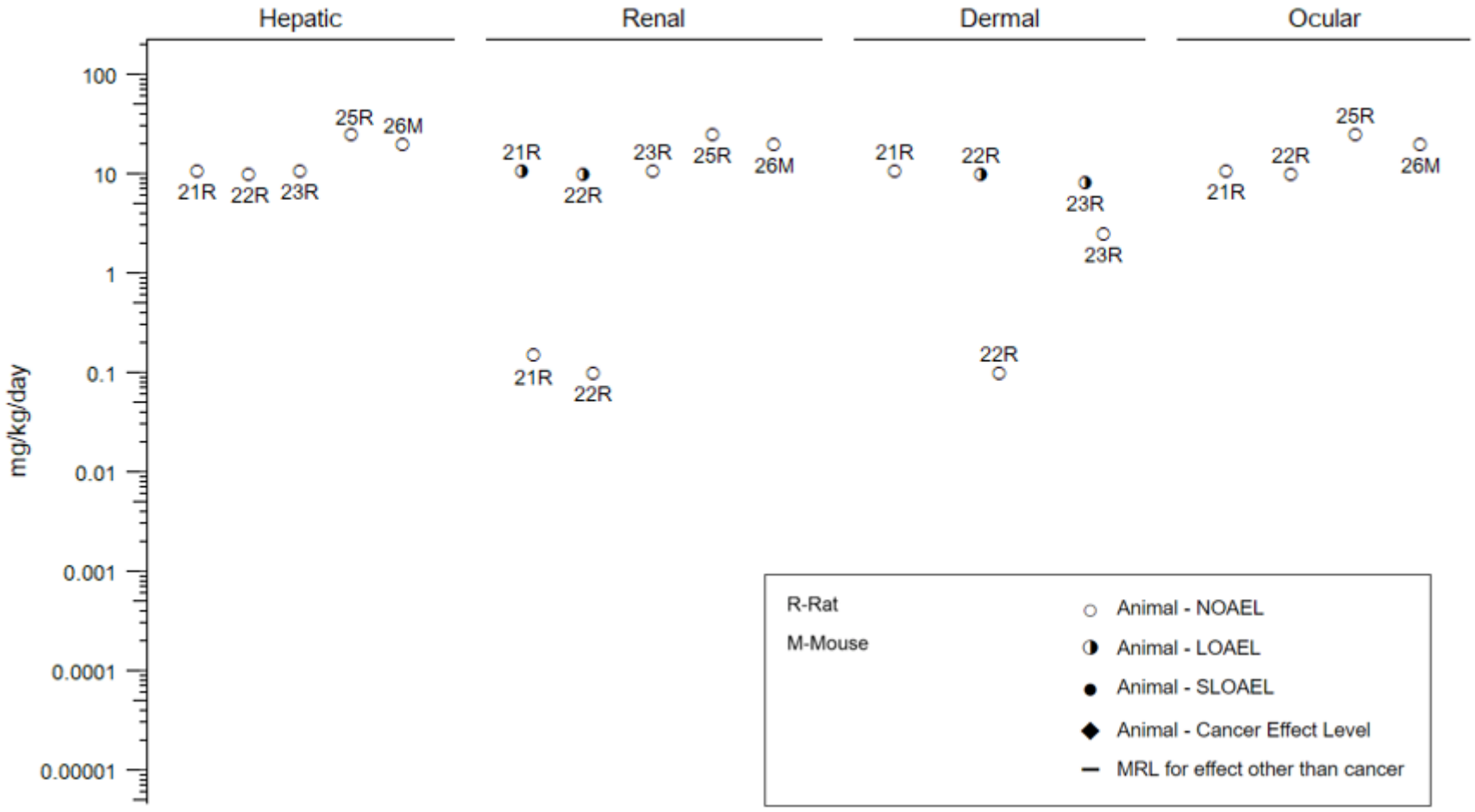

Figure 2-3. Levels of Significant Exposure to Acrylonitrile – Oral
Chronic (≥365 days)

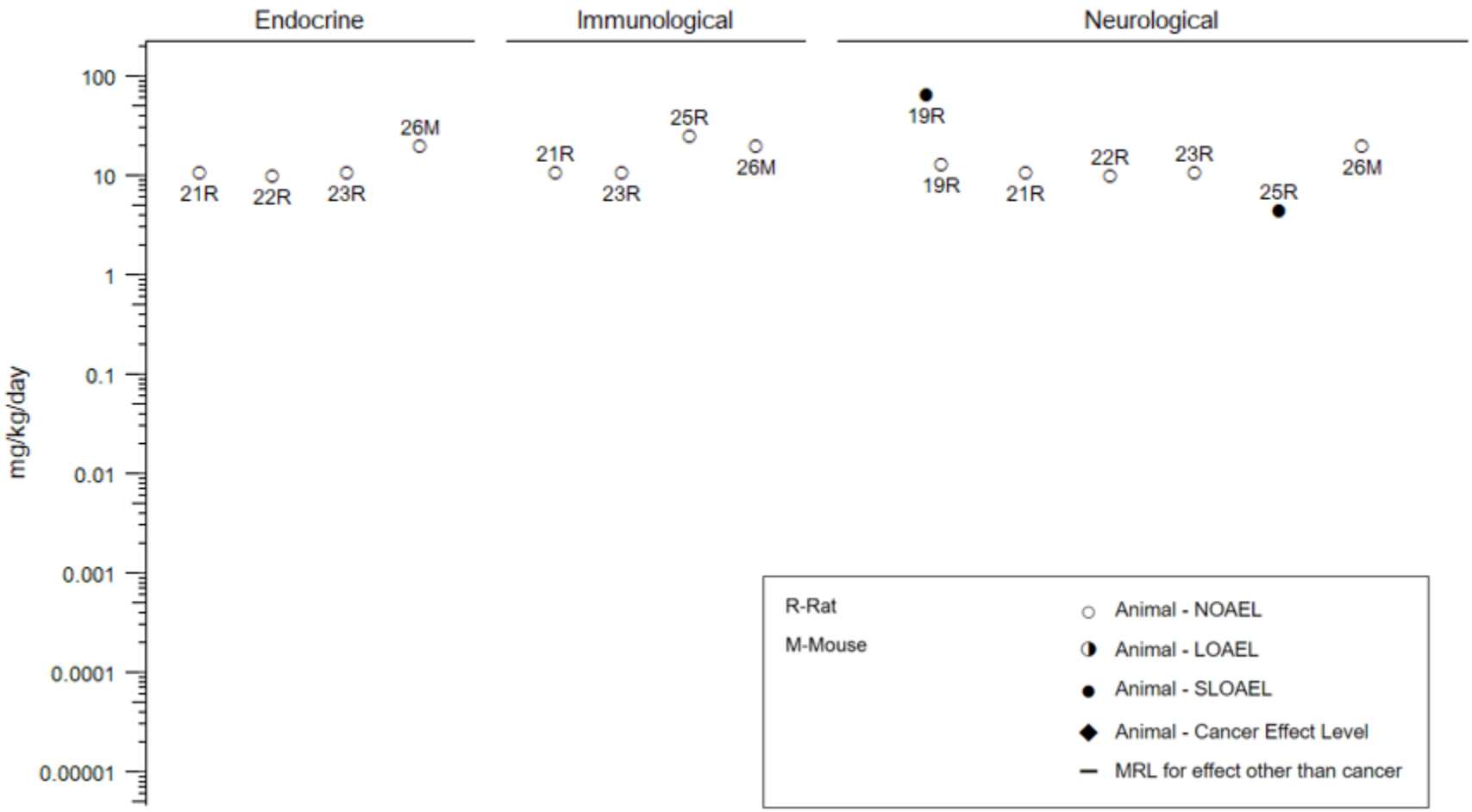

Figure 2-3. Levels of Significant Exposure to Acrylonitrile – Oral
Chronic (≥365 days)

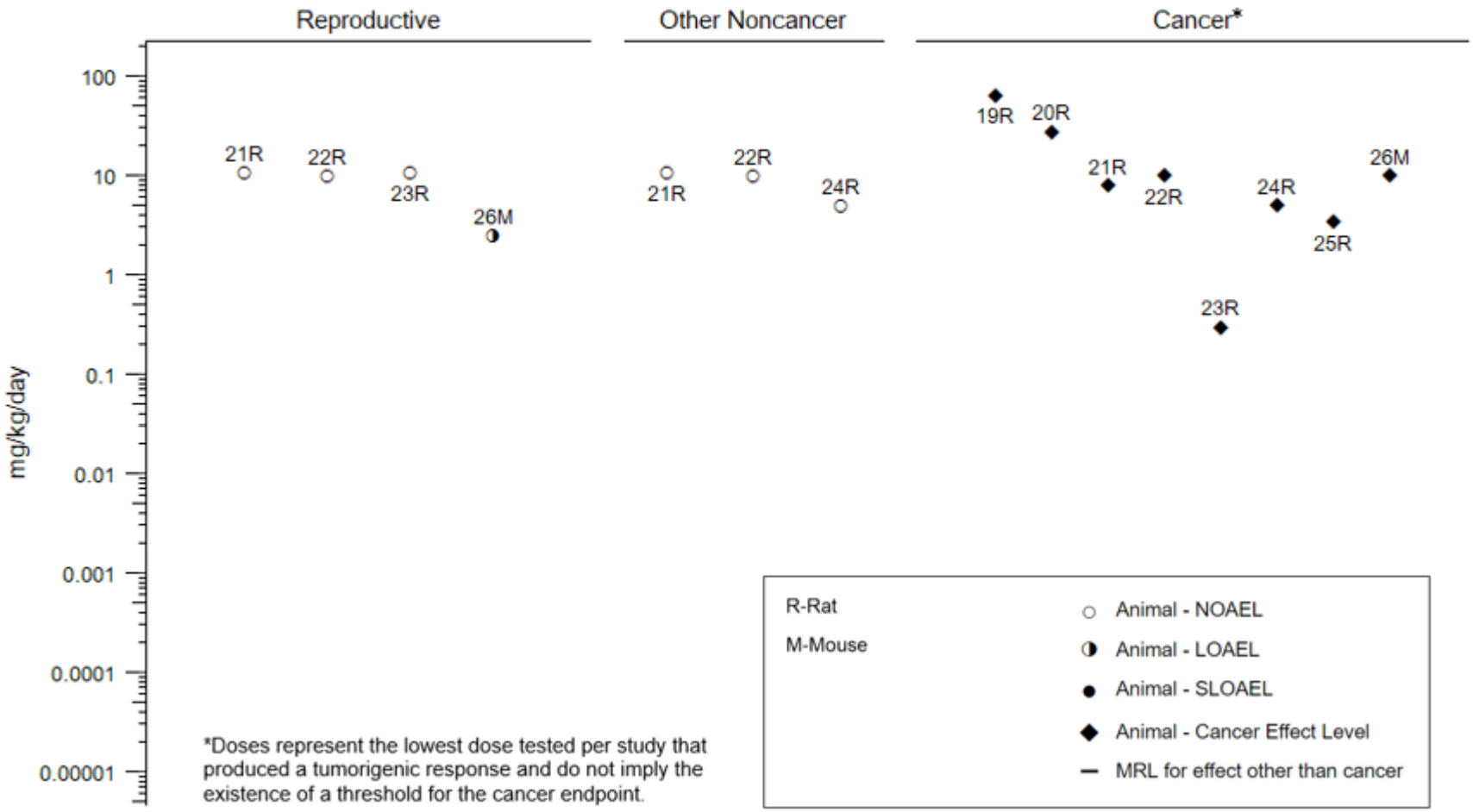

Table 2-3. Levels of Significant Exposure to Acrylonitrile – Dermal

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).