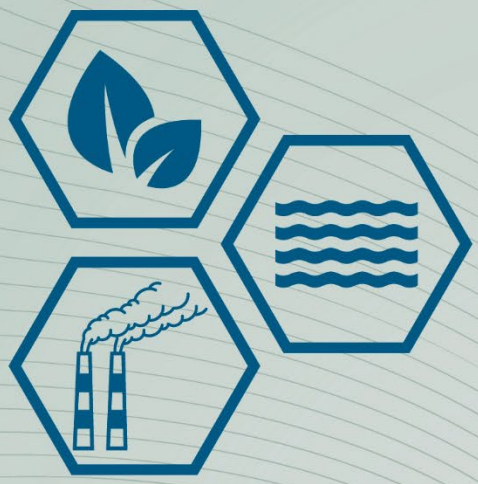

Toxicological Profile for Acrolein

Draft for Public Comment

May 2024

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

CS274127-A

DISCLAIMER

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FOREWORD

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

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

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

Each profile includes the following:

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

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

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

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public. ATSDR plans to revise these documents in response to public comments and as additional data become available. Therefore, we encourage comments that will make the toxicological profile series of the greatest use.

Electronic comments may be submitted via: www.regulations.gov. Follow the on-line instructions for submitting comments.

Written comments may also be sent to:

Agency for Toxic Substances and Disease Registry
Office of Innovation and Analytics
Toxicology Section
1600 Clifton Road, N.E.
Mail Stop S106-5
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The toxicological profiles are developed under the Comprehensive Environmental Response, Compensation, and Liability Act of 1980, as amended (CERCLA or Superfund). CERCLA Section 104(i)(1) directs the Administrator of ATSDR to "…effectuate and implement the health-related authorities" of the statute. This includes the preparation of toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL) and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. In addition, ATSDR has the authority to prepare toxicological profiles for substances not found at sites on the NPL, in an effort to "…establish and maintain inventory of literature, research, and studies on the health effects of toxic substances" under CERCLA Section 104(i)(1)(B), to respond to requests for consultation under Section 104(i)(4), and as otherwise necessary to support the site-specific response actions conducted by ATSDR.

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

Christopher M. Reh, Ph.D.
Associate Director
Agency for Toxic Substances and Disease Registry
Centers for Disease Control and Prevention

VERSION HISTORY

Date	Description
May 2024	Draft for public comment toxicological profile released
August 2007	Final toxicological profile released
December 1990	Final toxicological profile released

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

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

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CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

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

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

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

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

1.2 SUMMARY OF HEALTH EFFECTS

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

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

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

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

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

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

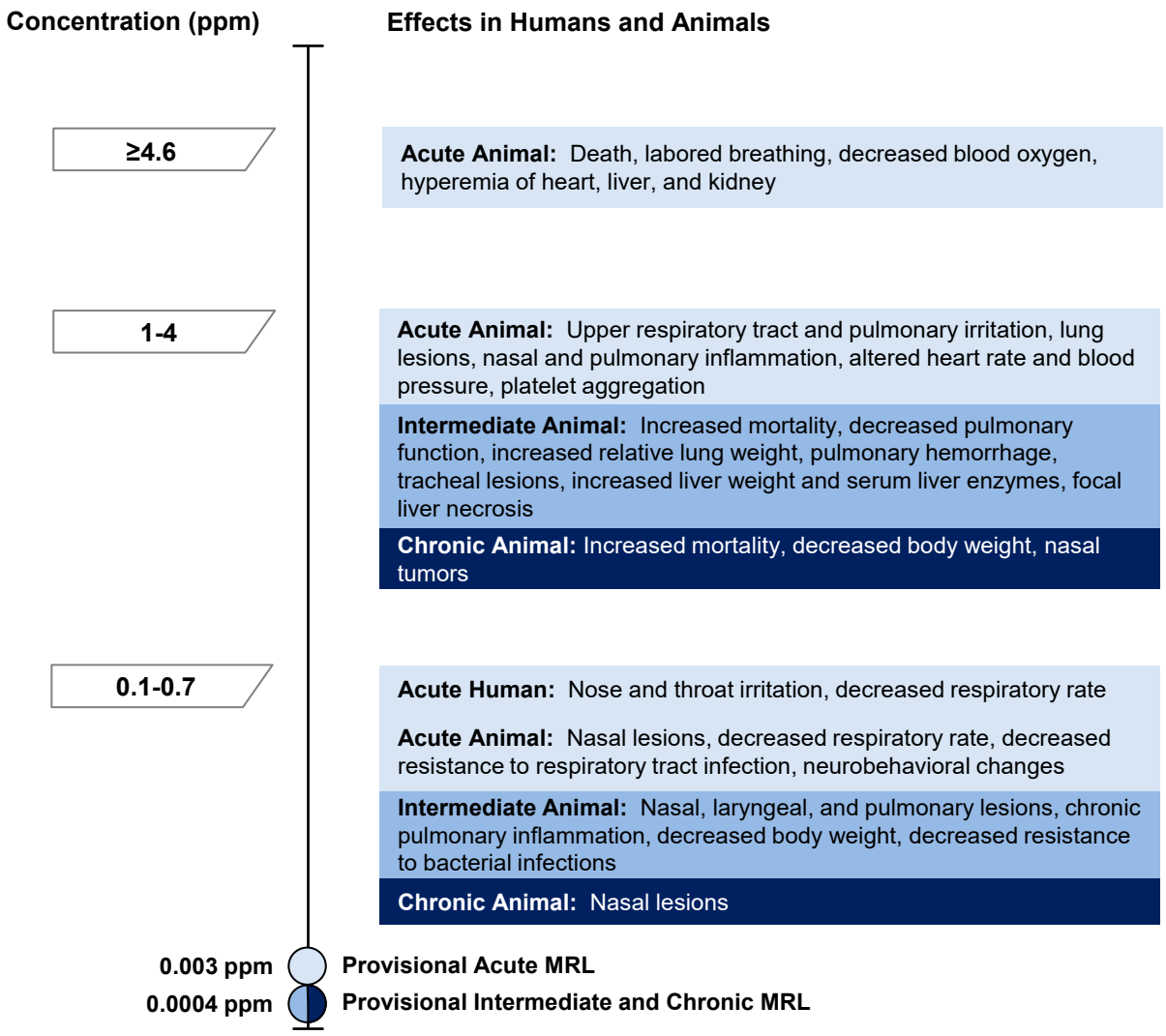
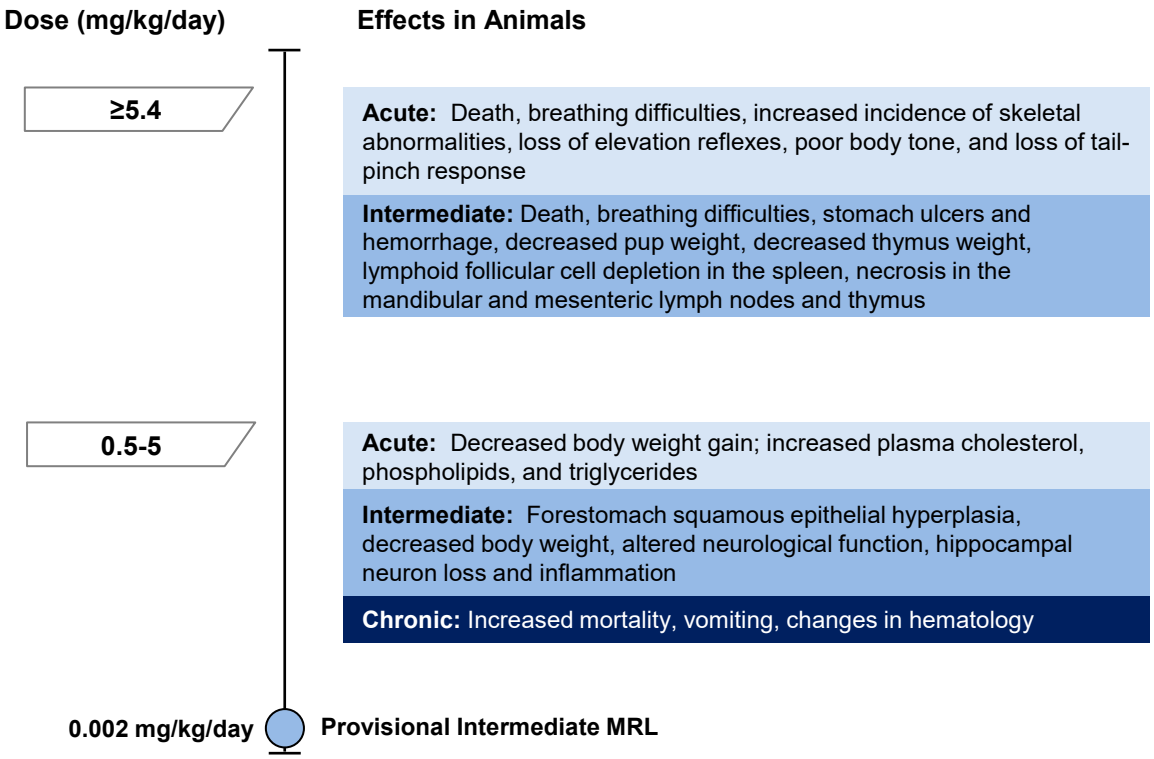


Figure 1-2. Health Effects Found in Animals Following Oral Exposure to Acrolein



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

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

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

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

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

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

1.3 MINIMAL RISK LEVELS (MRLs)

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

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

The MRL values are summarized in Table 1-1 and discussed in greater detail in Appendix A.

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

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

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

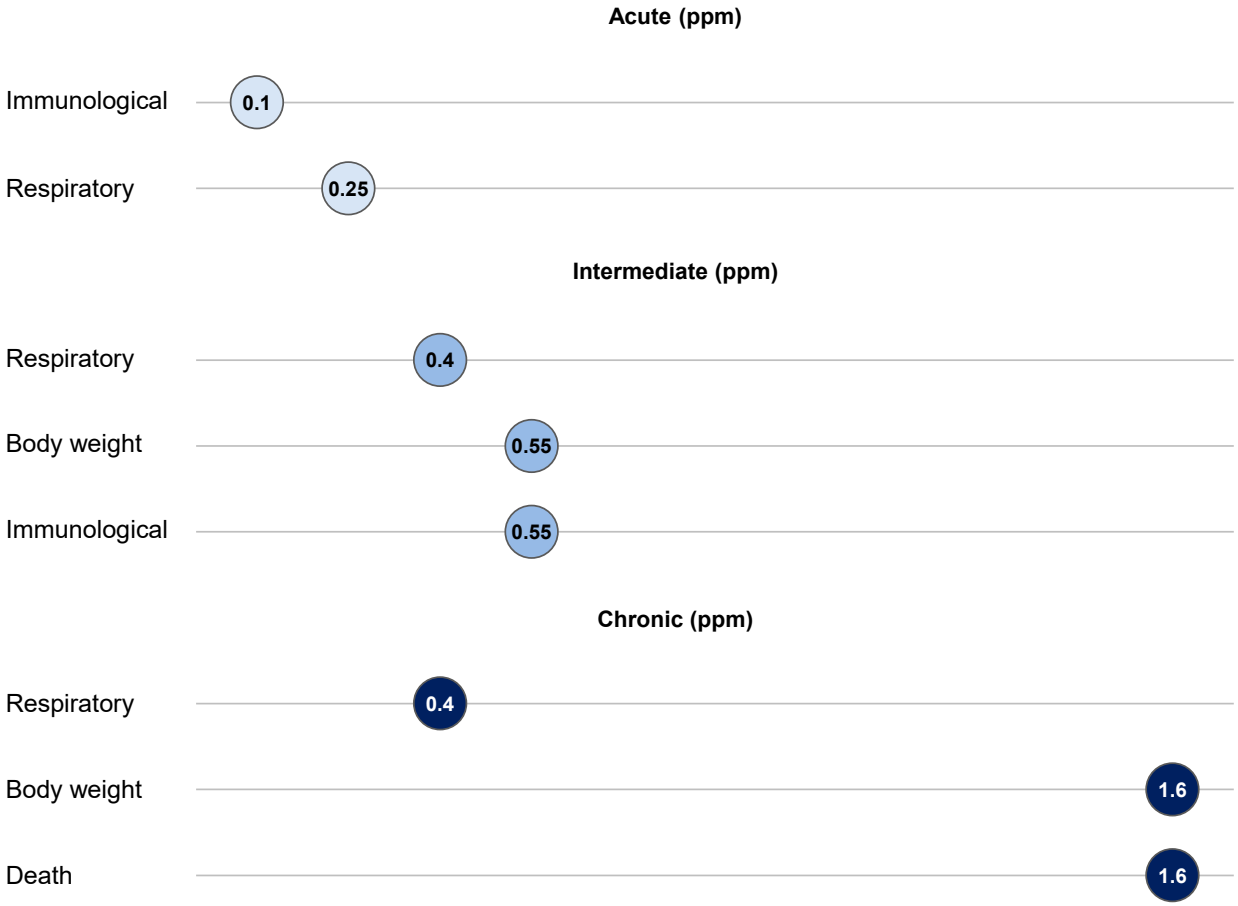


Figure 1-4. Summary of Sensitive Targets of Acrolein – Oral

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

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

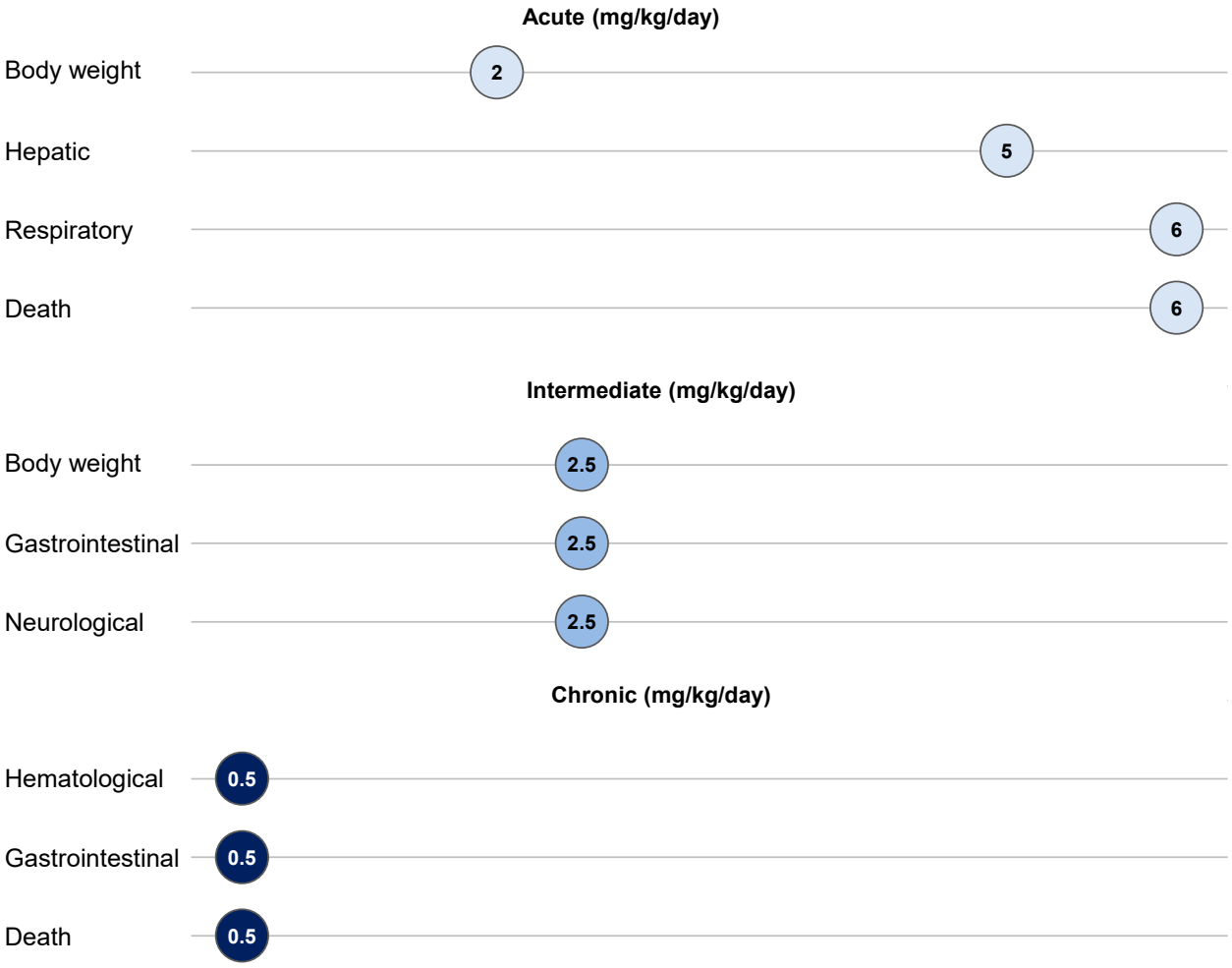


Table 1-1. Minimal Risk Levels (MRLs) for Acrolein[a]

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

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

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

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 acrolein. 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. Mechanisms of action are discussed along with the health effects data for respiratory, immunological and cancer outcomes. An overview of general mechanisms that contribute to multiple health effects is provided in Section 2.21 and 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 acrolein, 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 acrolein 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 human and animal dermal studies 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 acrolein are indicated in Table 2-1 and Figure 2-2.

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 acrolein have been evaluated in 20 human studies and 102 animal studies. As illustrated in Figure 2-1, most of the health effects data come from inhalation studies in animals. The ocular effects observed in acrolein inhalation studies are likely attributable to direct contact with acrolein vapors. Therefore, ocular effects from inhalation studies are counted as dermal exposure in Figure 2-1 and are listed in the dermal LSE table. For animal data, inhalation and oral studies are available for most health effects and exposure duration categories. The dermal animal database is limited to ocular effects, mostly after exposure to acrolein vapor. The most examined endpoints in animal studies were respiratory, death, body weight, hepatic and cardiovascular. The available human studies were predominantly focused on evaluation of respiratory and ocular effects.

A systematic review was conducted on potential toxicity targets of acrolein exposure, which included respiratory and immunological effects for inhalation exposure and gastrointestinal effects following oral exposure (see Appendix C for details).

- **Respiratory Effects.** Respiratory effects are a presumed health effect associated with acrolein exposure via inhalation based on moderate evidence in humans and a high level of evidence in animals. Rapid onset of nose and throat irritation and a reduction in breathing rate (believed to be a protective measure triggered by nose irritation) was reported by volunteers acutely exposed to

low levels of acrolein. Epidemiology studies have also reported associations between acrolein exposure and reporting of respiratory irritation symptoms, prevalence of asthma and decrements in pulmonary function. Numerous animal studies have reported nasal and pulmonary lesions, altered respiratory function and increased lung weight following acute-, intermediate-, and chronic-duration inhalation studies in rodents. While the entire respiratory tract may be affected by acrolein inhalation, the nasal epithelium appears to be more sensitive at lower exposures (<1 ppm), which is consistent with human perception of nasal irritation. The deeper respiratory regions (bronchiolar and alveolar regions) appear to be sensitive to higher exposure levels, with severe effects being observed from exposures of ≥100 ppm.

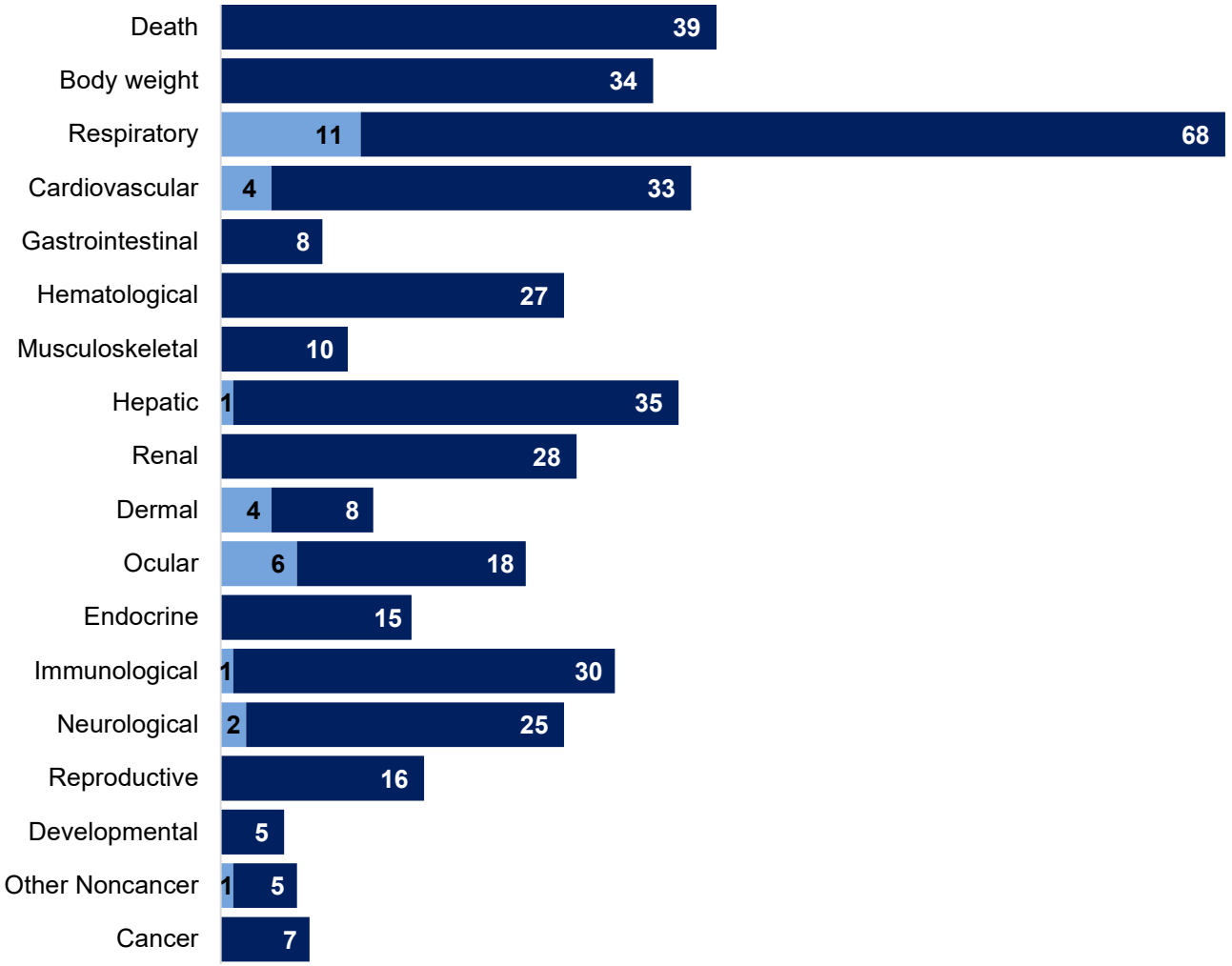
- **Immunological Effects.** Immunological effects following inhalation exposure are a suspected health effect based on a moderate level of evidence in animal studies; there is inadequate evidence in humans to make a conclusion. Although histological changes were not observed in immune organs (spleen, thymus) following inhalation, or in some cases oral exposure, acrolein exposure appears to alter immune function. Following inhalation of acrolein, several studies have reported decreased bactericidal activity, decreased numbers of alveolar macrophages, increased mortality from pulmonary bacterial infection, or suppression of the pulmonary immune response to ovalbumin challenge.

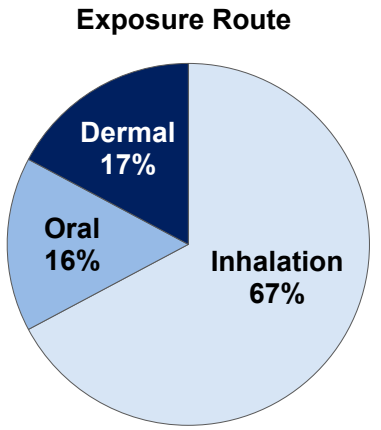
- **Gastrointestinal Effects.** Gastrointestinal effects following oral exposure are a suspected health effect based on a moderate level of evidence in animal studies; there is inadequate evidence in humans to make a conclusion. In animals, stomach lesions including ulcers, hemorrhage, hyperplasia of the forestomach, and/or erosion of the glandular mucosa were seen after intermediate-duration exposure. No histological changes were seen in rodents or dogs after chronic-duration oral exposure (2–4.5 mg/kg/day) suggesting possible adaptation to irritating effects may have occurred.

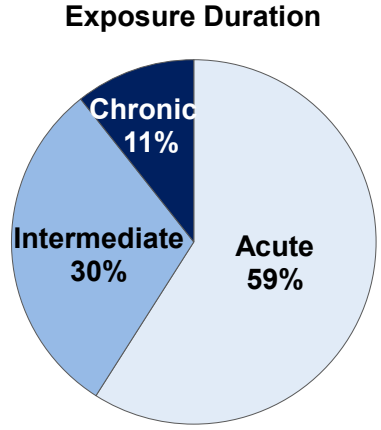
Figure 2-1. Overview of the Number of Studies Examining Acrolein Health Effects*

Most studies examined the potential respiratory effects of acrolein

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







*Includes studies discussed in Chapter 2. A total of 122 studies (including those finding no effect) have examined toxicity; most studies examined multiple endpoints.

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
ACUTE EXPOSURE									
Dwivedi et al. 2015									
1	Human 9 M, 9 F	2 hours	0, 0.05, 0.11	CS, OF, HP	Resp	0.11			
					Immuno	0.11			
Weber-Tschopp et al. 1977									
2	Human 21 M, 25 F	1 hour	0, 0.3	CS	Resp		0.3[b]		Nose and throat irritation (subjective symptoms); decreased respiratory rate
Arumugam et al. 1999a									
3	Rat (Wistar) 5 M	4 hours	0, 1, 2	HP	Resp		2		Desquamized cells and isolated peribronchial mononuclear cells in the bronchioles, hyperemia, emphysema
Babiuk et al. 1985									
4	Rat (Fischer-344) 4 M	10 minutes	0.5–10.0	OF	Resp		6		RD_{50}
Ballantyne et al. 1989									
5	Rat (Sprague-Dawley) 5 M, 5 F	1 hour	14, 22, 24, 31, 81	LE	Death			24 M 22F	2/5 males and 1/5 females died
					Bd wt	24			
					Resp		14	24 M 22F	LOAEL: Decreased breathing rate and conversion to audible and mouth breathing SLOAEL: congestion and intra-alveolar hemorrhage; fibrin deposition in the smaller airways; necrosis and exfoliation of bronchiolar epithelium in animals that died

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Ballantyne et al. 1989									
6	Rat (Sprague-Dawley) 5 M, 5 F	4 hours	4.8, 7, 9.1, 12.1	LE	Death			7.0 M 9.1 F	3/5 males and 4/5 females died
					Bd wt	7.0		9.1	Body weight loss 7 days after exposure (27 g in males, 18 g in females relative to pre-exposure weight)
					Resp		4.8	7.0 M 9.1 F	LOAEL: Decreased breathing rate and conversion to audible and mouth breathing SLOAEL: congestion and intra-alveolar hemorrhage; fibrin deposition in the smaller airways; necrosis and exfoliation of bronchiolar epithelium in decedents
Bergers et al. 1996									
7	Rat (Wistar) 4 M	20 minutes (N)	6.7, 13.4, 26.9, 53.8	CS, OF	Resp		4.6		RD_{50}
Cassee et al. 1996a									
8	Rat (Wistar) 5–6 M	6 hours	0, 0.67, 1.4	CS, HP	Resp	1.4			
Cassee et al. 1996a									
9	Rat (Wistar) 5–6 M	3 days 6 hours/day	0, 0.25, 0.67, 1.4	CS, HP	Resp		0.25		Disarrangement and thickening of the nasal epithelium, and basal cell hyperplasia
Cassee et al. 1996b									
10	Rat (Wistar) 4 M	30 minutes	1.73, 11.18, 31.9	CS, OF	Resp		9.2		RD_{50}

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Dorman et al. 2008									
11	Rat (F344) 12 M	4–14 days	0, 0.018, 0.052, 0.200, 0.586, 1.733	LE, CS, BW, HP	BW	0.586	1.733		≥10% decreased body weight after 4–6 days
					Resp	0.2	0.586		Mild nasal epithelial hyperplasia in the dorsal meatus and lateral wall, and respiratory epithelial squamous metaplasia in the septum after 4 days
Hazari et al. 2008									
12	Rat (Sprague-Dawley) 6 M	3 hours (WB)	0, 3	OF	Resp		3		Upper respiratory tract (increased pause between the end inspiration and start of expiration) and pulmonary or lower airway (increased pause between end of expiration and start of inspiration) irritation, decreased breathing frequency
					Cardio		3		Decreased heart rate
Kunkler et al. 2018									
13	Rat (Sprague-Dawley) 5–10 M	4 days 4 hours/day (WB)	0, 0.3	CS, NX	Neuro		0.3		Altered pain thresholds and behaviors (increased time spent in corners)
Morris 1996									
14	Rat (Fischer-344) 16–25 M	40 minutes	0, 0.9, 4.5, 9.1	BC	Resp	4.5	9.1		Increased albumin in nasal lavage fluid

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Murphy 1965									
15	Rat (Holtzman) 22 M	4 hours (WB)	0, 8	BI, OW, OF	Resp		8		Increased relative lung weight, pulmonary edema, inflammation
					Hepatic	8			
Murphy et al. 1964									
16	Rat (Sprague-Dawley) 20 M	4 hours	0, 12	CS, BC, BI	Resp			12	Severe respiratory tract irritation, gasping, dyspnea, decreased alkaline phosphatase activity in the lungs
Perez et al. 2013									
17	Rat (SH) 5–6 M	3 hours (WB)	0, 3	OF	Resp		3		Increased breathing frequency and minute volume
					Cardio		3		Increased heart rate and blood pressure
Perez et al. 2013									
18	Rat (WKY) 5–6 M	3 hours (WB)	0, 3	OF	Resp	3			
					Cardio		3		Increased blood pressure
Perez et al. 2015									
19	Rat (SH) 5–20 M	3 hours (WB)	0, 2.9	BI, OF	Resp		2.9		Decreased breathing frequency, increased expiratory time
					Cardio		2.9		Decreased arterial blood oxygen, increased arterial blood carbon dioxide and blood pressure
Perez et al. 2015									
20	Rat (WKY) 5–20 M	3 hours (WB)	0, 2.9	BI, OF	Cardio	2.9			

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Skog 1950									
21	Rat (NS) 8 NS	30 minutes	44–305	CS, GN, HP	Death			130	LC_{50}
					Resp			44	Respiratory difficulties, lung edema, hyperemia, and hemorrhages, degenerative changes in the bronchial epithelium
					Cardio		44		Heart hyperemia
					Hepatic		44		Liver hyperemia
					Renal		44		Kidney hyperemia
					Immuno	44			
					Neuro	44			
Snow et al. 2017									
22	Rat (Wistar) 6 M	1–2 days 4 hours/day (N)	0, 1.97, 4.00	BI, OF	Resp	1.97	4		Nasal and pulmonary inflammation, increased inspiratory and expiratory time, labored breathing
					Hemato	4			
					Hepatic	1.97	4		Increased cholesterol
					Endocr	1.97	4		Increased plasma corticosterone
					Other noncancer	1.97	4		Altered glucose tolerance
Snow et al. 2017									
23	Rat (GK) 6 M	1–2 days 4 hours/day (N)	0, 1.97, 4.00	BI, OF	Resp	1.97	4		Nasal and pulmonary inflammation, increased inspiratory and expiratory time, labored breathing
					Hemato	4			
					Hepatic	1.97	4		Increased cholesterol
					Endocr	4			

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Other noncancer	1.97	4		Altered glucose tolerance
Aranyi et al. 1986									
24	Mouse (CD-1) 18 F	5 days 3 hours/day	0, 0.1	IX	Immuno		0.1		Decreased bactericidal activity in the lungs
Aranyi et al. 1986									
25	Mouse (CD-1) 24 F	3 hours	0, 0.09	IX	Immuno	0.09			
Astry and Jakab 1983									
26	Mouse (Swiss-Webster) 6 F	8 hours	0, 3.0, 6.0	IX	Immuno		3		Decreased bactericidal activity in the lungs
Bein et al. 2021									
27	Mouse (B6C3F1) 20–32 M, 32–148 F	30 minutes (WB)	0, 50, 75	LE, GN, HP	Death			75 F	Increased mortality (79%)
								50 M	Increased mortality (60%)
					Resp	50 F	75 F		Alveolar wall thickening, proteinaceous deposit and leukocyte infiltrates in the lung
							50 M		Alveolar wall thickening, proteinaceous deposit and leukocyte infiltrates in the lung
Buckley et al. 1984									
28	Mouse (Swiss-Webster) 8–24 M	5 days 6 hours/day	0, 1.7	HP	Resp		1.7		Ulceration, necrosis, and squamous metaplasia of the respiratory and olfactory epithelium in the nasal passages

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Conklin et al. 2017a									
29	Mouse (C57BL/6) 4–23 M, 4–24 F	10–30 minutes (WB)	0, 100, 175, 210, 250, 275	LE, HE, BC, HP, OF	Death			225 M	LC_{50} (30 minutes)
					Resp			250	Labored breathing, gasping, nasal and tracheal lesions (epithelial sloughing, mucus accumulation, inflammatory cell infiltration), increased relative lung weights (males only)
					Cardio	250 F	250 M		Decreased blood oxygen saturation and cardiac output
					Hemato	250 F	250 M		Increased lymphocytes and decreased neutrophils
					Hepatic		250		Increased serum triglycerides
					Other noncancer		250		Decreased body temperature
Danyal et al. 2016									
30	Mouse (C57BL/6J) 6–16 NS	4 hours (WB)	0, 5	IX	Immuno		5		Suppressed inflammation response (reduced airway cytokine response to allergen challenge)
Kane and Alarie 1977									
31	Mouse (Swiss-Webster) 4 M	10 minutes	0, 0.5, 1.7	OF	Resp		1.7		RD_{50}
Kasahara et al. 2008									
32	Mouse (C57BL/6J) 3–6 M	3 days 6 hours/day (WB)	0, 5	HP, IX	Resp	5			
					Immuno	5			

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Kim et al. 2019									
33	Mouse (BALB/c) 8 F	10 minutes (NS)	0, 5	IX	Immuno		5		Increased airway inflammatory cells after exposure and after OVA challenge
Kim et al. 2020									
34	Mouse (C57BL/6) 3–6 M	12 hours (WB)	0, 10	HP	Resp		10		Air space enlargement in lungs
Kurhanewicz et al. 2017									
35	Mouse (C57BL/6) 8–12 F	3 hours (WB)	0, 3	OF	Cardio		3		Increased heart rate variability, number of arrhythmias, and left ventricle pressure
Kurhanewicz et al. 2018									
36	Mouse (C57BL/6) 6–8 F	3 hours (WB)	0, 3	OF	Resp		3		Increased expiratory time, tidal volume, and enhanced pause, decreased breathing frequency
					Cardio		3		Increased heart rate variability and the number of arrhythmias
Leikauf et al. 2011									
37	Mouse (129X1/ SvJ) 6–16 F	6–17 hours (NS)	0, 10	HP	Resp		10		Perivascular air space enlargement and leukocyte infiltration in the lungs
Leikauf et al. 2011									
38	Mouse (SM/J) 6–16 F	6–17 hours (NS)	0, 10	HP	Resp		10		Perivascular air space enlargement and leukocyte infiltration in the lungs

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Morris et al. 2003									
39	Mouse (C57BL/6N) 4–6 B	10 minutes	0, 1.3	CS	Resp		1.3		Decreased respiratory rate and increased expiratory pause and specific airway resistance
Morris et al. 2003									
40	Mouse (C57BL/6N) 3–6 B	10 minutes	0.3, 1.6, 3.9	CS	Resp		1.59		RD_{50}
Nielsen et al. 1984									
41	Mouse (CF-1) 35 M	30 minutes	0, 0.85, 1.27, 3.0, 7.25	OF	Resp		2.9		RD_{50}
O'Brien et al. 2016									
42	Mouse (C57BL/6) 5–14 M	2 weeks 4 days/week (WB)	0, 5	HP, IX	Resp Immuno	5 5			
Sithu et al. 2010									
43	Mouse (C57BL/6J) 6–8 M	6 hours (WB)	0, 4.9	HE, BC	Hemato Musc/skel Hepatic	 4.9 4.9	4.9		Platelet aggregation
Sithu et al. 2010									
44	Mouse (C57BL/6J) 6–8 M	4 days 6 hours/day (WB)	0, 1.1	HE, BC	Hemato Musc/skel Hepatic	 1.1 1.1	1.1		Platelet aggregation
Spiess et al. 2013									
45	Mouse (C57BL/6) 3–10 M	4 days 6 hours/day (WB)	0, 5	IX	Immuno		5		Suppressed allergic airway inflammatory response following OVA challenge

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Steinhagen and Barrow 1984									
46	Mouse (Swiss-Webster) 12–16 M	10 minutes	0.04, 0.22, 1.49, 4.92	CS, OF	Resp		1.03		RD_{50}
Steinhagen and Barrow 1984									
47	Mouse (B6C3F1) 12–16 M	10 minutes	0.08, 0.35, 2.68, 8.11	CS, OF	Resp		1.41		RD_{50}
Davis et al. 1967									
48	Guinea pig (NS) 6 NS	60 minutes	0, 17	OF	Resp		17		Decreased respiration rate
Murphy et al. 1963									
49	Guinea pig (NS) 10–14 M	2 hours	0, 0.6	OF	Resp		0.6		Increased respiratory flow resistance and tidal volume, decreased respiration rate
INTERMEDIATE EXPOSURE									
Lyon et al. 1970									
50	Monkey (Squirrel) 7–9 M	6 weeks 5 days/week 8 hours/day	0, 0.7, 3.7	CS, BW, BC, BI, HP, OF	Death			3.7	Increased mortality (2/7)
					Bd wt	3.7			
					Resp		0.7		Chronic inflammation in the lungs
					Hemato	3.7			
					Hepatic	3.7			
Lyon et al. 1970									
51	Monkey (Squirrel) 8–17 M	90 days 24 hours/day	0, 0.22 (0.21 and 0.23 combined), 1.0, 1.8	CS, BW, BC, BI, HP, OF	Bd wt	1.8			
					Resp		1.8		Tracheal squamous metaplasia and basal cell hyperplasia
					Hemato	1.8			

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Bouley et al. 1975									
52	Rat (OFA) 10–25 M	15-180 days 7 days/week 24 hours/day	0, 0.55	CS, BW, FI, BI, OW, DX	Bd wt		0.55		Decreased body weight (11%)
					Resp		0.55		Nasal irritation (sneezing)
					Immuno		0.55		Decreased number of alveolar macrophages and increased mortality from bacterial infection (after 18 days of exposure)
Bouley et al. 1975									
53	Rat (OFA) 3 M, 21 F	26 days 7 days/week 24 hours/day	0, 0.55	BW, RX, DX	Repro	0.55			
					Develop	0.55			
Costa et al. 1986; Kutzman et al. 1985; NTP 1981									
54	Rat (Fischer-344) 24 M, 24 F	62 days 5 days/week 6 hours/day	0, 0.4, 1.4, 4.0	CS, BW, BI, HP	Death			4 M	Increased mortality (56%)
					Bd wt	1.4			
							4 F		Decreased body weight (12%)
								4 M	Decreased body weight (27%)
					Resp	0.4	1.4	4	LOAEL: bronchiolar epithelial necrosis SLOAEL: Decreased pulmonary function, increased relative lung weight, pulmonary lesions (bronchiolar epithelial necrosis, bronchiolar edema fluid), acute rhinitis, and tracheal edema
					Cardio	4			
					Hemato	4			
					Renal	4			

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Neuro	4			
					Repro	4			
Dorman et al. 2008									
55	Rat (Fischer-344) 12 M	13 weeks 5 days/week 6 hours/day (WB)	0, 0.018, 0.052, 0.200, 0.586, 1.733	LE, CS, BW, HP	Bd wt	0.59		1.73	Decreased body weight (20%) at the end of exposure
					Resp	0.2	0.59		Nasal respiratory epithelial hyperplasia and squamous metaplasia, laryngeal respiratory squamous metaplasia
Feron et al. 1978									
56	Rat (Wistar) 6 M, 6 F	13 weeks 5 days/week 6 hours/day	0, 0.4, 1.4, 4.9	BW, FI, BC, BI, UR, OW, HP	Death			4.9	Increased mortality (6/12)
					Bd wt	0.4	1.4 F		Decreased body weight (13%)
							1.4 M		Decreased body weight (15%)
					Resp	0.4	1.4	4.9	SLOAEL: Lung lesions (patchy consolidation, collapsed dark areas, hemorrhages, bronchitis, hyperplasia, metaplasia), nasal lesions (necrotizing rhinitis, neutrophilic infiltration),tracheal lesions (severe damage, epithelial metaplasia). Alveolar edema in deceased animals. LOAEL: Nasal squamous metaplasia, and neutrophilic infiltration
					Cardio	4.9			
					Hemato	4.9			
					Hepatic	4.9			
					Renal	4.9			

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Endocr	4.9			
					Immuno	4.9			
					Neuro	4.9			
					Repro	4.9			
Kutzman et al. 1984									
57	Rat Dahl (hyper-tension-resistant) 10 F	62 days 5 days/week 6 hours/day	0, 0.39, 1.4, 3.96	CS, BW, BI, HP, OW	Death			3.96	Increased mortality (40%)
					Bd wt	1.40		3.96	Decreased body weight (23%)
					Resp	0.39	1.40	3.96	LOAEL: Increased relative lung weights; bronchiolar hyperplasia, peripheral lymphoid aggregation, and macrophage clusters SLOAEL: Pulmonary edema and interstitial pneumonitis
					Cardio	1.40	3.96		Increased relative heart weight
					Hepatic	1.40	3.96		Increased relative liver weight; increased serum ALT, ALP, and AST levels
					Renal	3.96			
					Neuro	3.96			

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Kutzman et al. 1984									
58	Rat Dahl (hyper-tension-sensitive) 10 F	62 days 5 days/week 6 hours/day	0, 0.39, 1.40, 3.96	CS, BW, BI, HP, OW	Death			3.96	Increased mortality (100% by day 11)
					Bd wt	1.40			
					Resp		0.39	3.96	LOAEL: Bronchiolar hyperplasia, peripheral lymphoid aggregation, and macrophage clusters SLOAEL: Severe airway epithelial necrosis with massive edema and hemorrhage
					Cardio	1.40			
					Hepatic	1.40			
					Renal	1.40			
					Neuro	1.40			
Leach et al. 1987									
59	Rat (Sprague-Dawley) 10–18 M	3 weeks 5 days/week 6 hours/day	0, 0.17, 1.07, 2.98	BW, OW, GN, HP	Bd wt	1.07	2.98		Decreased body weight at termination (15%)
					Resp		2.98		Nasal squamous metaplasia and degeneration of the respiratory epithelium, neutrophil infiltration, degeneration and atrophy of the olfactory epithelium
					Immuno	2.98			
Liu et al. 2019									
60	Rat (Sprague-Dawley) 36 M	4 weeks 5 days/week 5 hours/day (WB)	0, 3.1	HP	Resp		3.1		Laryngeal epithelial sloughing, cell death, and edema

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Lyon et al. 1970									
61	Rat (Sprague-Dawley) 7 M, 8 F	6 weeks 5 days/week 8 hours/day	0, 0.7, 3.7	CS, BW, BC, BI, GN, HP, OF	Bd wt	3.7 F 0.7 M		3.7 M	Decreased body weight (21%)
					Resp		0.7		Chronic inflammation in the lungs (peribronchial interstitial infiltration of mononuclear cells) and occasional alveolar distension/ emphysematous changes
					Hemato	3.7			
					Hepatic	3.7			
					Renal	3.7			
Lyon et al. 1970									
62	Rat (Sprague-Dawley) 7–15 M, 8–15 F	90 days 24 hours/day	0, 0.22, 1.0, 1.8	CS, BW, BC, GN, HP	Bd wt	0.22	1 F	1 M	Decreased body weight (11%) Decreased body weight (22%)
					Resp	0.22	1		Occasional pulmonary hemorrhage
					Cardio	1.8			
					Hemato	1.8			
					Hepatic	0.22	1		Focal liver necrosis
					Renal	1.8			
Sherwood et al. 1986									
63	Rat (Sprague-Dawley) 33 M	3 weeks 5 days/week 6 hours/day	0, 0.1, 1.0, 3.0	IX	Immuno	3			

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Conklin et el. 2017b									
64	Mouse (C57BL/6) 5–15 M	12 weeks 5 days/week 6 hours/day (WB)	0, 0.5, 1	BC, HE, HP, OW	Bd wt	1			
					Resp	1			
					Cardio	1			
					Hemato	0.5	1		Decreased total white blood cell count, neutrophils, lymphocytes, and monocytes
					Musc/skel	1			
					Hepatic	1			
					Renal	1			
					Immuno	1			
					Other noncancer	1			
Feron et al. 1978									
65	Hamster (Golden Syrian) 10 M, 10 F	13 weeks 5 days/week 6 hours/day	0, 0.4, 1.4, 4.9	BW, FI, BC, UR, OW, HP	Bd wt	1.4			
								4.9 F	Decreased body weight (31%)
								4.9 M	Decreased body weight (20%)
					Resp	0.4	1.4		Nasal cavity inflammation
					Cardio	4.9			
					Hemato	1.4 F 4.9 M	4.9 F		Increased number of erythrocytes, lymphocytes, packed cell volume, and hemoglobin content, decreased number of neutrophils
					Hepatic	4.9			
					Renal	4.9			
					Endocr	4.9			
					Immuno	4.9			

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Neuro	4.9			
					Repro	4.9			
Lyon et al. 1970									
66	Dog (Beagle) 2 M	6 weeks 5 days/week 8 hours/day	0, 0.7, 3.7	CS, BW, BC, BI, GN, HP, OF	Bd wt	3.7			
					Resp		0.7		Chronic inflammation in the lungs (peribronchial interstitial infiltration of mononuclear cells) and occasional alveolar distension/emphysematous changes
					Hemato	3.7			
					Hepatic	3.7			
Lyon et al. 1970									
67	Dog (Beagle) 2–4 M	90 days 24 hours/day	0, 0.22, 1.0, 1.8	CS, BW, BC, HP	Bd wt	1.8			
					Resp		0.22		Moderate emphysema and acute congestion of the lungs; focal vacuolization of the bronchiolar epithelial cells; increased secretory activity; and occasional constriction of bronchioles
					Cardio		0.22		Nonspecific inflammatory changes
					Hemato		0.22		Focal subcapsular hemorrhage of the spleen
					Hepatic		0.22		Nonspecific inflammatory changes
					Renal		0.22		Nonspecific inflammatory changes
					Endocr		0.22		Hyperplasia of the thyroid gland

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Feron et al. 1978									
68	Rabbit (Dutch) 2 M, 2 F	13 weeks 5 days/week 6 hours/day	0, 0.4, 1.4, 4.9	BW, FI, BC, BI, OW, GN, HP, UR	Bd wt	1.4	4.9		Decreased body weight (12%)
					Resp	1.4	4.9		Nasal lesions (necrotizing rhinitis, neutrophilic infiltration), tracheal lesions (hyperplastic epithelium, mucus cells), lung lesions (bronchitis, hyperplasia, metaplasia)
					Cardio	4.9			
					Hemato	4.9			
					Hepatic	4.9			
					Renal	4.9			
					Endocr	4.9			
					Immuno	4.9			
					Neuro	4.9			
					Repro	4.9			
Lyon et al. 1970									
69	Guinea pig (Hartley) 7 M, 8 F	6 weeks 5 days/week 8 hours/day	0, 0.7, 3.7	BW, OW, HP, OF	Bd wt	3.7			
					Resp		0.7		Chronic inflammation in the lungs (peribrochial interstitial infiltration of mononuclear cells) and occasional emphysema
					Hemato	3.7			
					Hepatic	0.7	3.7		Nonspecific inflammatory changes
					Renal	0.7	3.7		Nonspecific inflammatory changes

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Lyon et al. 1970									
70	Guinea pig (Hartley) 6–15 M, 8–15 F	90 days 24 hours/day	0, 0.22, 1.0, 1.8	CS, BW, BC, BI, GN, HP	Bd wt	1.8			
					Resp	0.22	1		Pulmonary inflammation (not further described)
					Cardio		0.22		
					Hemato				
					Hepatic		0.22		Nonspecific inflammatory changes
					Renal		0.22		Nonspecific inflammatory changes
CHRONIC EXPOSURE									
Matsumoto et al. 2021									
71	Rat (F344/DuCrlCrlj) 50 M, 50 F	2 years 5 days/week 6 hours/day (WB)	0, 0.1, 0.5, 2	LE, BW, FI, HE, BC, OW, HP	Death			2 F	Increased mortality (32%)
					Bd wt	2 F 0.5 M	2 M		Decreased terminal body weight (12%)
					Resp	0.5	2[c]		Nasal inflammation, metaplasia, eosinophilic changes, and goblet cell hyperplasia (BMCL = 0.012 ppm)
					Hemato	2			
					Hepatic	2			
					Renal	2			
					Dermal	2			
					Endocr	2			
					Immuno	2			
					Repro	2			
					Cancer			2	CEL: Nasal tumors (rhabdomyomas, 8%)

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Matsumoto et al. 2021									
72	Mouse (B6D2F1/ Crlj) 50 M, 50 F	93 weeks (males); 99 weeks (females) 5 days/week 6 hours/day (WB)	0, 0.1, 0.4, 1.6	LE, BW, FI, HE, BC, OW, HP	Bd wt	1.6 F 0.4 M	1.6 M		Decreased terminal body weight (17%)
					Resp	0.1 F	0.4 F		Nasal inflammation, hyperplasia, metaplasia, and regeneration
						0.4 M	1.6 M		Nasal inflammation, hyperplasia, metaplasia, and regeneration
					Hemato	1.6			
					Hepatic	1.6			
					Renal	1.6			
					Dermal	1.6			
					Endocr	1.6			
					Immuno	1.6			
					Repro	1.6			
					Cancer			1.6	CEL: Nasal tumors (adenomas, 32%)
Feron and Kruysse 1977									
73	Hamster (Golden Syrian) 18 M, 18 F	52 weeks 5 days/week 7 hours/day	0, 4.0	CS, BW, BC, BI, GN, OW, HP	Bd wt		4 F		Decreased body weight (10%)
							4 M		Decreased body weight (11%)
					Resp		4		Nasal inflammation and epithelial metaplasia, neutrophilic infiltrates, and submucosa thickening
					Cardio	4			
					Hemato	4 M	4 F		Increased hemoglobin content and packed cell volume

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Hepatic	4			
					Renal	4			
					Immuno	4			
					Neuro	4			
					Repro	4			

Green shading indicates studies selected for derivation of inhalation MRLs.

[a]The number corresponds to entries in Figure 2-2; differences in levels of health effects and cancer effects between male and females are not indicated in Figure 2-2. Where such differences exist, only the levels of effect for the most sensitive sex are presented.
[b]Used to derive a provisional acute-duration inhalation MRL of 0.003 ppm based on nose and throat irritation and decreased respiratory rate. See Appendix A for more detailed information regarding the MRL.
[c]Used to derive a provisional chronic-duration inhalation MRL of 0.0004 ppm based on nasal respiratory gland metaplasia. This MRL was also considered protective for intermediate-duration exposure and adopted for the intermediate-duration inhalation MRL. See Appendix A for more detailed information regarding the MRL.

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; B = both males and females; BC = blood chemistry; BI = biochemical changes; Bd wt or BW = body weight; Cardio = cardiovascular; CEL = cancer effect level; CS = clinical signs; Develop = developmental; DX = developmental toxicity; Endocr = endocrine; F = female(s); FI = food intake; GN = gross necropsy; HE = hematology; Hemato = hematological; HP = histopathology; Immuno = immunological; IX = immune function; LC_{50} = median lethal concentration; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); Musc/skeletal = muscular/skeletal; (N) = nose-only; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; NX = neurological function; OF = organ function; OW = organ weight; RD_{50} = exposure concentration producing a 50% respiratory rate decrease; Repro = reproductive; Resp = respiratory; RX = reproductive function; SLOAEL = serious lowest-observed-adverse-effect level; UR = urinalysis; (WB) = whole body

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

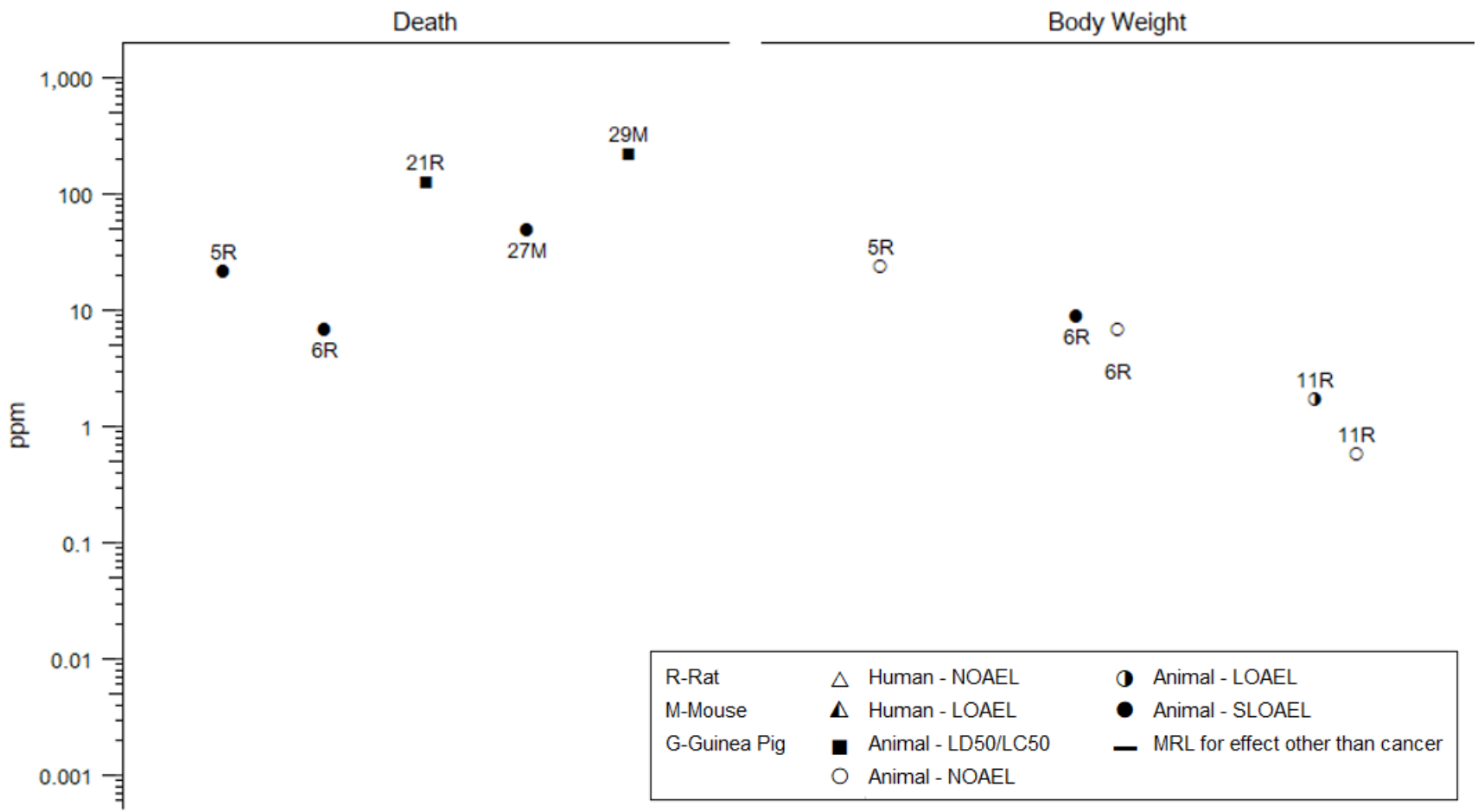


Figure 2-2. Levels of Significant Exposure to Acrolein – Inhalation
Acute (≤14 days)

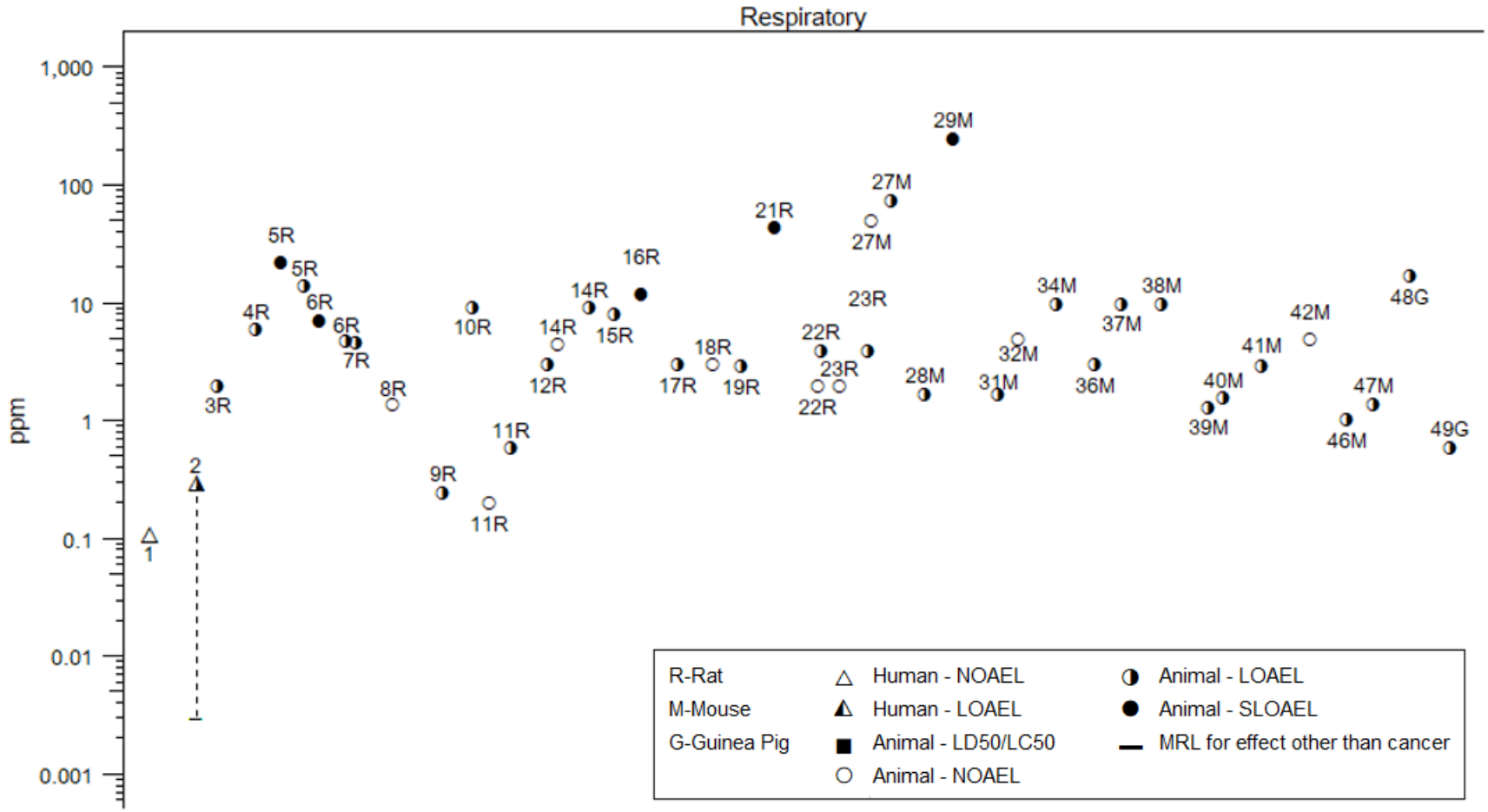


Figure 2-2. Levels of Significant Exposure to Acrolein – Inhalation
Acute (≤14 days)

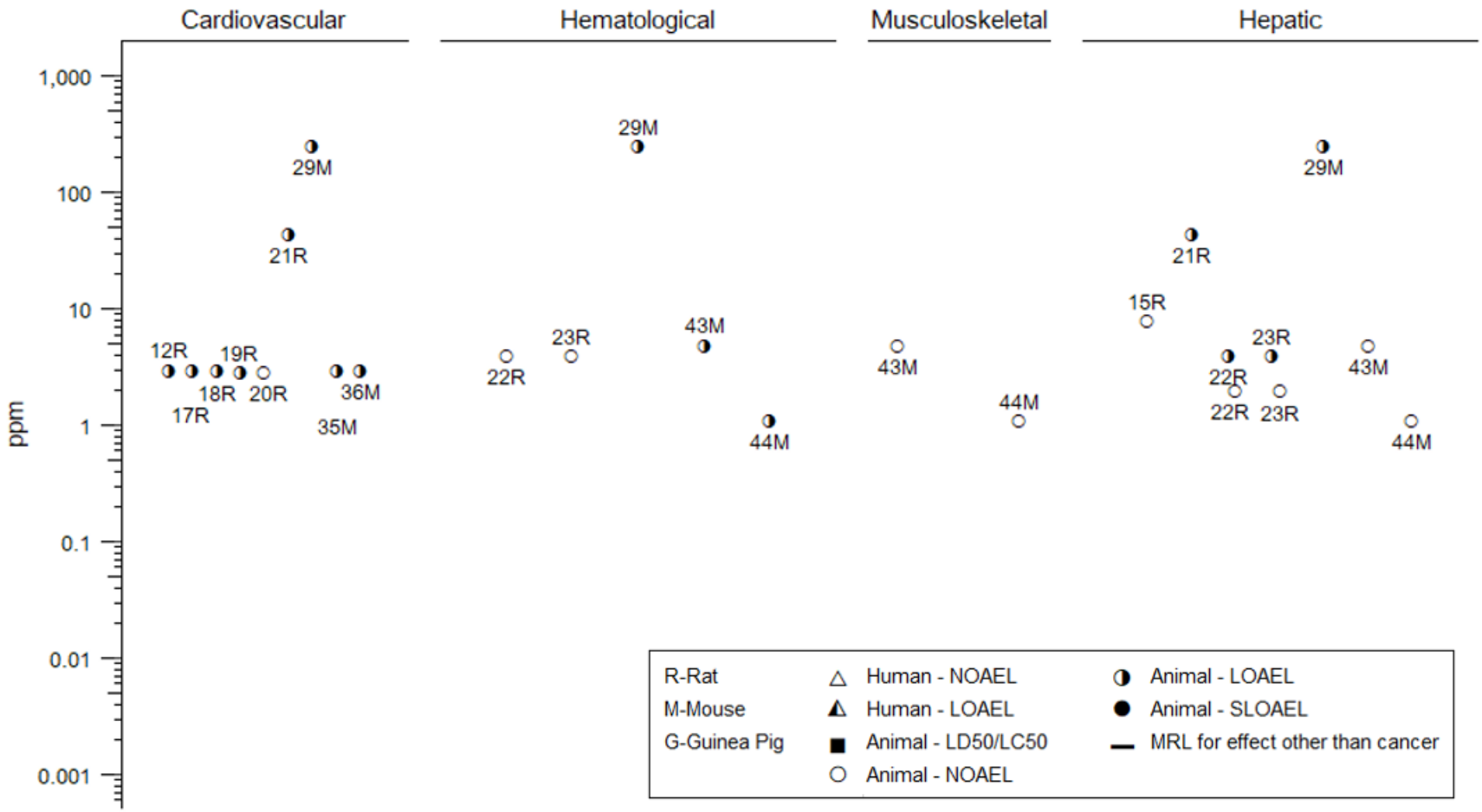


Figure 2-2. Levels of Significant Exposure to Acrolein – Inhalation
Acute (≤14 days)

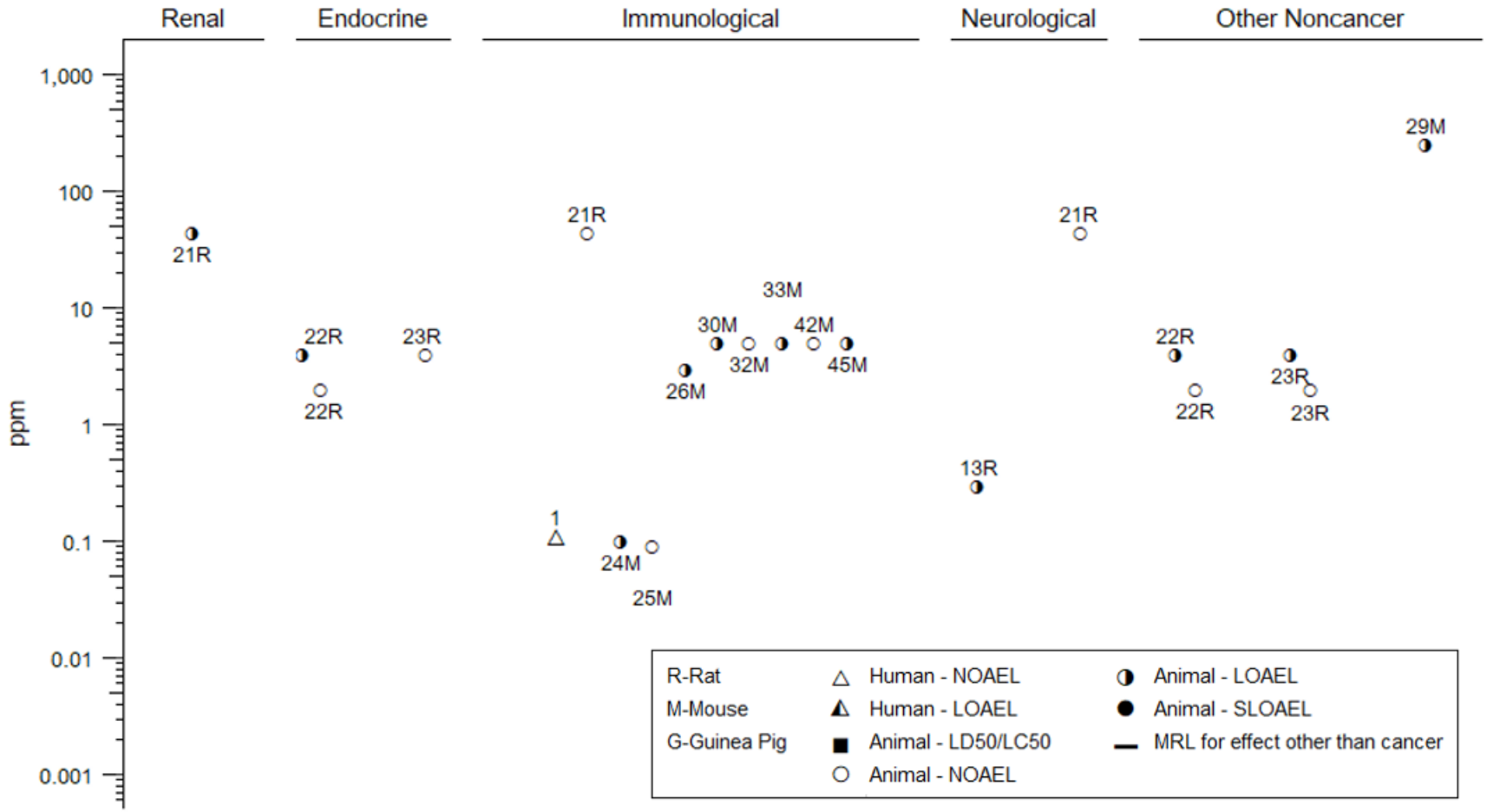


Figure 2-2. Levels of Significant Exposure to Acrolein – Inhalation
Intermediate (15–364 days)

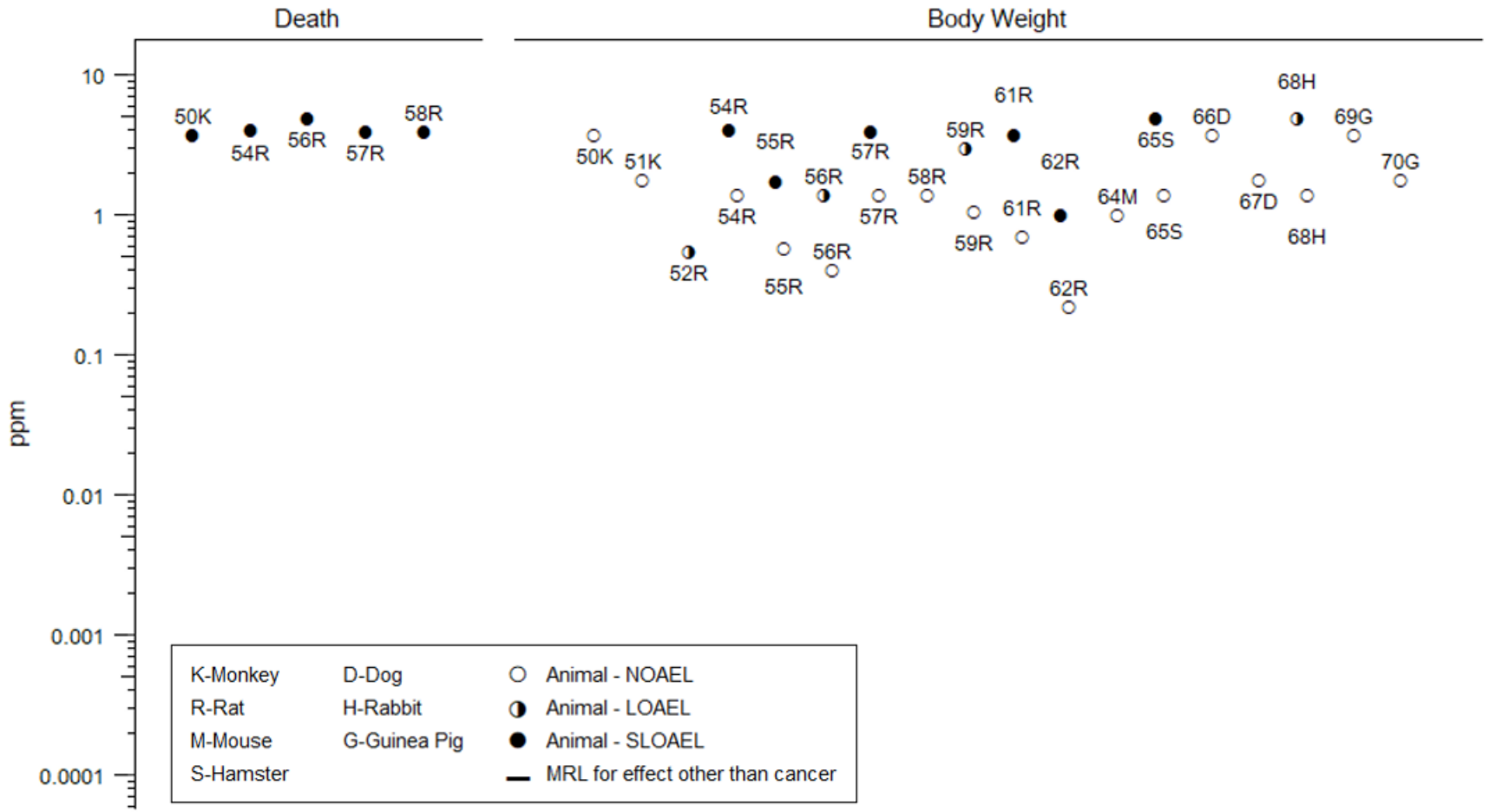


Figure 2-2. Levels of Significant Exposure to Acrolein – Inhalation
Intermediate (15–364 days)

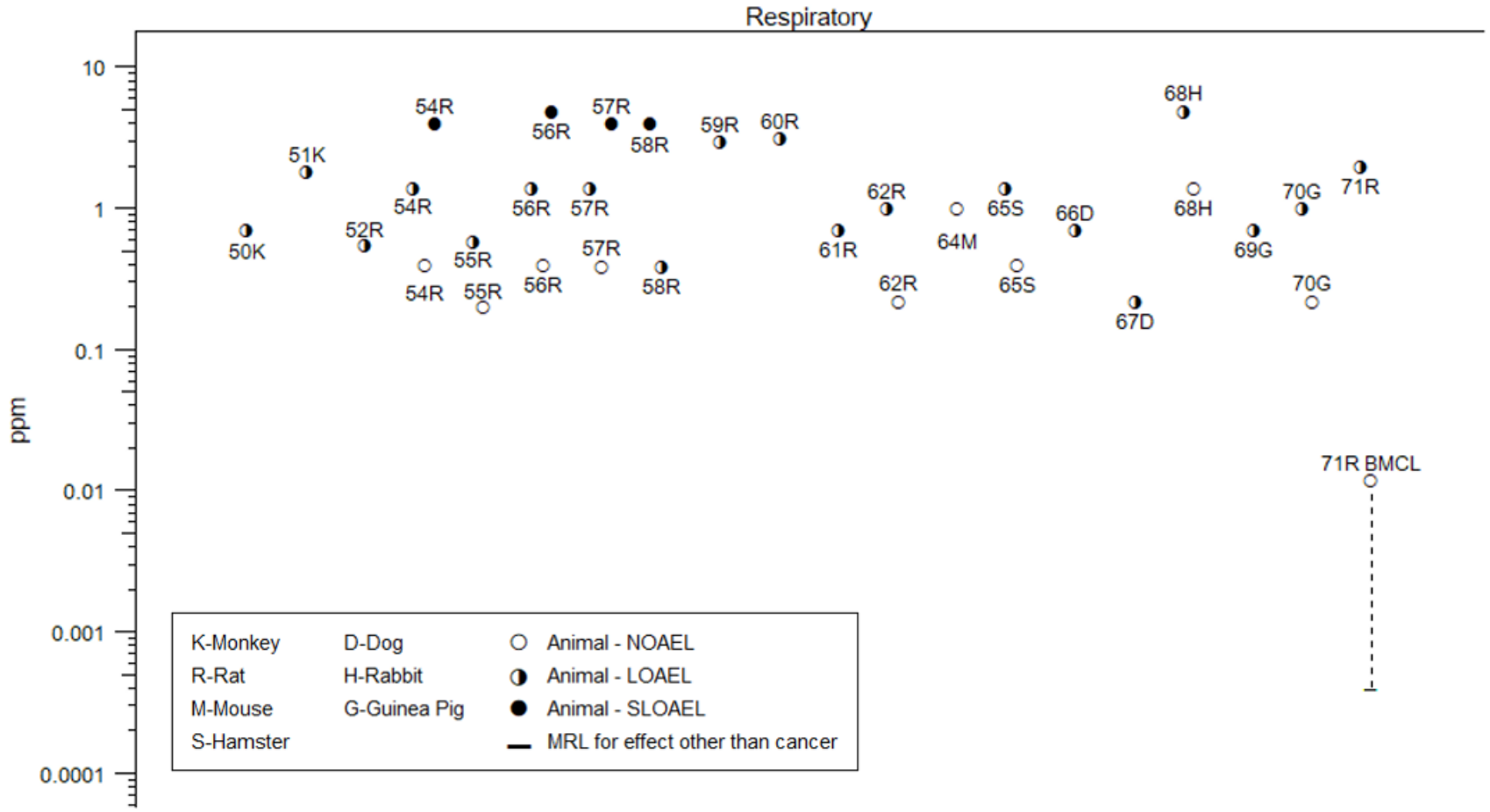


Figure 2-2. Levels of Significant Exposure to Acrolein – Inhalation
Intermediate (15–364 days)

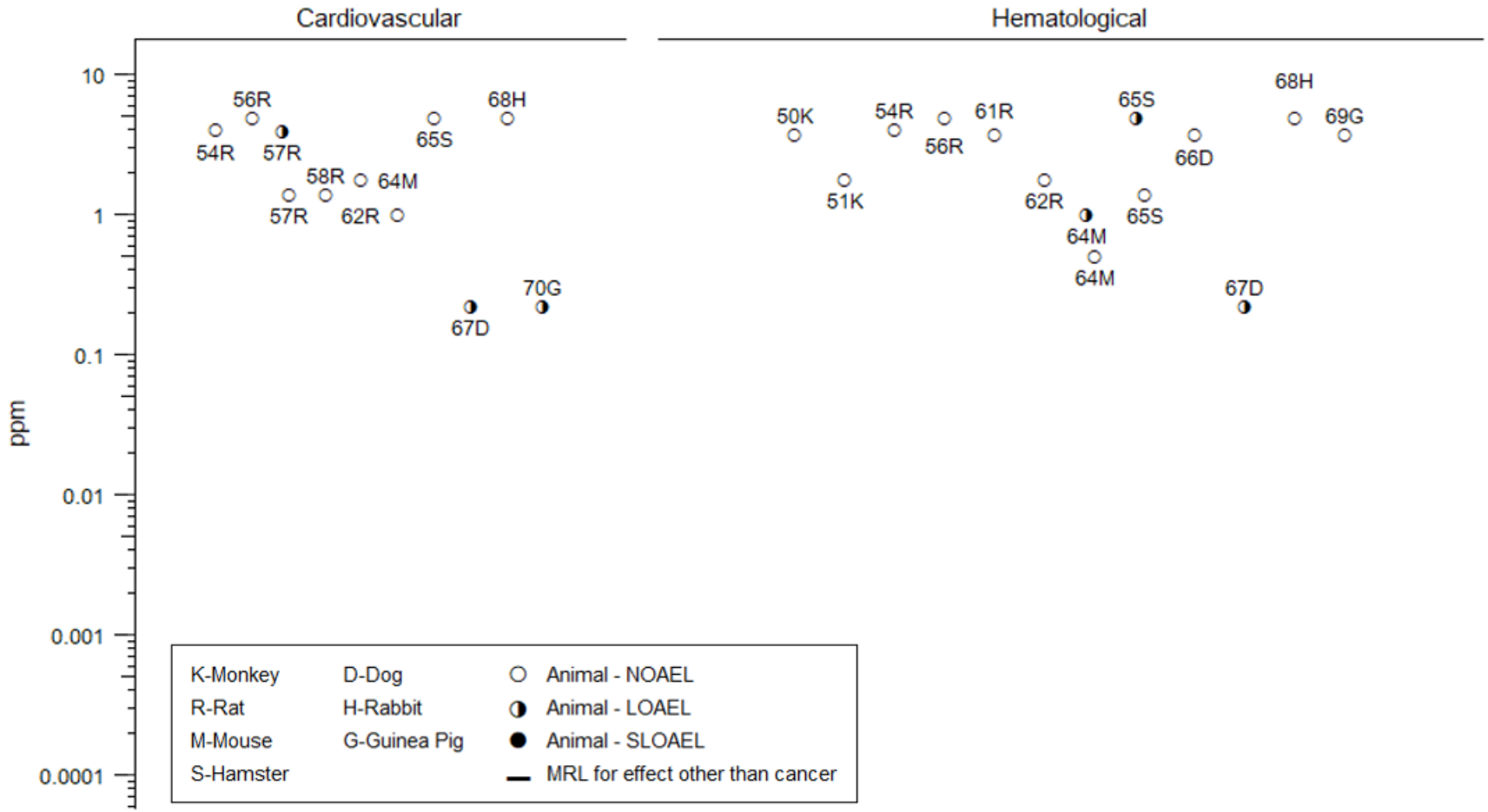


Figure 2-2. Levels of Significant Exposure to Acrolein – Inhalation
Intermediate (15–364 days)

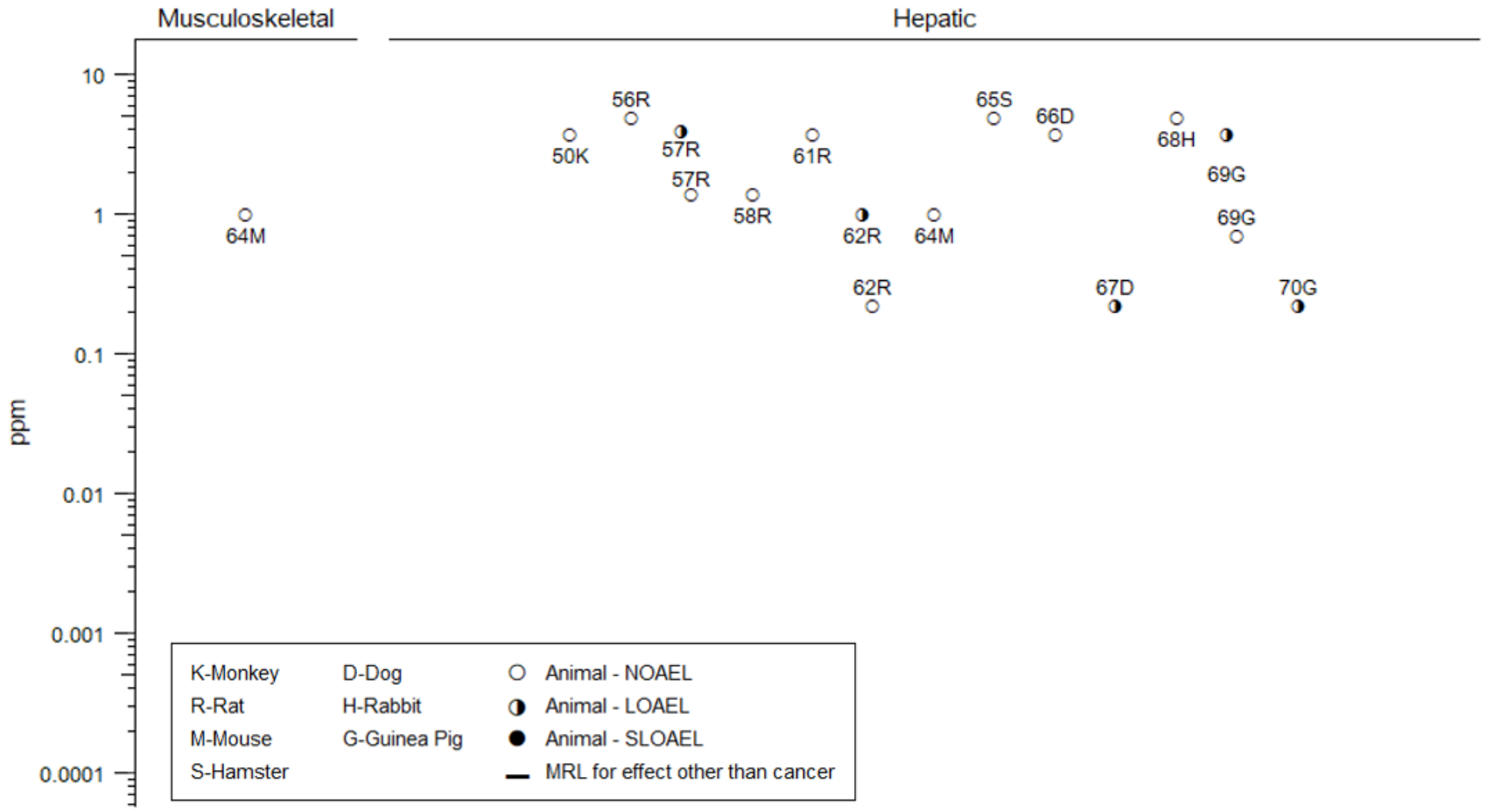


Figure 2-2. Levels of Significant Exposure to Acrolein – Inhalation
Intermediate (15–364 days)

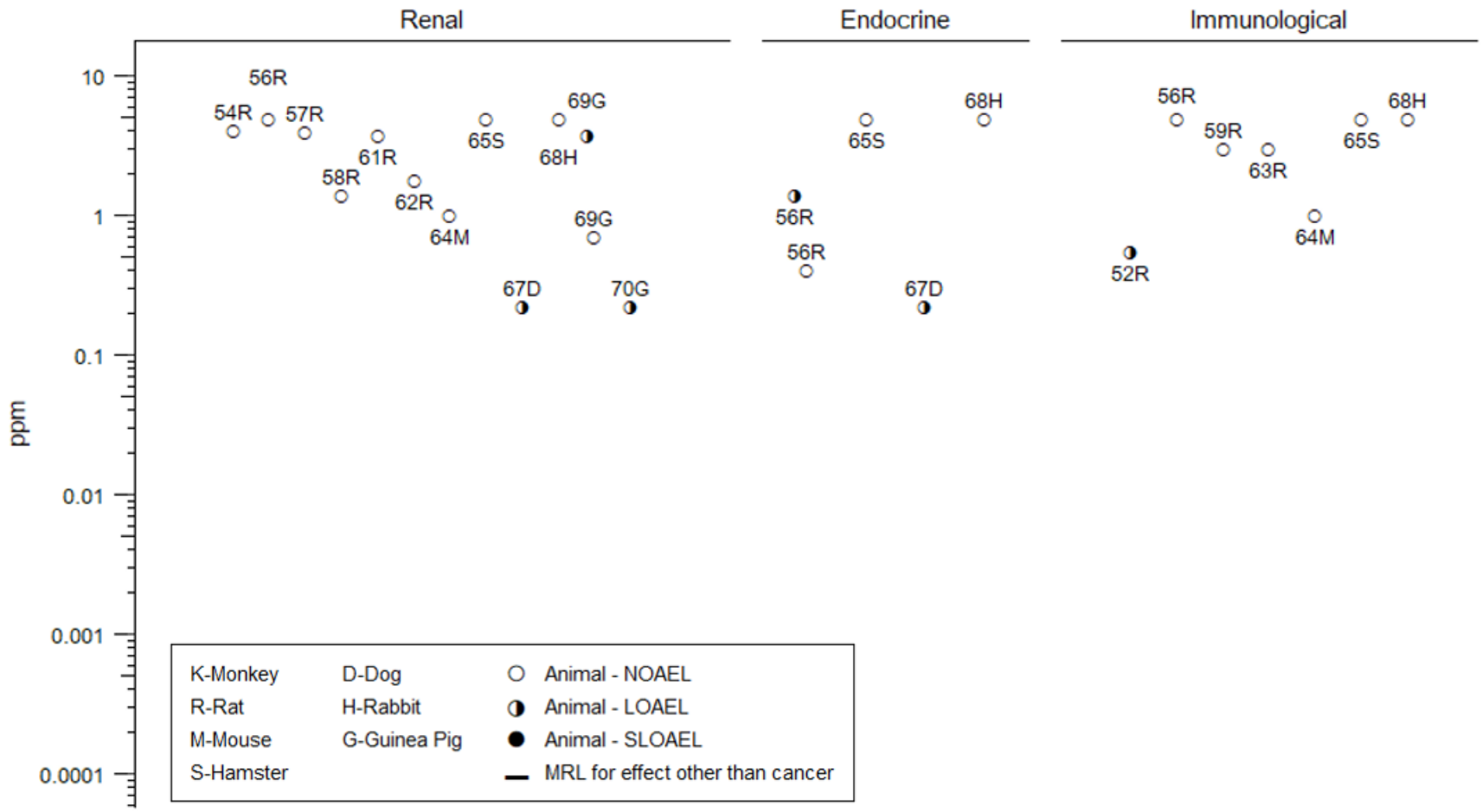


Figure 2-2. Levels of Significant Exposure to Acrolein – Inhalation
Intermediate (15–364 days)

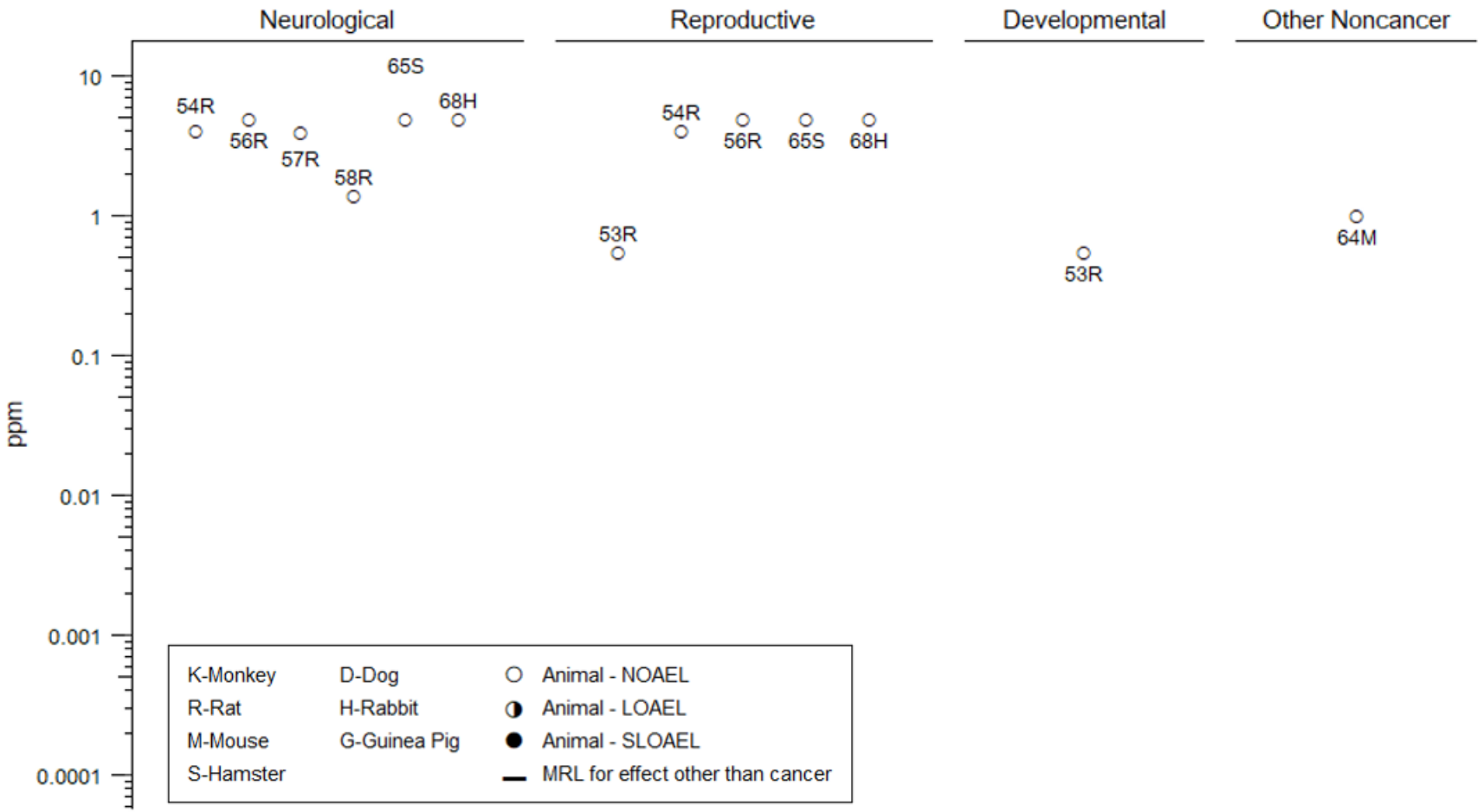


Figure 2-2. Levels of Significant Exposure to Acrolein – Inhalation
Chronic (≥365 days)

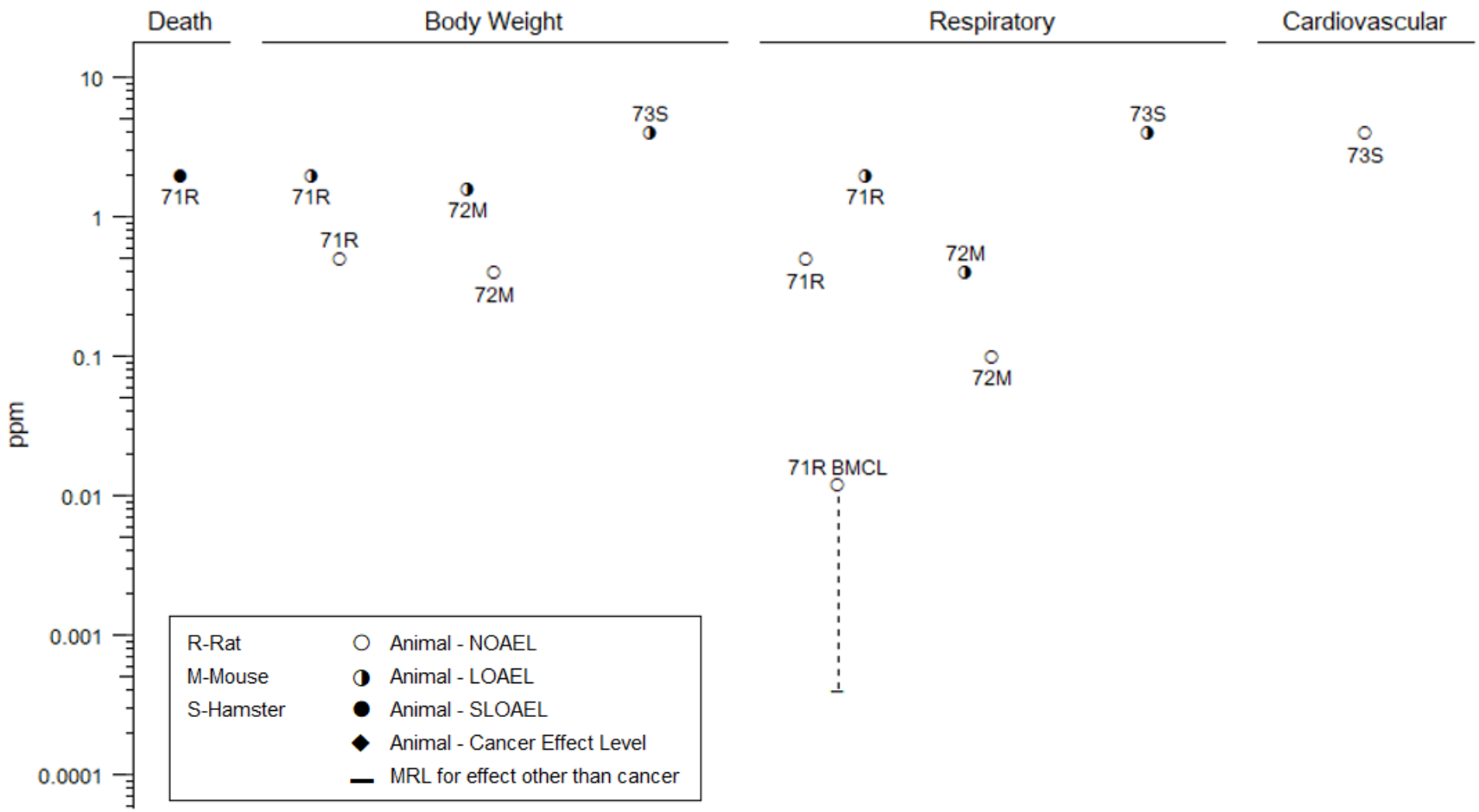


Figure 2-2. Levels of Significant Exposure to Acrolein – Inhalation
Chronic (≥365 days)

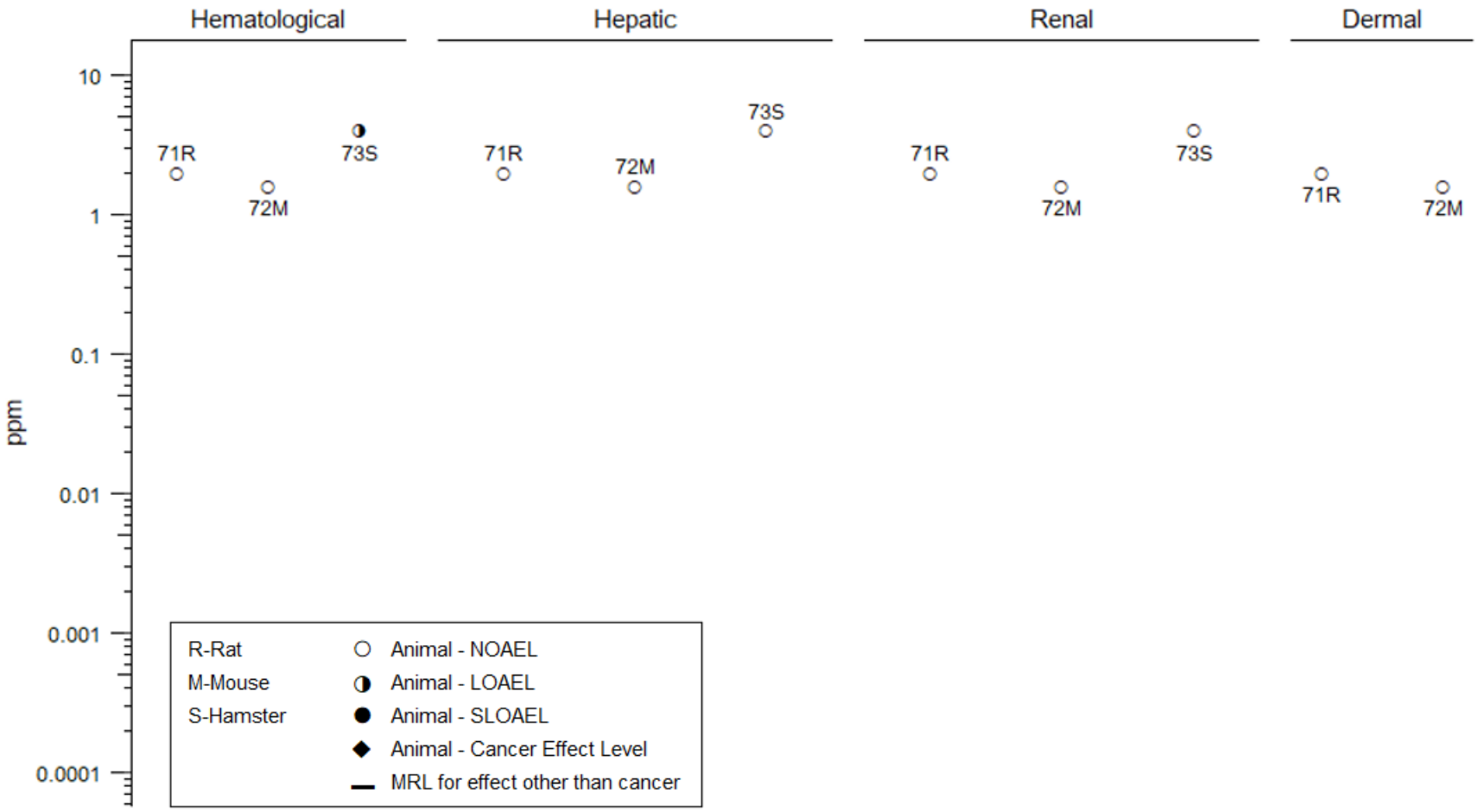


Figure 2-2. Levels of Significant Exposure to Acrolein – Inhalation
Chronic (≥365 days)

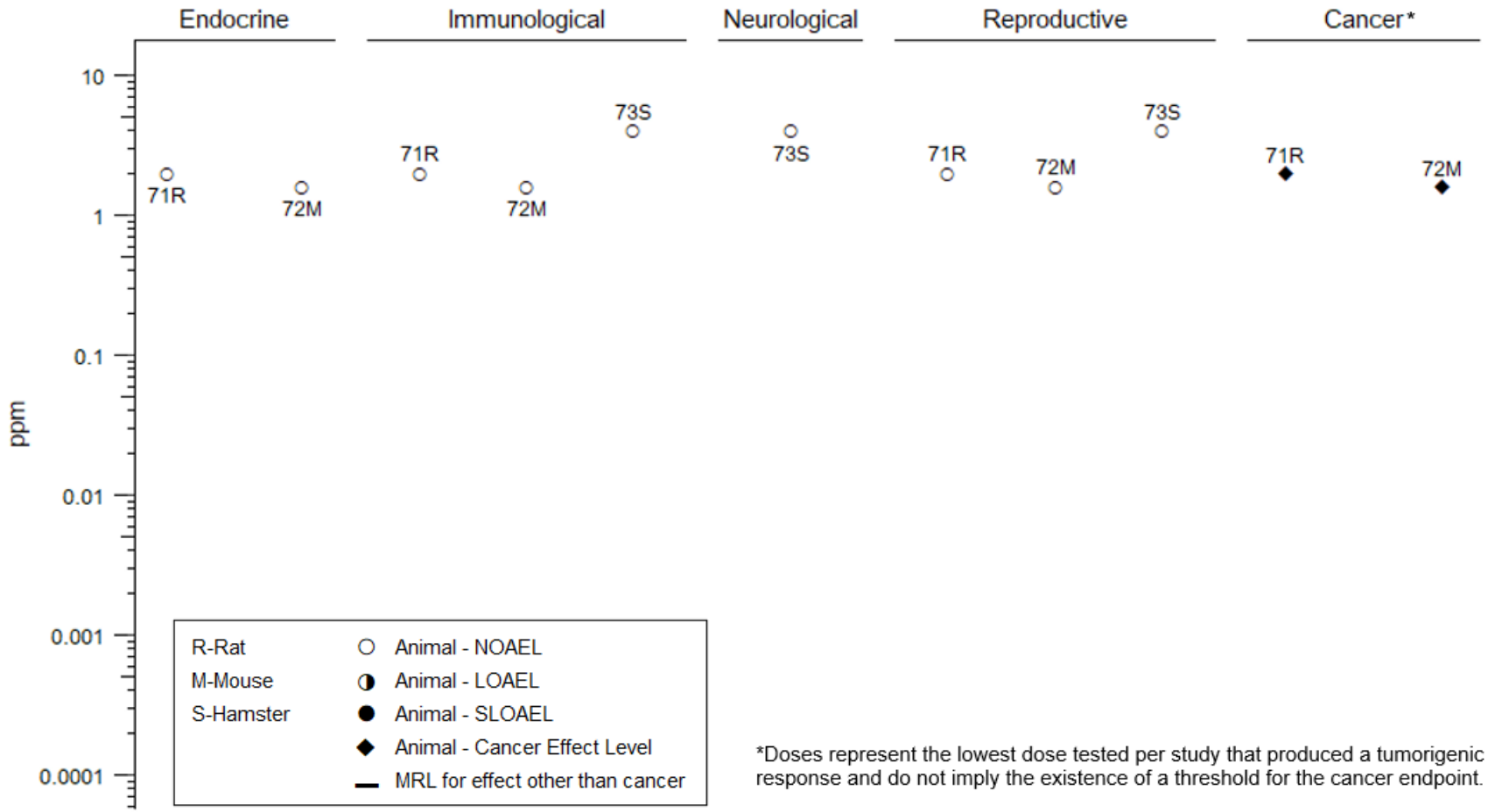


Table 2-2. Levels of Significant Exposure to Acrolein – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
ACUTE EXPOSURE									
Draminski et al. 1983									
1	Rat (Wistar) 10 F	Once (GO)	10		Death			10	LD_{50}
EPA 1983									
2	Rat (Sprague-Dawley) 40 F	13 days GDs 7–19 (GW)	0, 3.6, 6.0, 10.0	CS, BW, OW, GN, DX	Death			10	Increased mortality (30%)
					Bd wt	3.6		6	Decreased extra-gestational body weight gain (36%) (maternal weight gain minus gravid uterine weight)
					Develop	6		10	Increased incidence of skeletal abnormalities
Sprince et al. 1979									
3	Rat (CFE) 40 M	Once (G)	0, 11.2	CS	Death			11.2	Increased mortality (38/40)
					Neuro		11.2		Loss of elevation reflexes, poor body tone, and loss of tail-pinch response
Conklin et al. 2010									
4	Mouse (C57BL/6J) 3–9 M	Once (GW)	0, 0.1, 0.5, 1.0, 2.0, 5.0	BW, HE, BC, GN, OW, HP	Bd wt	5			
					Hemato	5			
					Hepatic	2	5		Increased plasma cholesterol, phospholipids, and triglycerides
					Renal	5			
Sithu et al. 2010									
5	Mouse C57BL/6J) 8 M	Single administration	0, 1, 2, 5	HE	Hemato		5		Platelet aggregation

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Parent et al. 1993									
6	Rabbit (New Zealand) 20 F	13 days GDs 7–19 (GW)	0, 0.1, 0.75, 2.0	CS, BW, GN, OW, DX	Bd wt	0.75	2		Body weight loss (80 versus 0 g in controls)
					Develop	2			
INTERMEDIATE EXPOSURE									
Auerbach et al. 2008; NTP 2006a									
7	Rat (Fischer-344) 10 M, 10 F	14 weeks 5 days/week (GW)	0, 0.75, 1.25, 2.5, 5, 10	BW	Death			10	Increased mortality (80%)
					Bd wt	5			
							10 F		Decreased body weight (10%)
								10 M	Decreased body weight (22%)
					Resp	5	10		Abnormal breathing, nasal inflammation
					Cardio	10			
					Gastro			10	Glandular stomach hemorrhage, necrosis, inflammation
						1.25 F	2.5 F		Forestomach squamous epithelial hyperplasia
						2.5 M	5 M		Forestomach squamous epithelial hyperplasia
					Hemato	2.5	5		Increased reticulocyte and platelet counts
					Musc/skel	10			
					Hepatic	10			
					Renal	10			
					Dermal	10			
					Ocular	10			
					Endocr	10			

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Immuno	5		10	Decreased thymus weight, thymocyte atrophy and necrosis, lymphoid follicular cell depletion in the spleen
					Neuro	10			
					Repro	10			
Huang et al. 2013									
8	Rat (Sprague-Dawley) 15 M	8 weeks (GW)	0, 2.5	CS, BW, HP, NX	Bd wt	2.5			
					Cardio	2.5			
					Neuro		2.5		Increased escape latency (Morris water maze), neuronal loss and inflammation in the hippocampus
Parent et al. 1992c									
9	Rat (Sprague-Dawley) 30 M, 30 F	140 days 2 generations (GW)	0, 1, 3, 6	CS, BW, FI, DX	Death			6	Increased mortality (20% in F0, 19% in F1)
					Bd wt	6			
					Resp	3		6	Breathing difficulties (rales, labored breathing, gasping, hyperpnea)
					Cardio	6			
					Gastro	3		6	Stomach ulcers, erosion of the glandular mucosa, and hyperplasia in the forestomach
					Hepatic	6			
					Renal	6			
					Endocr	6			
					Immuno	6			
					Neuro	6			
					Repro	6			

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Develop	3	6		Decreased pup weight (7% at PND 21 in F1 generation)
Auerbach et al. 2008; NTP 2006a									
10	Mouse (B6C3F1) 10 M, 10 F	14 weeks 5 days/week (GW)	0, 1.25, 2.5, 5, 10, 20	BW	Death			20	Increased mortality (100%)
					Bd wt	10			
					Resp	20			
					Cardio	20			
					Gastro			20	Glandular stomach hemorrhage, epithelial necrosis, and chronic active inflammation
						2.5 F	5 F		Forestomach squamous epithelial hyperplasia
						1.25 M	2.5 M[b]		Forestomach squamous epithelial hyperplasia (BMDL = 0.22 mg/kg/day)
					Hemato	10			
					Musc/skel	20			
					Hepatic	20			
					Renal	20			
					Dermal	20			
					Ocular	20			
					Endocr	20			
					Immuno	10		20	Necrosis in the mandibular and mesenteric lymph node, depletion of the lymphoid follicle in the spleen, necrosis in the thymus
					Neuro	20			

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Repro	20			
Chen et al. 2019									
11	Mouse (ICR) 4-6 M	4 weeks (GW)	0, 2.5, 5	CS, BW, HP	Bd wt		2.5		Decreased body weight (15%)
					Musc/skel		2.5		Decreased soleus muscle weight and cross-sectional area
					Neuro		2.5		Decreased rotarod latency
Ismahil et al. 2011									
12	Mouse (C57BL/6J) 8–16 M	48 days (GW)	0, 1	LE, CS, BW, HP, OF	Bd wt	1			
					Cardio		1		Myocardial inflammation, myocyte hypertrophy and cell death, left ventricle remodeling and dysfunction
Wang et al. 2021									
13	Mouse (ICR) 8 M	4 weeks (GW)	0, 2.5, 5	BI	Other noncancer		2.5		Increased blood glucose and insulin, impaired glucose tolerance
CHRONIC EXPOSURE									
Parent et al. 1992a									
14	Rat (Sprague-Dawley) 50 M, 50 F	102 weeks (GW)	0, 0.05, 0.5, 2.5	CS, BW, FI, HE, BC, UR, OP, OW, GN	Death			0.5 F	Increased mortality
					Bd wt	2.5			
					Resp	2.5			
					Cardio	2.5			
					Gastro	2.5			
					Hemato	2.5			
					Musc/skel	2.5			
					Hepatic	2.5			
					Renal	2.5			
					Dermal	2.5			

Table 2-2. Levels of Significant Exposure to Acrolein – 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	2.5			
					Endocr	2.5			
					Immuno	2.5			
					Neuro	2.5			
					Repro	2.5			
Parent et al. 1991a									
15	Mouse (CD-1) 70–75 M, 70–75 F	18 months (GW)	0, 0.5, 2.0, 4.5	BW, OW, FI, GN, HP, HE	Death			4.5 M	Increased mortality (28%)
					Bd wt	4.5			
					Resp	4.5			
					Cardio	4.5			
					Gastro	4.5			
					Hemato	4.5			
					Musc/skel	4.5			
					Hepatic	4.5			
					Renal	4.5			
					Dermal	4.5			
					Ocular	4.5			
					Endocr	4.5			
					Immuno	4.5			
					Neuro	4.5			
					Repro	4.5			

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Parent et al. 1992b									
16	Dog (Beagle) 24 M, 24 F	53 weeks (C)	0, 0.1, 0.5, 1.5–2.0	BC, BW, CS, GN, HP, HE, UR, OW	Bd wt	2			
					Resp	2			
					Cardio	2			
					Gastro	0.1	0.5		Vomiting
					Hemato	2			
					Musc/skel	2			
					Hepatic	2			
					Renal	2			
					Dermal	2			
					Ocular	2			
					Endocr	2			
					Immuno	2			
					Neuro	2			
					Repro	2			

Green shading indicates the study selected for derivation of oral MRL.

[a]The number corresponds to entries in Figure 2-3; differences in levels of health effects and cancer effects between male and females are not indicated in Figure 2-3. Where such differences exist, only the levels of effect for the most sensitive sex are presented.
[b]Used to derive a provisional intermediate-duration oral MRL of 0.002 mg/kg/day based on forestomach squamous epithelial hyperplasia. See Appendix A for more detailed information regarding the MRL.

BC = blood chemistry; BI = biochemical changes; Bd wt or BW = body weight; (C) = capsule; Cardio = cardiovascular; CS = clinical signs; Develop = developmental; DX = developmental toxicity; Endocr = endocrine; F = female(s); FI = food intake; (G) = gavage; Gastro = gastrointestinal; GD = gestation day; GN = gross necropsy; (GO) = gavage in oil; (GW) = gavage in water; HE = hematology; Hemato = hematological; HP = histopathology; Immuno = immunological; LD_{50} = median lethal dose; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); Musc/skeletal = muscular/skeletal; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NX = neurological function; OF = organ function; OP = ophthalmology; OW = organ weight; PND = postnatal day; Repro = reproductive; Resp = respiratory; RX = reproductive function; UR = urinalysis

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

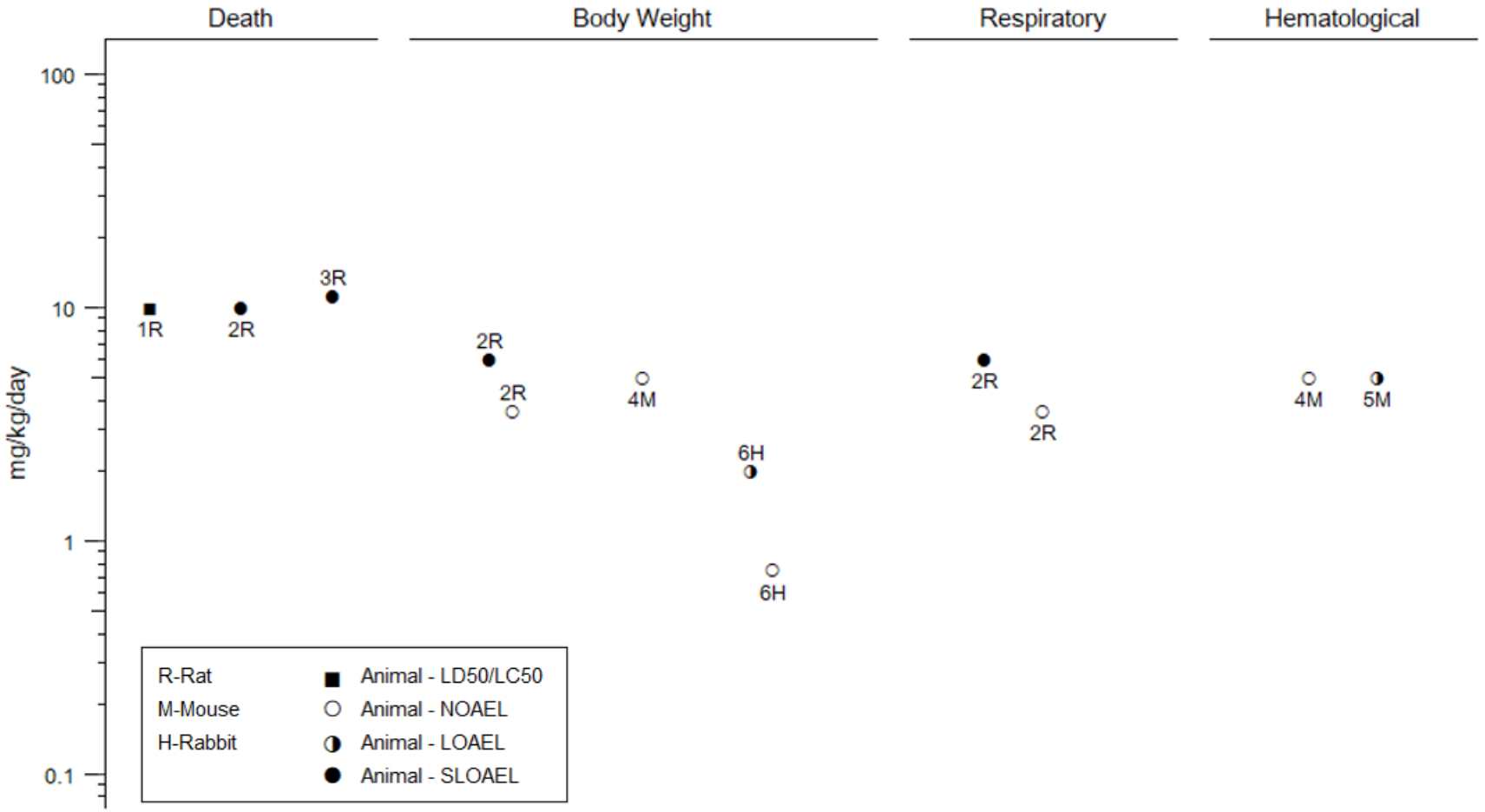


Figure 2-3. Levels of Significant Exposure to Acrolein – Oral
Acute (≤14 days)

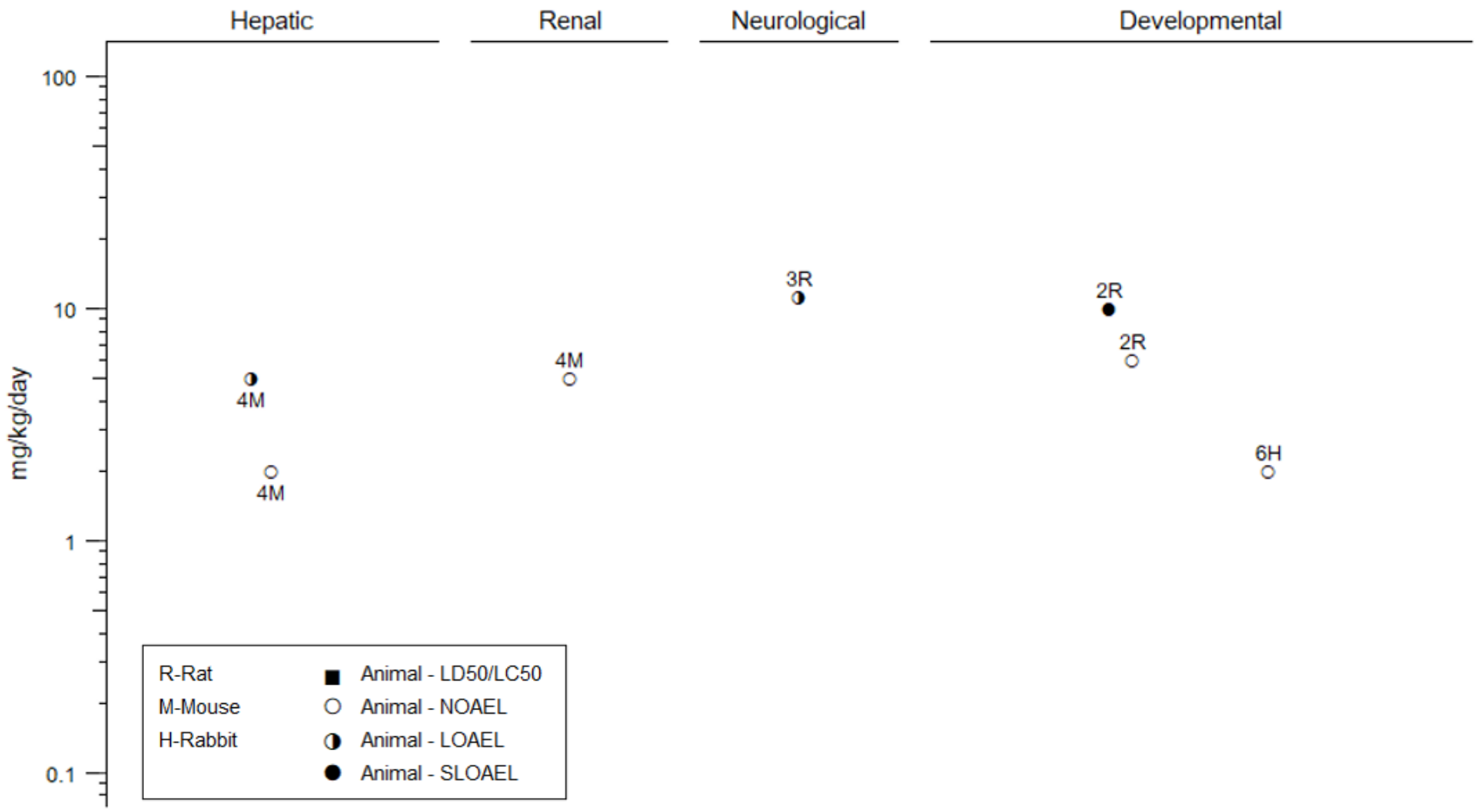


Figure 2-3. Levels of Significant Exposure to Acrolein – Oral
Intermediate (15–364 days)

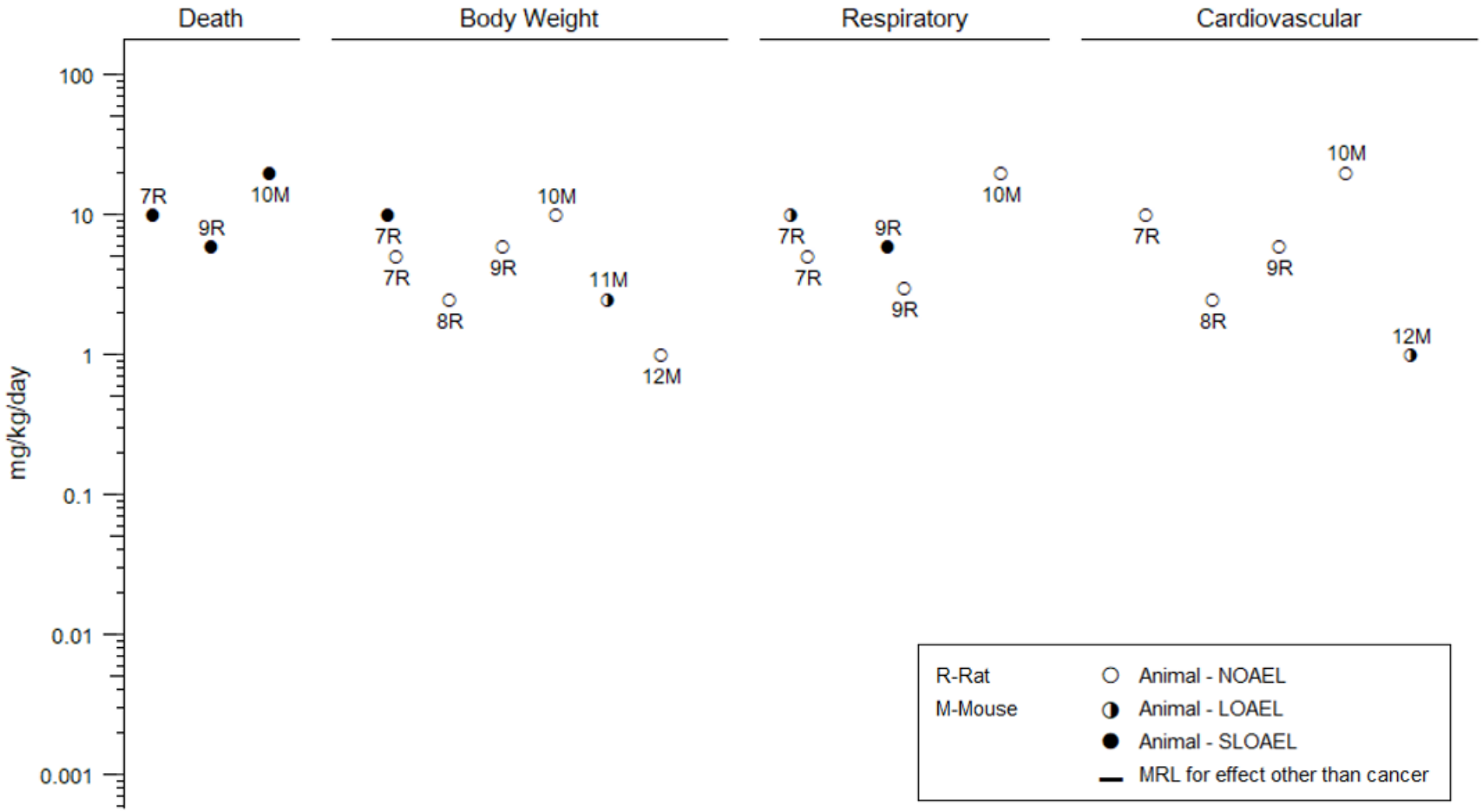


Figure 2-3. Levels of Significant Exposure to Acrolein – Oral
Intermediate (15–364 days)

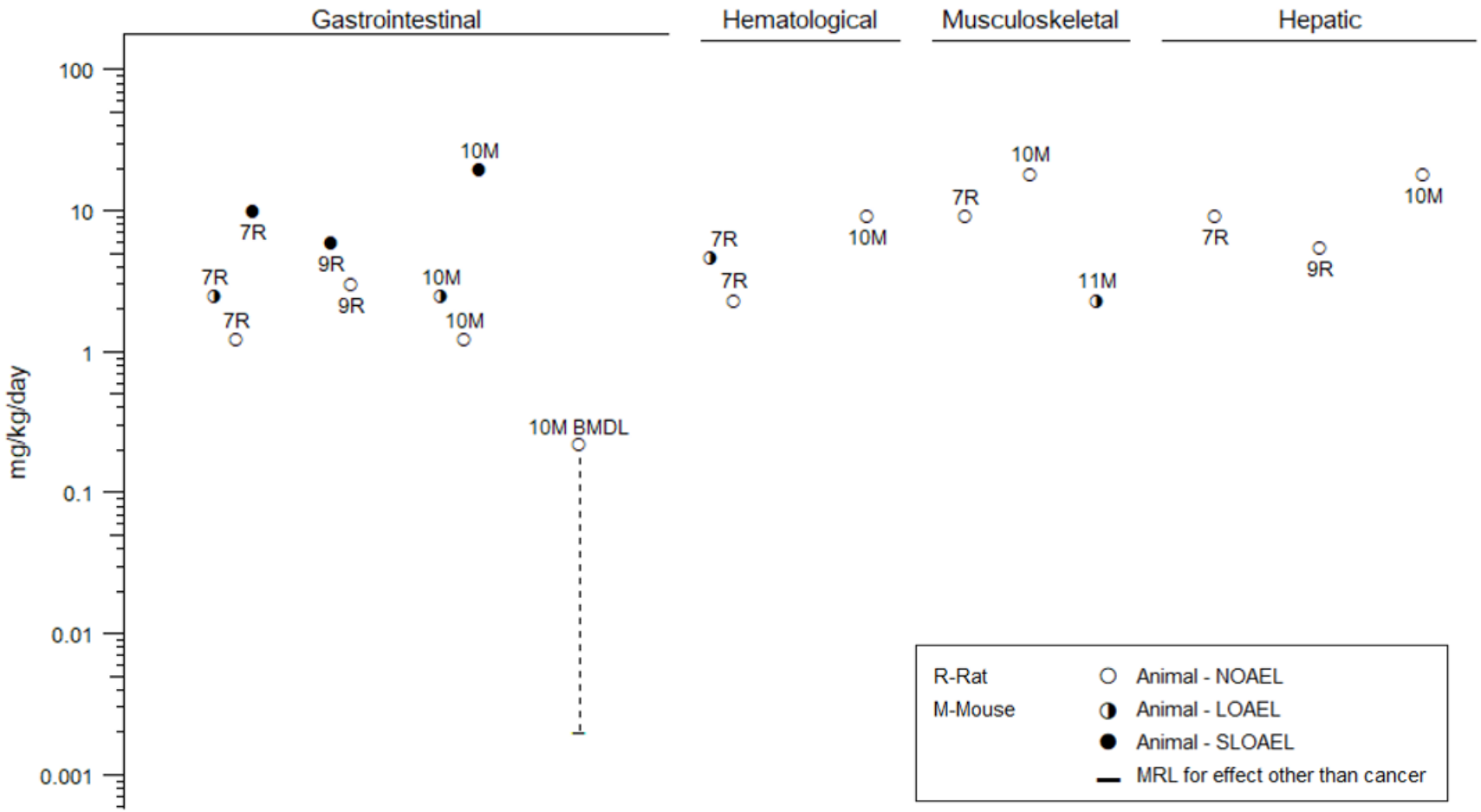


Figure 2-3. Levels of Significant Exposure to Acrolein – Oral
Intermediate (15–364 days)

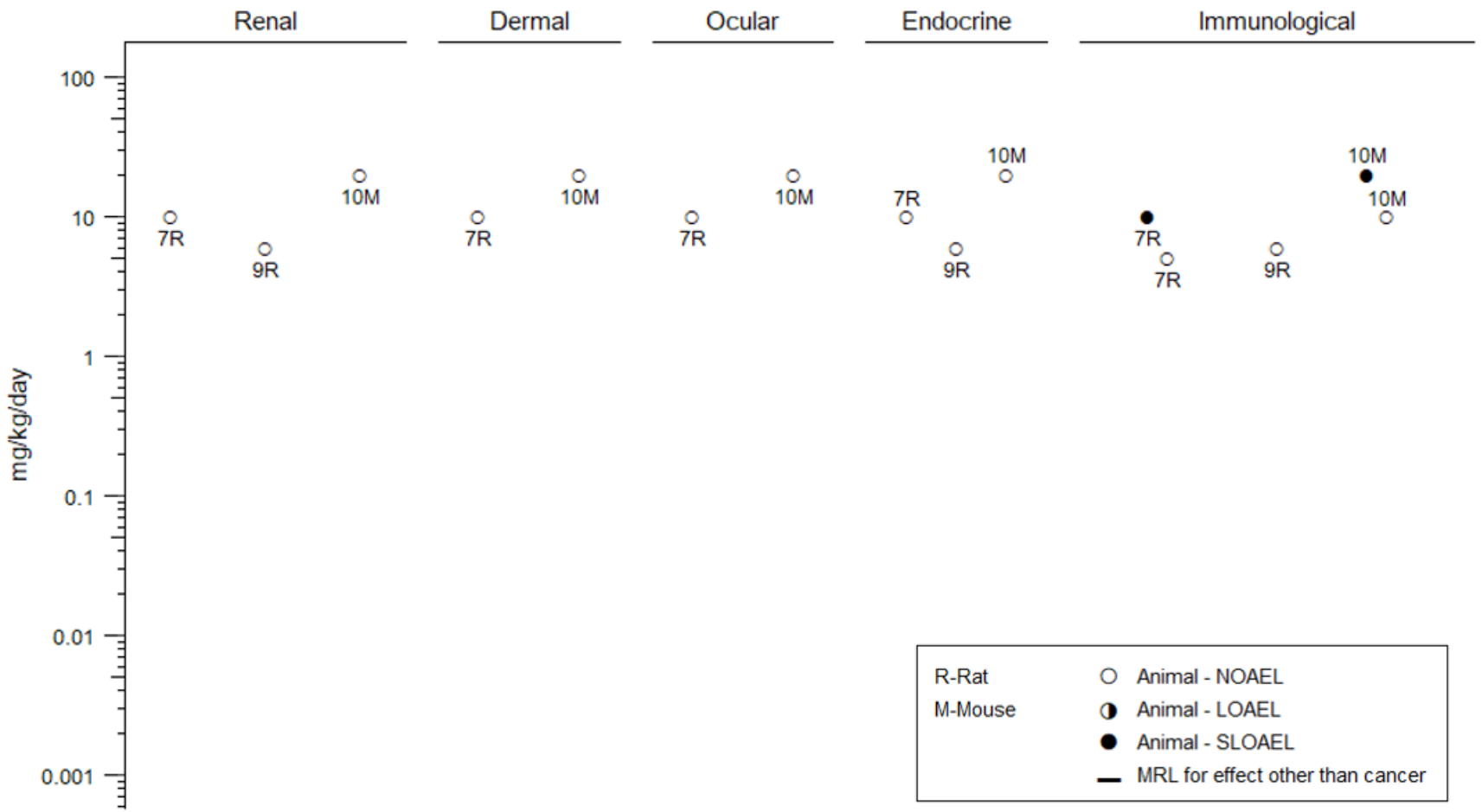


Figure 2-3. Levels of Significant Exposure to Acrolein – Oral
Intermediate (15–364 days)

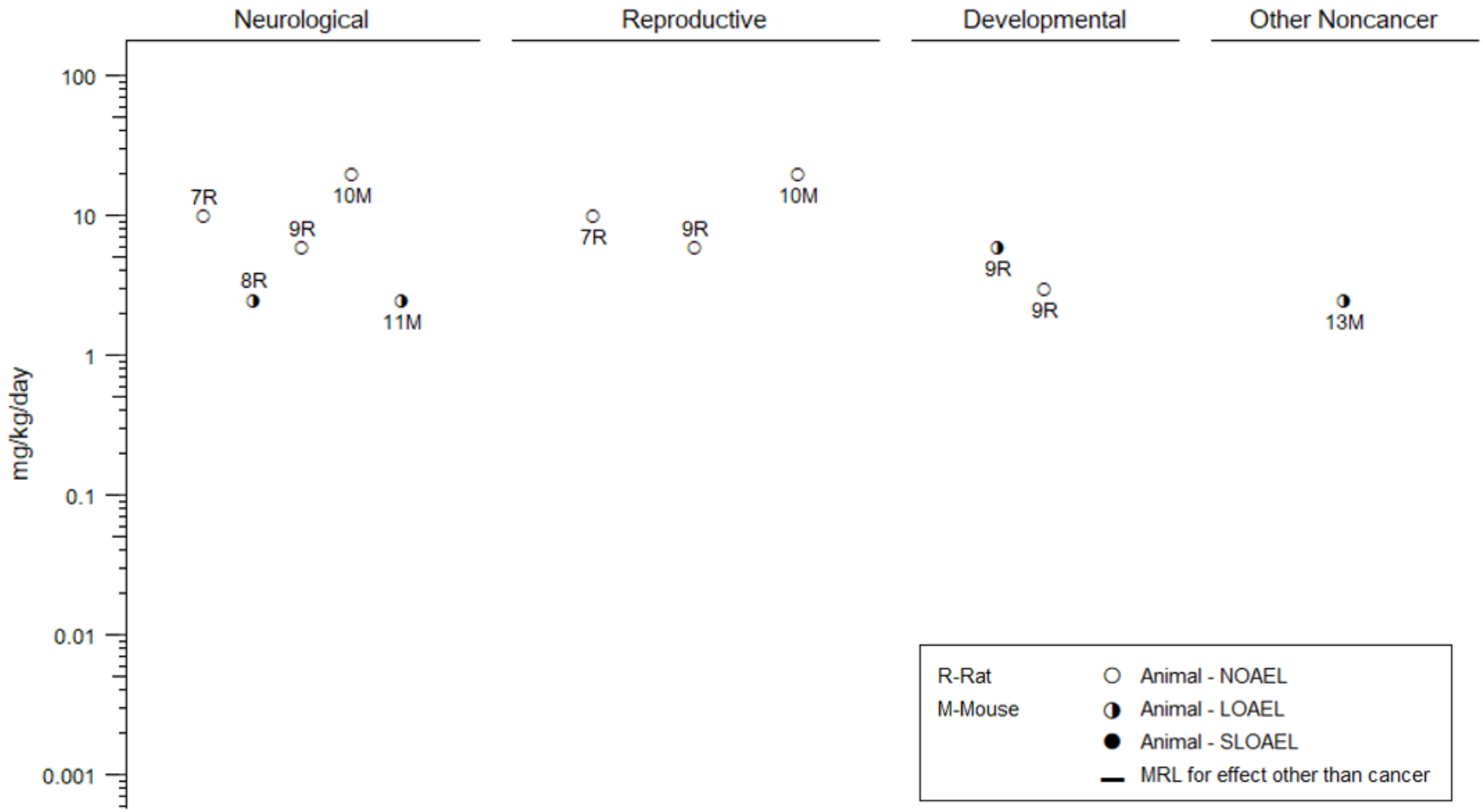


Figure 2-3. Levels of Significant Exposure to Acrolein – Oral
Chronic (≥365 days)

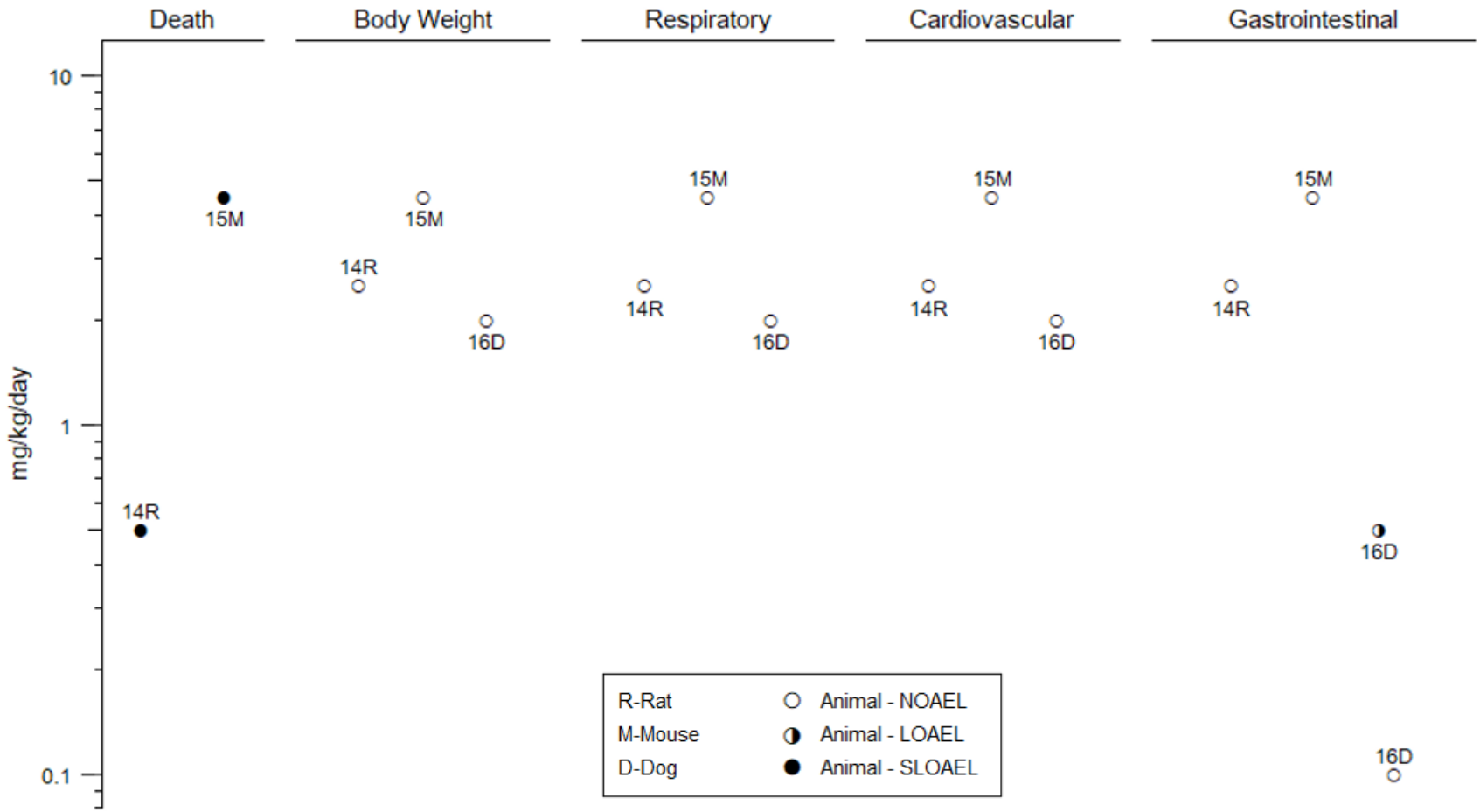


Figure 2-3. Levels of Significant Exposure to Acrolein – Oral
Chronic (≥365 days)

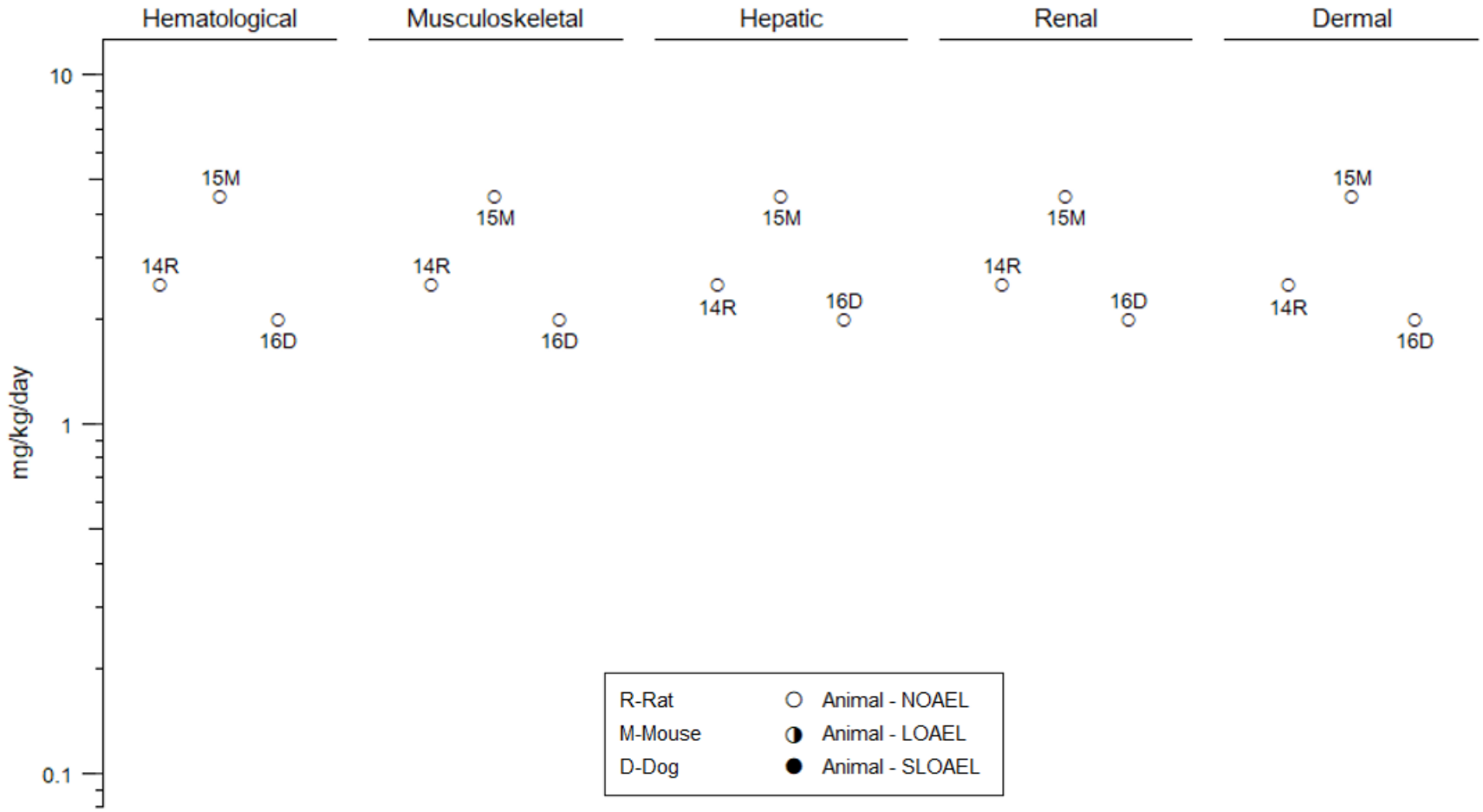


Figure 2-3. Levels of Significant Exposure to Acrolein – Oral
Chronic (≥365 days)

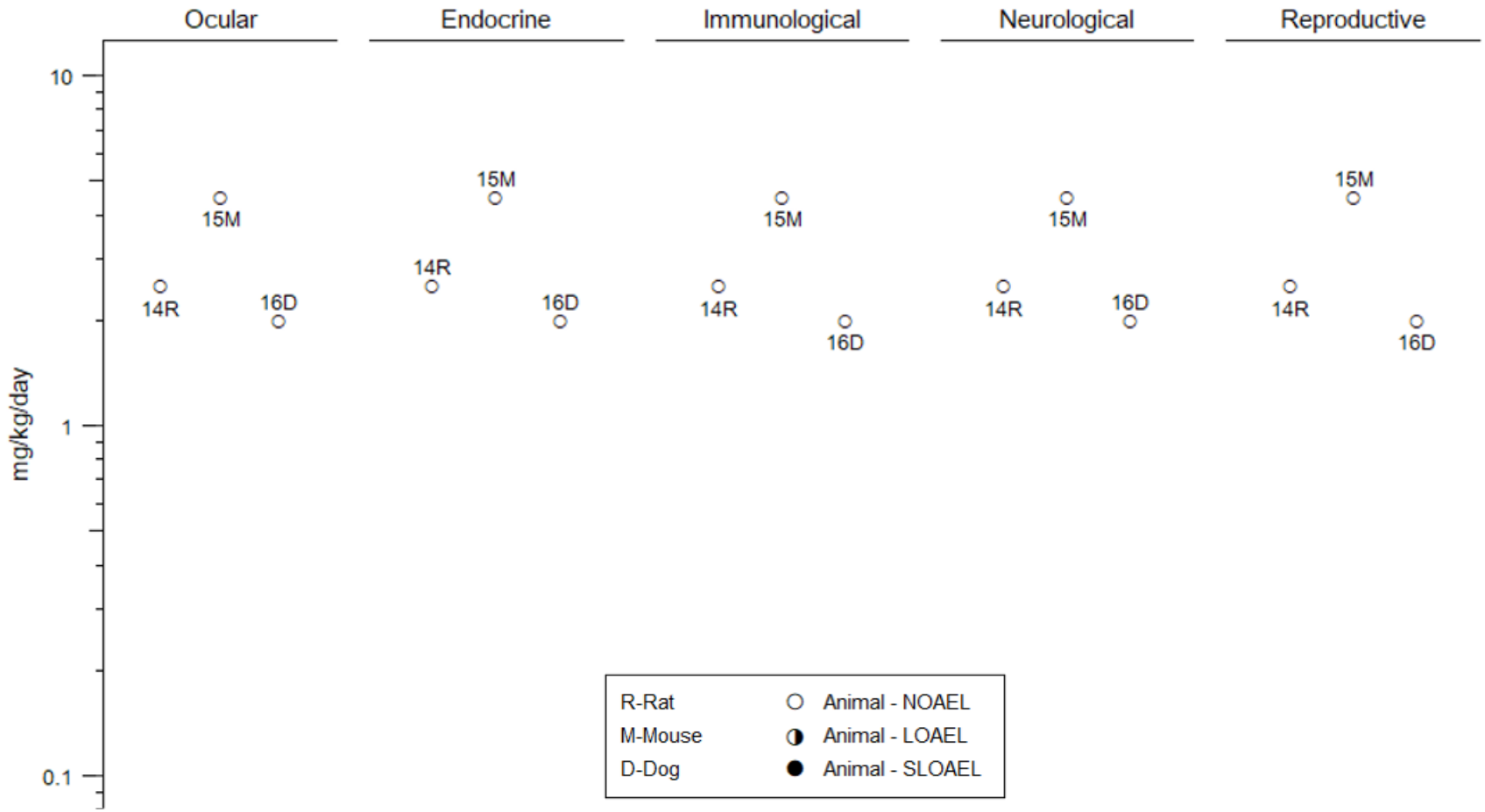


Table 2-3. Levels of Significant Exposure to Acrolein – Dermal

Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
ACUTE EXPOSURE								
Dwivedi et al. 2015								
Human 9 M, 9 F	2 hours	0, 0.05, 0.11 ppm	CS	Ocular	0.05	0.11		Eye irritation (blink rate and subjective symptoms)
Lacroix et al. 1976								
Human NS	Once	10%	CS, HP	Dermal			10	Severe skin irritation
Sim and Pattle 1957								
Human 24 M	5–10 minutes	0.81, 1.22 ppm	CS	Ocular		0.81		Eye irritation (lacrimation)
Weber-Tschopp et al. 1977								
Human 21 M, 25 F	1 hour	0, 0.3 ppm	CS	Ocular		0.3		Eye irritation (blink rate)
Ballantyne et al. 1989								
Rat (Sprague-Dawley) 5 M, 5 F	1 hour	14, 22, 24, 31, 81	LE	Ocular		14		Eye irritation (lacrimation)
Ballantyne et al. 1989								
Rat (Sprague-Dawley) 5 M, 5 F	4 hours	4.8, 7, 9.1, 12.1	LE	Ocular		4.8		Eye irritation (lacrimation)
Murphy et al. 1964								
Rat (Sprague-Dawley) 20 M	4 hours	0, 12 ppm	CS	Ocular			12	Severe eye irritation
Dachir et al. 2015								
Rabbit (New Zealand) 8–12 F	4 minutes	10, 20, 30 µL	CS, OP, HP	Ocular		10	30	LOAEL: Corneal erosions SLOAEL: Severe inflammation, corneal erosions, edema

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

Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Gupta et al. 2020								
Rabbit (New Zealand) 6 B	1–5 minutes	0, 30 µL	OP, HP	Ocular			30	Severe eyelid swelling and inflammation, corneal opacity, excessive tear secretion, corneal edema
Skog 1950								
Rat (NS) 8 NS	30 minutes	44–305	CS, GN, HP	Ocular			44	Lacrimation
INTERMEDIATE EXPOSURE								
Lyon et al. 1970								
Monkey (Squirrel) 7–9 M	6 weeks 5 days/week 8 hours/day	0, 0.7, 3.7 ppm	CS	Ocular	0.7	3.7		Eye irritation (frequent blinking, eyes closed)
Lyon et al. 1970								
Monkey (Squirrel) 8–17 M	90 days 24 hours/day	0, 0.22, 1.0, 1.8 ppm	CS	Ocular	0.22	1		Eye irritation (eyes closed)
Lyon et al. 1970								
Rat (Sprague-Dawley) 7 M, 8 F	6 weeks 5 days/week 8 hours/day	0, 0.7, 3.7 ppm	CS	Ocular	3.7			
Lyon et al. 1970								
Rat (Sprague-Dawley) 7–15 M, 8–15 F	90 days 24 hours/day	0, 0.22, 1.0, 1.8 ppm	CS	Ocular	1.8			
Lyon et al. 1970								
Dog (Beagle) 2 M	6 weeks 5 days/week 8 hours/day	0, 0.7, 3.7 ppm	CS	Ocular	0.7	3.7		Eye irritation (blinking rate, eyes closed)
Lyon et al. 1970								
Dog (Beagle) 2–4 M	90 days 24 hours/day	0, 0.22, 1.0, 1.8 ppm	CS	Ocular	0.22	1		Eye irritation (ocular discharge)

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

Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Feron et al. 1978								
Hamster (Golden Syrian) 10 M, 10 F	13 weeks 5 days/week 6 hours/day	0, 0.4, 1.4, 4.9 ppm	CS	Ocular	1.4	4.9		Eye irritation (eyes closed)
Lyon et al. 1970								
Guinea pig (Hartley) 7 M, 8 F	6 weeks 5 days/week 8 hours/day	0, 0.7, 3.7 ppm	CS	Ocular	3.7			
Lyon et al. 1970								
Guinea pig (Hartley) 6–15 M, 8–15 F	90 days 24 hours/day	0, 0.22, 1.0, 1.8 ppm	CS	Ocular	1.8			

B = both males and females; CS = clinical signs; F = female(s); GN = gross necropsy; HP = histopathology; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); NOAEL = no-observed-adverse-effect level; OP = ophthalmology; SLOAEL = serious lowest-observed-adverse-effect level

2.2 DEATH

No studies were located regarding lethality in humans after exposure to acrolein from any route.

The data in experimental animals clearly indicate that respiratory toxicity is a primary cause of acrolein lethality following inhalation exposure and show an inverse relationship between the exposure concentration and the time it takes for death to occur after acute-duration exposures. Skog (1950) identified a 30-minute inhalation LC_{50} of 0.3 mg/L (130 ppm) in rats, while Ballantyne et al. (1989) reported 1- and 4-hour LC_{50} values of 26 and 8.3 ppm, respectively, in rats. A 30-minute inhalation LC_{50} of 225 ppm was reported for mice wherein wild-type males were more sensitive than females, but no age-related effects were observed (Conklin et al. 2017a). Increased mortality was seen in male mice exposed for 30 minutes to 75 ppm (100%) and 50 ppm (60%), and in female mice at 75 ppm (79%) within 5 days after treatment; no deaths were seen in females at 50 ppm (Bein et al. 2021).

Intermediate-duration inhalation studies have also reported 40–60% increases in mortality, particularly in rats exposed to acrolein concentrations ≥4 ppm (Costa et al. 1986; Feron et al. 1978; Kutzman et al. 1984, 1985; NTP 1981). Exposure to 4 ppm resulted in 100% mortality in a hypertension-sensitive rat strain, while a hypertension-resistant strain was somewhat protected (only 40% within 62 days of treatment) (Kutzman et al. 1984). No mortality was observed in rats exposed up to 1.733 ppm for 13 weeks (Dorman et al. 2008). Two out of 7 monkeys died following intermittent exposure to 3.7 ppm acrolein for 6 weeks (8 hours/day, 5 days/week), but no treatment-related deaths occurred in similarly treated dogs, guinea pigs, or rats, or in animals continuously exposed at lower concentrations for a longer period (≤1.8 ppm, 24 hours/day for 90 days) (Lyon et al. 1970). Weighted concentrations were calculated to compare the continuous (162 ppm-days) and intermittent (37 ppm-days) concentrations above and suggest that the monkeys were more sensitive. No exposure-related deaths occurred in rabbits and hamsters exposed to 4.9 ppm for 13 weeks (Feron et al. 1978) or in hamsters exposed to 4 ppm acrolein for 52 weeks (Feron and Kruysse 1977). In a 2-year chronic-duration inhalation study, only female rats had decreased survival at 2 ppm, while male rats and male and female mice had rates similar to controls (Matsumoto et al. 2021).

Increased mortality has also been reported following oral exposure to acrolein. Two oral LD_{50} values have been reported for acrolein: 10 mg/kg in female Wistar rats (Draminski et al. 1983) and 46 mg/kg in unspecified rats (Smyth et al. 1951). Additional acute-duration studies have observed >40% mortality with single gavage doses of 10 or 25 mg/kg in rats (Sakata et al. 1989; Sprince et al. 1979), although no

mortality was observed in mice given a single gavage dose of 5 mg/kg (Conklin et al. 2010). All Beagle dogs gavaged with 2.5 mg/kg/day (for 3 days), 5 mg/kg/day (for 2 days), or 10 mg/kg/day (once) were euthanized due to weight loss, excessive vomiting, or moribund state (Parent et al. 1992b). No mortality was observed in rats gavaged with 2.5 mg/kg/day for 8 weeks (Huang et al. 2013), or in mice gavaged with 1 mg/kg/day for 48 days (Ismahil et al. 2011). Parent et al. (1992b) (the range finding portion), Smyth et al. (1951), and Sakata et al. (1989) were not included in Table 2-2 or plotted in Figure 2-2 because of limited reporting or the absence of a control group.

Increased maternal mortality (30%) was observed in pregnant rats gavaged with 10 mg/kg/day on gestation days (GDs) 7–19 (EPA 1983), although no treatment-related deaths were observed in rabbits gavaged with 2 mg/kg/day on GDs 7–19 (Parent et al. 1993). In a set of 2-generation reproductive studies, increased mortality (20% in F0, 19% in F1) was observed in male and female rats gavaged with 6 mg/kg/day (Parent et al. 1992c).

Increased mortality (80–100% incidence) was also observed in rats (10 mg/kg/day) and mice (20 mg/kg/day) gavaged for 14 weeks (Auerbach et al. 2008; NTP 2006a), in male (but not female) mice (28% incidence) gavaged with 4.5 mg/kg/day for 18 months (Parent et al. 1991a), and in female (but not male) rats (incidence not reported) gavaged with 2.5 mg/kg/day for 106 weeks (Parent et al. 1992a). The overall survival rate was not affected in dogs exposed to 1.5–2 mg/kg/day by capsule dosing for 53 weeks (Parent et al. 1992b).

2.3 BODY WEIGHT

No studies were located regarding body weight changes in humans after inhalation, oral, or dermal exposure to acrolein.

Mixed results have been reported regarding body weight changes following inhalation exposure to acrolein. Decreased body weights (10–30%) have been observed following intermediate-duration exposure to concentrations as low as 0.55 ppm in rats (Bouley et al. 1975; Costa et al. 1986; Dorman et al. 2008; Feron et al. 1978; Kutzman et al. 1984; Leach et al. 1987; Lyon et al. 1970) and 4.9 ppm in rabbits and hamsters (Feron et al. 1978). In the Feron et al. (1978) study, decreased food consumption in rats and rabbits may have contributed to the observed body weight decrements. Exposure to acrolein for 2 years (5 days/week, 6 hours/day) resulted in decreased body weight in male rats (12% at 2 ppm) and male mice (17% at 1.6 ppm); no changes in body weights were seen in female rats or mice at these

concentrations (Matsumoto et al. 2021). Body weight was decreased by 10–11% in hamsters chronically exposed to 4 ppm acrolein for 52 weeks (Feron and Kruysse 1977). No differences in body weights were observed in guinea pigs, dogs, or monkeys intermittently exposed up to 3.7 ppm for 8 hours/day, 5 days/week for 6 weeks or exposed continuously up to 1.8 ppm for 90 days (Lyon et al. 1970). Similarly, no change in body weight was reported in hypertension-sensitive rats exposed to 1.4 ppm for 6 hours/day, 5 days/week for 62 days (Kutzman et al. 1984) or in rats exposed up to 1.07 ppm for 3 weeks (Leach et al. 1987). No changes in body weights were observed in mice exposed up to 1 ppm acrolein for 12 weeks (Conklin et al. 2017b).

No body weight changes were observed in mice gavaged with a single dose of up to 5 mg/kg (Conklin et al. 2010). Maternal extra-gestational body weight gain (final body weight-gravid uterus weight and initial body weight) was decreased 36% in pregnant rats gavaged with 6 mg/kg/day on GDs 7–19 compared to controls (EPA 1983). Rabbits gavaged with 2 mg/kg/day on GDs 7–19 exhibited reduced body weights early in the dosing schedule (GDs 7–10) but returned to weights similar to controls at the end of dosing (Parent et al. 1993). In a 2-generation reproductive study, no changes in body weights were observed in rats gavaged with up to 6 mg/kg/day (Parent et al. 1992c).

Decreased body weights were observed in male (22%) and female (10%) rats gavaged with 10 mg/kg/day for 14 weeks, but not in similarly exposed male and female mice (Auerbach et al. 2008; NTP 2006a). Mice gavaged with 2.5 mg/kg/day for 4 weeks showed a 15% decrease in body weight (Chen et al. 2019), although no difference in body weight was observed in mice gavaged with 1 mg/kg/day for 48 days (Ismahil et al. 2011) or in rats gavaged with 2.5 mg/kg/day for 8 weeks (Huang et al. 2013). No differences in body weights were observed in dogs given 2 mg/kg/day for 12 months (Parent et al. 1992b), in male and female mice gavaged with 4.5 mg/kg/day for 18 months (Parent et al. 1991a), or in rats gavaged with 2.5 mg/kg/day for 2 years (Parent et al. 1992a).

2.4 RESPIRATORY

Although human data are limited and often lack the necessary exposure information, the available studies point to the respiratory system as the primary target of inhaled acrolein. Several epidemiological studies have evaluated potential associations between acrolein exposure and reporting of respiratory symptoms, prevalence of asthma, and decrements in pulmonary function. Indoor acrolein concentrations were associated with self-reported sick building syndrome, including respiratory irritation symptoms (Sakellaris et al. 2021). Case reports of occupational workers exposed to acrolein have also reported

symptoms of respiratory toxicity. A case report details an aquatic pesticide worker who experienced throat tightness, difficulty breathing, inability to swallow, moderate phlegm production, and dyspnea following exposure to an unknown amount of acrolein, while two additional workers also experienced dyspnea (CDC 2013). In an occupational accident, an employee sprayed in the face and who breathed in high concentration of acrolein experienced dyspnea and chemical pneumopathy (Champeix et al. 1966). An association between indoor acrolein concentrations and increased prevalence of asthma was observed in a cross-sectional study of school children in France (Annesi-Maesano et al. 2012). Similar findings were reported in a general population study in the United States, where outdoor air concentrations of acrolein (0.05–0.46 $\mu g/m^3$) were associated with an increase in the prevalence of having at least one asthma attack in the prior year (deCastro et al. 2014). A case-control study of children with asthma in China, reported an increase in the probability of asthma associated with concentrations of a urinary metabolite of acrolein (3-hydroxypropylmercapturic acid [3-HPMA]) (Kuang et al. 2021). An increase in the concentration of urinary acrolein metabolites (3-HPMA and N-acetyl-S-(2-carboxyethyl)-L-cysteine [also known as carboxyethyl mercapturic acid or CEMA]) was also associated with decreased forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV1) in an urban population in China (Wang et al. 2022). It should be noted that urinary 3-HPMA is not a specific biomarker for acrolein exposure and does not provide a means of distinguishing between exogenous and endogenous acrolein (see Section 3.3.1, Biomarkers of Exposure).

Human controlled exposure studies have also evaluated the respiratory effects of inhaled acrolein. Volunteers exposed to increasing levels of acrolein vapors for 40 minutes reported significant nose irritation at 0.26 ppm, throat irritation at 0.43 ppm, and a decrease in respiratory rate (25%) at 0.60 ppm (Weber-Tschopp et al. 1977). Severity of irritation was subjectively scored as “not at all” to “a little.” No significant difference was observed between controls and subjects exposed to 0.17 ppm. In the same study, nasal irritation was reported by subjects exposed to 0.6 ppm acrolein for 1.5 minutes, following prior exposure to lower concentrations (0.15, 0.30, and 0.45 ppm; 8-minute recovery between exposures). These experiments were not presented in Table 2-1 and Figure 2-2 due to changing exposure concentrations over time (continuous exposure) or exposure of the same subjects to multiple exposure concentrations (discrete exposure). The irritation response was reported to be stronger for continuous exposure compared to discrete exposure at the same concentration, suggesting that irritation severity increases over time with cumulative exposure (Weber-Tschopp et al. 1977). Constant exposure to 0.3 ppm acrolein for 60 minutes resulted in reports of mild nose irritation shortly after onset of exposure, while throat irritation was reported after 10 minutes (Weber-Tschopp et al. 1977). A significant decrease in respiratory rate (20%) occurred after 60 minutes of exposure to 0.3 ppm (Weber-Tschopp et al. 1977).

No change in pulmonary function (FVC, FEV1) or breathing frequency was observed in volunteers exposed to 0.11 ppm for 2 hours (Dwivedi et al. 2015).

The overall evidence from acute-, intermediate-, and chronic-duration inhalation studies in experimental animals indicates that the respiratory system is the primary target for acrolein. Acute-duration exposures for ≤1 hour at concentrations ≥0.3 ppm resulted in respiratory irritation, decreased pulmonary function, increased albumin in nasal lavage fluid (Morris 1996), increased lung weight, and respiratory tract histopathology in rats, mice, and guinea pigs (see Tables 2-4, 2-5, and 2-6). Changes in respiratory function persisted following removal of exposure (Conklin et al. 2017a). Several RD_{50} values (the concentration that suppresses the respiratory rate by 50%) are available for acrolein, ranging from 4.6 to 9.2 ppm in rats and from 1.03 to 2.9 ppm in mice (see Table 2-7). Acute-duration exposures for ≤1 hour at concentrations ≥250 ppm, resulted in labored breathing and lung edema (Conklin et al. 2017a; Skog 1950). Conklin et al. (2017a) found more effects in the upper airway as opposed to the lower airway and female rats showed less extreme nasal congestion and buildup of albumin in the lungs as evidenced by reduced conversion to mouth breathing compared to male rats following inhalation of high concentrations of acrolein.

Table 2-4. Respiratory Lesions in Animals Following Inhalation Exposure to Acrolein

Species; duration	Concentration (ppm)	Histology	Lesion details	Reference
Acute-duration				
Wistar rat; 3 days, 6 hours/day	0.25	↑	Nasal lesions (disarrangement and thickening of the respiratory epithelium, basal cell hyperplasia)	Cassee et al. 1996a
Fischer-344 rat; 14 days, 6 hours/day	0.586	↑	Nasal respiratory epithelial hyperplasia and epithelial squamous metaplasia in limited tissues	Dorman et al. 2008
Wistar rat; 6 hours	1.4	↔	Nasal cavity	Cassee et al. 1996a
Swiss Webster mouse; 5 days, 6 hours/day	1.7	↑ ↔	Nasal lesions (ulceration, necrosis, and squamous metaplasia of respiratory and olfactory epithelium) Trachea, lungs	Buckley et al. 1984

Table 2-4. Respiratory Lesions in Animals Following Inhalation Exposure to Acrolein

Species; duration	Concentration (ppm)	Histology	Lesion details	Reference
Fischer-344 rat; 14 days, 6 hours/day	1.8	↑	Olfactory epithelial atrophy (dorsal meatus, septum, ethmoid turbinate)	Dorman et al. 2008
Wistar rat; 4 hours	2	↑	Lung lesions (epithelial cell sloughing and mononuclear cells in the bronchioles, hyperemia, emphysema)	Arumugam et al. 1999a
C57BL/6J mouse; 3 days, 6 hours/day	5	↔	Lungs	Kasahara et al. 2008
Hotzman rat; 4 hours	8	↑	Pulmonary edema, inflammation	Murphy 1965
C57BL/6J mouse; 12 hours	10	↑	Lung lesions (air space enlargement)	Kim et al. 2020
129X1/SvJ mouse; 6–17 hours	10	↑	Lung lesions (perivascular enlargement, leukocyte infiltration)	Leikauf et al. 2011
SM/J mouse; 6–17 hours	10	↑	Lung lesions (perivascular enlargement, leukocyte infiltration)	Leikauf et al. 2011
Rat (NS); 30 minutes	44–305	↑	Lung lesions (edema, hyperemia, and hemorrhages, degenerative changes in the bronchial epithelium)	Skog 1950
B6C3F1 mouse; 30 minutes	50 M 75 F	↑	Lung lesions (alveolar wall thickening, proteinaceous deposit, leukocyte infiltrates)	Bein et al. 2021
C57BL/6J mouse; 30 minutes	250	↑	Nasal and tracheal lesions (epithelial sloughing, mucus accumulation, inflammatory cell infiltration)	Conklin et al. 2017a
Intermediate-duration				
Beagle dog; 90 days continuously	0.22	↑	Emphysema, acute congestion, focal vacuolization of the bronchiolar epithelial cells, constriction of the bronchioles	Lyon et al. 1970

Table 2-4. Respiratory Lesions in Animals Following Inhalation Exposure to Acrolein

Species; duration	Concentration (ppm)	Histology	Lesion details	Reference
Fischer-344 rat; 13 weeks, 5 days/week, 6 hours/day	0.586	↑ ↑	Nasal lesions (respiratory epithelial hyperplasia [dorsal meatus and lateral wall] and epithelial squamous metaplasia [lateral wall]), most resolving with post-exposure recovery period Laryngeal lesions (respiratory epithelial squamous metaplasia)	Dorman et al. 2008
Squirrel monkey; 6 weeks, 5 days/week, 8 hours/day	0.7	↑	Chronic inflammation of the lung	Lyon et al. 1970
Sprague-Dawley rat; 6 weeks, 5 days/week, 8 hours/day	0.7	↑	Chronic inflammation of the lung	Lyon et al. 1970
Beagle dog; 6 weeks, 5 days/week, 8 hours/day	0.7	↑	Chronic inflammation of the lung	Lyon et al. 1970
Hartley guinea pig; 6 weeks, 5 days/week, 8 hours/day	0.7	↑	Chronic inflammation of the lung	Lyon et al. 1970
Sprague-Dawley rat; 90 days continuously	1.0	↑	Pulmonary hemorrhage	Lyon et al. 1970
Hartley guinea pig; 90 days continuously	1.0	↑	Pulmonary inflammation	Lyon et al. 1970
Wistar rat; 13 weeks, 5 days/week, 6 hours/day	1.4	↑ ↔	Nasal lesions (squamous metaplasia, neutrophilic infiltration) Lungs	Feron et al. 1978
Syrian hamster; 13 weeks, 5 days/week, 6 hours/day	1.4	↑ ↔	Nasal lesions (inflammation) Lungs	Feron et al. 1978

Table 2-4. Respiratory Lesions in Animals Following Inhalation Exposure to Acrolein

Species; duration	Concentration (ppm)	Histology	Lesion details	Reference
Fischer-344 rat; 13 weeks, 5 days/week, 6 hours/day	1.8	↑ ↑	Nasal lesions (respiratory epithelial hyperplasia; respiratory and olfactory epithelial squamous metaplasia) throughout the nose Lesions in the larynx (epithelial inflammation; olfactory epithelial squamous metaplasia) and trachea (olfactory epithelial squamous metaplasia)	Dorman et al. 2008
Squirrel monkey; 90 days, continuously	1.8	↑	Tracheal squamous metaplasia and basal cell hyperplasia	Lyon et al. 1970
Sprague-Dawley rat; 3 weeks, 5 days/week, 6 hours/day	3.0	↑ ↔	Nasal lesions (squamous metaplasia and degeneration of the respiratory epithelium, neutrophil infiltration, degeneration and atrophy of the olfactory epithelium) Lungs	Leach et al. 1987
Sprague-Dawley rat; 4 weeks, 5 days/week, 5 hours/day	3.1	↑	Laryngeal lesions (epithelial sloughing, cell death, edema)	Liu et al. 2019
Squirrel monkey; 6 weeks, 5 days/week, 8 hours/day	3.7	↑	Hemorrhagic spots in lungs	Lyon et al. 1970
Fischer-344 rat; 62 days, 5 days/week, 6 hours/day	4.0	↑	Bronchiolar epithelial necrosis, bronchiolar edema fluid, acute rhinitis, tracheal edema	Costa et al. 1986; Kutzman et al. 1985; NTP 1981
Dutch rabbit; 13 weeks, 5 days/week, 6 hours/day	4.9	↑ ↑ ↑	Nasal lesions (necrotizing rhinitis, neutrophilic infiltration) Lung lesions (bronchitis, hyperplasia, metaplasia) Tracheal lesions (hyperplastic epithelium, mucus cells)	Feron et al. 1978
Chronic-duration				
B6D2F1/Crlj mouse; 2 years, 5 days/week, 6 hours/day	0.4	↑ F	Nasal lesions (inflammation, hyperplasia, metaplasia, regeneration)	Matsumoto et al. 2021

Table 2-4. Respiratory Lesions in Animals Following Inhalation Exposure to Acrolein

Species; duration	Concentration (ppm)	Histology	Lesion details	Reference
Fischer-344/DuCrlCrlj rat; 2 years, 5 days/week, 6 hours/day	2.0	↑	Nasal lesions (inflammation, metaplasia, eosinophilic changes, goblet cell hyperplasia)	Matsumoto et al. 2021
B6D2F1/Crlj mouse; 2 years, 5 days/week, 6 hours/day	1.6	↑ M	Nasal lesions (inflammation, hyperplasia, metaplasia, regeneration)	Matsumoto et al. 2021
Syrian hamster; 52 weeks, 5 days/week, 7 hours/day	4	↑ ↔	Nasal lesions (inflammation and epithelial metaplasia, neutrophilic infiltrates, submucosa thickening) Lungs	Feron and Kruysse 1977

↑ = increase in histopathological lesions; ↔ = no change; F = female(s); F-344 = Fischer-344; M = male(s); NS = not specified

Table 2-5. Respiratory Function in Animals Following Inhalation Exposure to Acrolein

Species; duration	Concentration (ppm)	Effect	Respiratory function	Reference
Acute-duration				
Guinea pig (NS); 2 hours	0.6	↑ ↓	Resistance, tidal volume Respiration rate	Murphy et al. 1963
C57BL/6N mouse; 10 minutes	1.3	↑ ↓	Resistance Respiration rate	Morris et al. 2003
Spontaneous hypertensive rat; 3 hours	2.9	↑	Decreased breathing frequency, increased expiratory time	Perez et al. 2015
Sprague-Dawley rat; 3 hours	3.0	↑ ↓	Respiratory irritation (upper and lower airways) Respiration rate	Hazari et al. 2008
Spontaneous hypertensive rat; 3 hours	3	↑	Increased breathing frequency and minute volume	Perez et al. 2013

Table 2-5. Respiratory Function in Animals Following Inhalation Exposure to Acrolein

Species; duration	Concentration (ppm)	Effect	Respiratory function	Reference
WKY rat; 3 hours	3	↔		Perez et al. 2013
C57BL/6 mouse; 6 hours	3	↑	Expiratory time, tidal volume	Kurhanewicz et al. 2017
		↓	Respiration rate	
Wistar rat; 1–2 days, 4 hours/day	4	↑	Inspiratory and expiratory time, labored breathing	Snow et al. 2017
		↔	Breathing frequency, minute volume, tidal volume	
Sprague-Dawley rat; 4 hours	4.8	↓	Decreased breathing rate and a conversion to mouth breathing	Ballantyne et al. 1989
Sprague-Dawley rat; 60 minutes	14	↓	Decreased breathing rate and a conversion to mouth breathing	Ballantyne et al. 1989
Guinea pig (NS); 60 minutes	17	↑	Resistance, tidal volume	Davis et al. 1967
		↓	Respiration rate, minute volume	
C57BL/6J mouse; 30 minutes	250	↑	Expiratory and inspiratory time	Conklin et al. 2017a
		↓	Respiration rate	
Intermediate-duration				
Fischer-344 rat; 62 days, 5 days/week, 6 hours/day	4	↑	Resistance, tidal volume	Costa et al. 1986; Kutzman et al. 1985; NTP 1981
		↓	Respiration rate	

↑ = increase; ↓ = decrease; ↔ = no change; NS = not specified; WHY = Wistar Kyoto

Table 2-6. Lung Weight in Animals Following Inhalation Exposure to Acrolein

Species; duration	Concentration (ppm)	Effect	Percent change	Reference
Acute-duration				
Hotzman rats; 4 hours	8	↑	19% (relative)	Murphy 1965
C57BL/6J mouse; 30 minutes	250	↑	75% (males)	Conklin et al. 2017a

Table 2-6. Lung Weight in Animals Following Inhalation Exposure to Acrolein

Species; duration	Concentration (ppm)	Effect	Percent change	Reference
Intermediate-duration				
C57BL/6J mouse; 12 weeks, 5 days/week, 6 hours/day	1	↔		Conklin et al. 2017b
Wistar rat; 13 weeks, 5 days/week, 6 hours/day	1.4	↑ ↑	13% (males) 26% (females)	Feron et al. 1978
Syrian hamster; 13 weeks, 5 days/week, 6 hours/day	1.4	↑ ↑	34% (males) 18% (females)	Feron et al. 1978
Fischer-344 rat; 62 days, 5 days/week, 6 hours/day	4	↑	66%	Costa et al. 1986; Kutzman et al. 1985; NTP 1981
Dutch rabbit; 13 weeks, 5 days/week, 6 hours/day	4.9	↔		Feron et al. 1978

↑ = increase in lung weight; ↔ = no change in lung weight; NS = not specified; OFA = Oncins France Strain A

Table 2-7. RD_{50} Values in Animals Following Inhalation Exposure to Acrolein

Species; duration	Concentration (ppm)	RD_{50} (ppm)	Reference
Acute-duration			
B6C3F1 mouse; 10 minutes	0.04–8	1.41	Steinhagen and Barrow 1984
Swiss Webster mouse; 10 minutes	0.04–8	1.03	Steinhagen and Barrow 1984
C57BL/6J mouse; 10 minutes	0.3–3.9	1.59	Morris et al. 2003
Swiss Webster mouse; 10 minutes	0–10	1.7	Kane and Alarie 1977
CF-1 mouse; 30 minutes	0.85–7.25	2.9	Nielsen et al. 1984
Wistar rat; 20 minutes	6.7–54	4.6	Bergers et al. 1996
Fischer-344 rats; 10 minutes	0.5–10	6	Babiuk et al. 1985
Wistar rats; 30 minutes	1.7–32	9.2	Cassee et al. 1996b

RD_{50} = exposure concentration producing a 50% respiratory rate decrease

Similar effects have been observed at the highest concentrations following acute-duration acrolein exposures ≥1 hour, although the effects are often more severe. Decreased respiratory function, increased

lung weights, and nasal and pulmonary lesions and inflammation are commonly reported in rodent studies with the most sensitive portion being the lateral wall at level II of the nasal cavity (see Tables 2-4, 2-5, and 2-6). Exposure to 2.9 ppm acrolein for 3 hours altered the breathing frequency, minute volume, and expiratory time in a spontaneous hypertensive rat model, but not in the similarly exposed normotensive rat line (Perez et al. 2013, 2015), suggesting a relationship between the observed respiratory and cardiovascular effects. Similar effects were observed in another study, where the incidence of mild, terminal bronchiolar hyperplasia occurred at a higher incidence in hypertension-sensitive rats compared to hypertension-resistant rats; however, the concentration at which these effects occurred was not clearly reported (Kutzman et al. 1984).

Nasal lesions including ulceration, necrosis, inflammation, and squamous hyperplasia and metaplasia of the respiratory and olfactory epithelium appear to be the most common effects of acrolein exposure following acute-, intermediate-, and chronic-duration inhalation in rodents (see Table 2-4). Additional changes in lung weights and tracheal and pulmonary histopathology have also been observed in longer-duration studies (see Tables 2-5 and 2-6). Alveolar edema was noted only in rats that died from 13-week acrolein exposure (Feron et al. 1978).

As expected, oral studies in animals do not produce the same respiratory effects observed following inhalation exposure. No histopathological changes were reported in the lungs of rats exposed to a single dose of 25 mg/kg acrolein (Sakata et al. 1989), although wheezing was observed in pregnant rats gavaged with ≥3.6 mg/kg/day for 13 days (EPA 1983). Sakata et al. (1989) was not included in Table 2-2 or plotted in Figure 2-3 because a control group was not included. Abnormal breathing (wheezing, dyspnea) was also a common observance in rats and mice following intermediate-duration gavage exposure to concentrations ≥5 mg/kg/day (Auerbach et al. 2008; NTP 2006a; Parent et al. 1992c). Additional histopathological analyses reveal lung congestion in rats gavaged with 6 mg/kg/day (Parent et al. 1992c), and acute nasal inflammation in rats gavaged with 10 mg/kg/day (Auerbach et al. 2008; NTP 2006a). In contrast, histopathological examination of the respiratory system (i.e., lungs, trachea) revealed no effects after intermediate-duration oral exposure to acrolein in rats or mice (Auerbach et al. 2008; NTP 2006a) or chronic-duration exposure in rats (Parent et al. 1992a), mice (Parent et al. 1991a), or dogs (Parent et al. 1992b).

Immunological effects of acrolein in the respiratory tract, including altered responses to allergen or bacterial challenge, are discussed in the Section 2.14 (Immunological).

Mechanisms. The molecular mechanisms of acrolein toxicity are discussed in detail in Section 2.21, Mechanisms of Toxicity. Yeager et al. (2016) proposed a mode of action for acrolein-induced respiratory effects, with a focus on respiratory effects associated with tobacco smoking (e.g., chronic obstructive pulmonary disorder [COPD]). The key events in this mode-of-action analysis, which are consistent with the mechanisms outlined in Section 2.21, are as follows: (1) direct interaction with cellular proteins and macromolecules; (2) increased oxidative stress, oxidative damage, and inflammation; and (3) cell death via apoptosis, necrosis, and oncosis (cell death by swelling); and tissue destruction and remodeling.

2.5 CARDIOVASCULAR

Human studies examining cardiovascular effects are limited, primarily due to lack of exposure information. Urinary levels of the acrolein metabolite, 3-HPMA, were associated with increased risk of cardiovascular disease (DeJarnett et al. 2014) and higher blood pressure (McGraw et al. 2021) in participants of the Louisville Healthy Heart Study. Plasma levels of 3-HPMA were also associated with cardiovascular disease diagnoses, independent of smoking status (Lorenz et al. 2021). A population-based study identified an association between urinary acrolein metabolites and dyslipidemia risk (Feng et al. 2022a).

Several acute-duration inhalation studies have identified cardiovascular effects in rodents. Exposure to 44–305 ppm acrolein for 30 minutes resulted in hyperemia of the heart in rats (Skog 1950). Blood oxygen saturation and cardiac output were decreased in male (but not female) mice exposed to 250 ppm acrolein for 30 minutes (Conklin et al. 2017a). Mice exposed to 3 ppm acrolein for 3 hours showed increased heart rate variability and an increase in the number of arrhythmias (Kurhanewicz et al. 2017, 2018), while rats experienced decreased heart rates (Hazari et al. 2008).

Following intermediate-duration exposure to acrolein, increased relative heart weights have been observed primarily in male rats (22%) and female hamsters (11%) exposed to concentrations as low as 4 ppm, but body weights were decreased at the same exposure concentrations (Feron et al. 1978; NTP 1981). In contrast, other studies in hamsters, rabbits, and mice have not identified changes in cardiovascular organ weights (Conklin et al. 2017b; Feron and Kruysse 1977; Feron et al. 1978), and no associated histopathology was found in any species. Nonspecific inflammatory changes in the heart were reported in rats, dogs, monkeys, and guinea pigs after a continuous 90-day exposure to 0.22 ppm acrolein (Lyon et al. 1970), although the toxicological significance of these changes is unknown. No alterations in

heart rate (NTP 1981) or blood pressure (Kutzman et al. 1984) were observed in rats exposed to 4 ppm acrolein for 62 days.

Mice gavaged with 1 mg/kg/day acrolein for 48 days showed signs of cardiomyopathy, including myocardial inflammation, myocyte hypertrophy and cell death, and left ventricle remodeling and dysfunction (Ismahil et al. 2011). In contrast, histopathological examination of the cardiovascular system revealed no effects after longer, intermediate-duration oral exposure to higher doses of acrolein in rats (up to 10 mg/kg/day) or mice (up to 20 mg/kg/day) (NTP 2006a; Parent et al. 1992c) or chronic-duration exposure in rats (up to 2.5 mg/kg/day), mice (up to 4.5 mg/kg/day), or dogs (up to 2 mg/kg/day) (Parent et al. 1991a, 1992a, 1992b). In addition, no changes in blood pressure were observed in rats gavaged with 2.5 mg/kg/day for 8 weeks (Huang et al. 2013). Absolute heart weight was decreased in female rats gavaged for 14 weeks with ≥5 mg/kg/day (5 days/week); however, no histological changes were seen (NTP 2006a).

Several studies have examined the cardiovascular effects of acrolein exposure in rodent models of disease, including genetic knockout animals. Exposure to 2.9 ppm acrolein for 3 hours caused decreased arterial blood oxygen and increased arterial blood carbon dioxide and heart rate in a spontaneous hypertensive rat model, but not in the similarly exposed normotensive rat line, although blood pressure was increased in both strains. (Perez et al. 2013, 2015). Other studies have looked at the effects of acrolein in a cardiovascular disease mouse model prone to atherosclerosis, apoE$^{-/-}$ mice. Gavage exposure to 2.5 mg/kg/day acrolein for 8 weeks resulted in an increase in lesions and macrophage accumulation in the aorta (Srivastava et al. 2011), while oral exposure to 3 mg/kg/day in drinking water for 1 month caused an increase in aortic cholesterol, triglycerides, and lipid peroxides (Rom et al. 2017). A knockout mouse model for an ion channel protein TRPA1 showed resistance to the cardiovascular effects observed in wild-type mice following acrolein exposure (Kurhanewicz et al. 2017, 2018).

2.6 GASTROINTESTINAL

No studies were located regarding gastrointestinal effects in humans following exposure to acrolein by any route.

Gastrointestinal effects following inhalation exposure are limited. Exposure to high concentrations (100–275 ppm) of acrolein by inhalation for 10–30 minutes caused rats, which are obligate nose breathers, to convert to mouth breathing resulting in notable air ingestion and thus proximal gastrointestinal tract

distension (morphometrically) (Conklin et al. 2017a). Other gastrointestinal tract parameters were not reported.

Gastrointestinal irritation is the primary effect of oral exposure to acrolein; no studies were located regarding gastrointestinal effects in animals following dermal exposure to acrolein. Rats administered a single gavage dose of 25 mg/kg of acrolein showed severe multifocal ulceration of the forestomach and glandular stomach 48 hours after dosing, although no controls were used for comparison. The areas of ulceration showed severe inflammation, focal hemorrhage, and edema (Sakata et al. 1989). Due to the lack of a control group, this study was not included in Table 2-2 or plotted in Figure 2-3.

Similar lesions have been observed following intermediate-duration exposure. Stomach lesions, including ulcers, hemorrhage, hyperplasia of the forestomach, and erosion of the glandular mucosa, were found in 2 generations of rats gavaged with 6 mg/kg/day (Parent et al. 1992c). Forestomach squamous epithelial hyperplasia was observed in male and female rats gavaged with ≥5 and ≥2.5 mg/kg/day, respectively, and in mice gavaged with ≥2.5 mg/kg/day for 14 weeks (Auerbach et al. 2008; NTP 2006a). At higher concentrations, glandular stomach hemorrhage was observed in rats gavaged with 10 mg/kg/day and in mice gavaged with 20 mg/kg/day, while stomach necrosis was also observed in mice (Auerbach et al. 2008; NTP 2006a).

Although the reported lesions are consistent and dose-related for intermediate-duration exposures, possible adaptation to irritating effects may have important implications for chronic-duration exposures. No significant gastrointestinal effects (i.e., histopathology) of acrolein exposure were reported in rats (Parent et al. 1992a) or mice (Parent et al. 1991a) after chronic-duration gavage dosing with up to 2.5 or 4.5 mg/kg/day, respectively. While no unusual gross or significant histological lesion in the gastrointestinal tract were observed in dogs given up to 2 mg/kg/day for 53 weeks (Parent et al. 1992b), increased incidences of vomiting were observed during and shortly after dosing (beginning at 0.5 mg/kg/day), suggesting gastrointestinal irritation. However, adaptation seemed to occur, as vomiting frequency near the end of the study was reduced compared to the first 4 weeks of the study in high-dose animals.

2.7 HEMATOLOGICAL

No studies were located regarding hematological effects in humans following exposure to acrolein by any route.

Hematological changes, particularly alterations in white blood cell counts, have been observed in rodents following inhalation exposure to acrolein. Lymphocytes were increased and neutrophils were decreased in male mice (but not female mice) exposed to 250 ppm acrolein for 30 minutes (Conklin et al. 2017a), although rats exposed to 4 ppm over 1 or 2 days had no differences in total white blood cells or lymphocytes (Snow et al. 2017). Platelet and platelet-leukocyte aggregation, and increased platelet-fibrinogen binding were observed in mice exposed by inhalation to 4.9 ppm acrolein for 6 hours or 1.1 ppm for 6 hours/day for 4 days (Sithu et al. 2010). Calculations for time-weighted concentrations (ppm-hour) for comparison between single (29.4 ppm-hour) and intermittent (26.4 ppm-hour) dosing suggest similar cumulative exposures.

Female hamsters exposed to 4.9 ppm acrolein for 13 weeks had increased numbers of erythrocytes, packed cell volume, hemoglobin content, and lymphocyte count, and decreased numbers of neutrophilic leukocytes, although these differences were not observed in male hamsters, rats, or rabbits (Feron et al. 1978). Similarly, female hamsters exposed to 4 ppm acrolein for 52 weeks had increased hemoglobin content and packed cell volume, although this was not observed in similarly exposed males, and no other alterations in hematological parameters were reported (Feron and Kruysse 1977). No adverse hematological effects were observed following intermediate-duration exposure in rats (NTP 1981), guinea pigs, dogs, or monkeys (Lyon et al. 1970), or following chronic-duration exposure in rats or mice (Matsumoto et al. 2021).

A single oral dose of 5 mg/kg in mice increased ADP-induced platelet and platelet-leukocyte aggregations and reduced the bleeding time (Sithu et al. 2010). Longer duration oral exposure does not result in the same hematological effects that are seen with inhalation exposure. Increased platelet and reticulocyte counts were observed in rats gavaged with 5 mg/kg/day for 14 weeks (Auerbach et al. 2008; NTP 2006a), while bone marrow hyperplasia was observed at 10 mg/kg/day. Decreased serum albumin, calcium, and total protein levels, and changes in red blood cell parameters were seen in Beagle dogs gavaged with 2 mg/kg/day for 12 months (Parent et al. 1992b); however, the toxicological significance of this is unclear. No pathological changes in liver or kidney were observed that would support these changes. Furthermore, extensive vomiting was seen in these animals and could have contributed to the changes. No altered hematological effects were observed in mice given a single gavage dose of up to 5 mg/kg/day (Conklin et al. 2010), gavage doses up to 10 mg/kg/day, 5 days/week for 14 weeks (Auerbach et al. 2008; NTP 2006a), or gavage doses of up to 4.5 mg/kg/day acrolein for 18 months (Parent et al. 1991a); in rats

given gavage doses of up to 2.5 mg/kg/day for 2 years (Parent et al. 1992a); or in dogs given 2 mg/kg/day for 12 months (Parent et al. 1992b).

2.8 MUSCULOSKELETAL

No studies were located regarding musculoskeletal effects in humans following inhalation, oral, or dermal exposure to acrolein.

Few studies have examined potential musculoskeletal effects in animals following acrolein exposure. Plasma creatine kinase levels were unchanged in mice exposed to 4.9 ppm acrolein for 6 hours, or to 1.1 ppm for 6 hours/day for 4 days (Sithu et al. 2010). Similar results were observed in mice exposed to 1 ppm for 12 weeks (Conklin et al. 2017b).

The weight and cross-sectional area of the soleus muscle were decreased in mice gavaged with 2.5 mg/kg/day acrolein for 4 weeks (Chen et al. 2019). No histopathological changes were observed in musculoskeletal tissues after intermediate-duration oral exposure in rats or mice (Auerbach et al. 2008; NTP 2006a) or in chronically exposed rats (Parent et al. 1992a), mice (Parent et al. 1991a), or dogs (Parent et al. 1992b).

2.9 HEPATIC

Studies examining the potential hepatic effects of acrolein exposure in humans are limited. The urinary acrolein metabolites, CEMA and 3-HPMA, were associated with elevated levels of alkaline phosphatase (ALP) in subjects from the Health, Environment, and Action in Louisville (HEAL) study, while the metabolite, 3-HPMA, was positively associated with bilirubin in nonsmokers in the study (Wahlang et al. 2022).

Mixed results have been reported for hepatic effects in experimental animal studies. Single 30-minute inhalation exposures between 44 and 305 ppm have resulted in hyperemia, perivascular edema, and necroses of the liver in rats (Skog 1950) and increased serum triglycerides in mice (Conklin et al. 2017a). In rats following 4-hour exposures to 4–8 ppm acrolein for 1 or 2 days, alterations in ALP activity (Murphy 1965; Murphy et al. 1964), cholesterol levels (Snow et al. 2017), and liver weights (Murphy et al. 1964) have been observed. Decreases in serum cholesterol and triglyceride levels were seen in mice exposed to 1.1 ppm of acrolein 6 hours/day for 4 days. No significant changes in these parameters were

reported in mice exposed to 5 ppm acrolein for 6 hours in a single-day exposure, which resulted in a similar cumulative exposure (Sithu et al. 2010). The biological relevance of the lipid decreases is unclear considering that other studies reported significant increases in these parameters following inhalation and oral exposures to acrolein (Conklin et al. 2010; Rom et al. 2017; Snow et al. 2017). Plasma alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activity were unchanged in mice exposed to 4.9 ppm acrolein for 6 hours or 1.1 ppm of acrolein 6 hours/day for 4 days (Sithu et al. 2010).

Continuous exposure to ≥1 ppm for 90 days led to focal liver necrosis in rats and guinea pigs (Lyon et al. 1970); however, other intermediate-duration studies that employed intermittent exposures to 1.4–4.9 ppm acrolein for 6–8 hours/day, 5 days/week for 6–13 weeks did not result in histopathological changes in the liver of monkeys, rats, guinea pigs, hamsters, rabbits, or dogs (Feron et al. 1978; Kutzman et al. 1985; Lyon et al. 1970; NTP 1981). Relative liver weights, ALP, ALT, and AST were increased in hypertension-resistant rats exposed to 4 ppm acrolein for 62 days (Kutzman et al. 1984), but not in hypertension-sensitive rats (Kutzman et al. 1984) or F-344 rats (Kutzman et al. 1985; NTP 1981). No changes in ALP, ALT, or AST were seen in monkeys, rats, guinea pigs, or dogs following exposure of up to 3.7 ppm for 8 hours/day, 5 days/week for 6 weeks (Lyon et al. 1970) or in mice exposed up to 1 ppm for 6 hours/day, 5 days/week for 12 weeks (Conklin et al. 2017b). In chronic-duration studies, female hamsters showed a decrease in absolute liver weights following exposure to 4 ppm acrolein for 52 weeks, but there were no differences in male liver weights and no associated histopathology (Feron and Kruysse 1977). No exposure-related changes in liver weights, histopathology, or clinical chemistry were observed in rats or mice chronically exposed to 2 or 1.6 ppm acrolein, respectively (Matsumoto et al. 2021).

A single gavage dose of 5 mg/kg resulted in increased plasma cholesterol, phospholipids, and triglycerides in mice (Conklin et al. 2010), while 25 mg/kg of acrolein resulted in eosinophilic degeneration of the liver in rats 48 hours after dosing (Sakata et al. 1989). Sakata et al. (1989) was not included in Table 2-2 or plotted in Figure 2-3 because a control group was not included. In an intermediate-duration study increased liver weights were observed in female rats (≥ 5 mg/kg/day) and male mice (10 mg/kg/day) (Auerbach et al. 2008; NTP 2006a). Male and female rats also exhibited increased ALP activity and decreased serum albumin at doses ≥2.5 mg/kg/day. However, since no histopathological changes were observed in the livers of either species (Auerbach et al. 2008; NTP 2006a), the toxicological significance is unknown and these changes may reflect adaptive responses. No liver effects were observed upon gross pathological or histological examinations in rats after intermediate-duration exposure up to 7.2 mg/kg/day acrolein (Parent et al. 1992c). Similarly, no

significant liver histopathology was observed in chronically exposed rats (Parent et al. 1992a), mice (Parent et al. 1991a), or dogs (Parent et al. 1992b) at doses of 2–4.5 mg/kg/day.

Several studies have examined alterations in cholesterol and lipid content following acrolein exposure in a cardiovascular disease mouse model prone to atherosclerosis (apoE$^{-/-}$). Mice given a single gavage dose of 5 mg/kg had increased plasma cholesterol and triglycerides compared to controls, similar to what was seen in wild type mice (Conklin et al. 2010). Gavage exposure to 2.5 mg/kg/day acrolein for 8 weeks resulted in an increase in serum cholesterol and low-density lipids (Srivastava et al. 2011). Exposure to 3 mg/kg/day acrolein in drinking water for 1 month resulted in an increase in serum cholesterol, triglycerides, and lipid peroxides (Rom et al. 2017).

2.10 RENAL

No studies were located regarding renal effects in humans following exposure to acrolein by any route.

No consistent renal effects have been identified in animal studies following acrolein exposure. Exposure to 44–305 ppm acrolein for 30 minutes resulted in renal hyperemia in rats, although the severity was not described (Skog 1950). Slightly increased relative kidney weights (6–18% were observed following intermediate-duration inhalation exposure to 4.0 or 4.9 ppm in rats and hamsters (Feron et al. 1978; NTP 1981), but body weights were decreased at the same exposure concentrations. Most intermediate- and chronic-duration studies in rats, mice, rabbits, and other species have not observed similar weight differences and no associated histopathology was found in any species (Conklin et al. 2017b; Feron and Kruysse 1977; Feron et al. 1978; Kutzman et al. 1984; Matsumoto et al. 2021).

Following intermediate-duration oral exposure, increased urea nitrogen was observed in rats gavaged for 14 weeks, although the study authors suggested a non-renal cause (Auerbach et al. 2008; NTP 2006a). Histopathological examination of the renal system (i.e., kidneys, bladder) revealed no effects after acute-duration oral exposure to acrolein in rats (Sakata et al. 1989), intermediate-duration exposure in rats or mice (Auerbach et al. 2008; NTP 2006a; Parent et al. 1992c), or chronic-duration exposure in rats (Parent et al. 1992a), mice (Parent et al. 1991a), or dogs (Parent et al. 1992b). Sakata et al. (1989) was not included in Table 2-2 or plotted in Figure 2-3 because a control group was not included. Negative results were also obtained from the urinalysis of mice after single gavage of up to 5 mg/kg (Conklin et al. 2010) and in dogs exposed to up 2 mg/kg/day for 53 weeks (Parent et al. 1992b).

2.11 DERMAL

Very few studies have assessed the potential dermal effects of acrolein exposure. Two aquatic pesticide workers experienced skin irritation and burns following occupational exposure to acrolein (CDC 2013). Volunteers receiving topical applications of ≥1% solution of acrolein in ethanol exhibited evidence of dermal irritation, and a 10% solution resulted in papillary edema, polymorphonuclear infiltrates, and epidermal necrosis 48 hours after exposure (Lacroix et al. 1976). In an occupational accident, an employee sprayed in the face with a high concentration of acrolein experienced burns to his checks and eyelids and edema of the eyelids which reduced the palpebral opening to a few millimeters (Champeix et al. 1966). This study was not included in Table 2-3 because the exposure concentration was not known.

Histopathological examination of the external skin revealed no effects after chronic-duration inhalation exposure to acrolein in mice and rats (Matsumoto et al. 2021), intermediate-duration oral exposure in rats or mice (Auerbach et al. 2008; NTP 2006a), or chronic-duration orally exposed mice (Parent et al. 1991a), or rats (Parent et al. 1992a). However, scattered areas of dermatitis were reported in two of six female dogs exposed to 2 mg/kg/day for 53 weeks (Parent et al. 1992b).

2.12 OCULAR

Eye irritation appears to be a sensitive effect of airborne acrolein and a more sensitive effect than nose or throat irritation. An aquatic pesticide worker experienced burning, watery eyes immediately following exposure to an unknown amount of acrolein, while five additional workers also exhibited eye irritation (CDC 2013). Volunteers reported eye irritation in a 90-second exposure to 0.6 ppm acrolein (following prior exposure to 0.15, 0.30, and 0.45 ppm; 8-minute recovery between exposures), while exposure to gradually increasing acrolein levels revealed that acrolein concentrations ≥0.26 ppm for 40 minutes resulted in irritation, measured by increasing eye blink frequency and subjective reporting (Weber-Tschopp et al. 1977). Blink rate peaked at 0.5 ppm and decreased at the higher dose. These experiments were not presented in the LSE table due to changing exposure concentrations over time (continuous exposure) or exposure of the same subjects to discrete short-term increasing exposure concentrations (discrete exposure). The irritation response was reported to be stronger for continuous exposure compared to discrete exposure at the same concentration, suggesting that irritation severity increases over time with cumulative exposure (Weber-Tschopp et al. 1977). Eye irritation from a 60-minute, 0.3-ppm exposure was greater than nose and throat irritation and was scored by participants as “a little” at 10 minutes and “medium” at 40 minutes with no further increase in severity. At 40 minutes, the

respective nose and throat irritation scores were "a little" and "not at all" (Weber-Tschopp et al. 1977). In other studies, lacrimation occurred within 20 seconds in individuals exposed to 0.81 ppm, and within 5 seconds at 1.22 ppm (Sim and Pattle 1957), while eye irritation, measured by eye blink frequency and subjective reporting, was reported following 100 minutes of exposure to 0.11 ppm (Dwivedi et al. 2015).

The ocular effects observed in experimental animals are qualitatively similar to those described in humans. Direct liquid or vapor application of 30 µL into the eyes of rabbits caused severe eyelid swelling and inflammation, corneal opacity, excessive tear secretion, and corneal edema (Gupta et al. 2020). Exposure to vapors generated after 10 µL of acrolein was applied to a filter paper disc and then placed in a glass goggle resulted in corneal erosions in rabbit eyes (Dachir et al. 2015). Vapor concentrations of 0.7–3.7 ppm acrolein caused eye irritation in dogs and monkeys as evidenced by lacrimation, excessive salivation, and closing of the eyes, but guinea pigs and rats appeared to be less sensitive, since concentrations up to 3.7 ppm had no noticeable effect in these species (Lyon et al. 1970). At 4.9 ppm, rats, hamsters, and rabbits kept their eyes closed most of the time, hamsters salivated with nasal drainage, and rabbits had respiratory difficulty and sneezed (Feron et al. 1978). Severe eye irritation was reported in rats exposed to 12 ppm for 4 hours (Murphy et al. 1964) and lacrimation was observed in rats exposed to 14 ppm for 1 hour and to 4.8 ppm for 4 hours (Ballantyne et al. 1989). It is important to note that humans have the ability to articulate feelings of irritation, while in rodents, signs of irritation are blinking, closing eyes, and drainage; therefore, it is unclear if humans were, in fact, more sensitive despite lacrimation at concentrations of 0.81 ppm, compared with ≥3.7ppm in animals.

Increased discharge from the eyes was observed in rats orally administered 10 mg/kg/day for 14 weeks (Auerbach et al. 2008; NTP 2006a). Histopathological examination of the eyes revealed no effects after intermediate-duration oral exposure to acrolein in rats or mice (Auerbach et al. 2008; NTP 2006a) or chronic-duration exposure in rats (Parent et al. 1992a), mice (Parent et al. 1991a), or dogs (Parent et al. 1992b).

2.13 ENDOCRINE

No studies were located regarding endocrine effects in humans following exposure to acrolein by any route.

Data on potential endocrine effects in animals are also limited. Plasma corticosterone was increased in rats exposed to 4 ppm acrolein over 1 or 2 days (Snow et al. 2017). Increased adrenal weights have been

reported in rats exposed to 6.4 ppm for 4 hours (Murphy et al. 1964) or to 4.9 ppm for 13 weeks (Feron et al. 1978), although no differences were observed in similarly exposed hamsters or rabbits, and no associated histopathology was found in any species. Exposure for 2 years (6 hours/day, 5 days/week) did not affect weights or presence of non-neoplastic lesions in the adrenals, pituitary, or thyroid glands in mice or rats (Matsumoto et al. 2021).

Histopathological examination of the endocrine system (i.e., thyroid, parathyroid, pituitary, adrenals) revealed no effects after intermediate-duration oral exposure to acrolein in rats or mice (Auerbach et al. 2008; NTP 2006a; Parent et al. 1992c) or chronic-duration exposure in rats (Parent et al. 1992a), mice (Parent et al. 1991a), or dogs (Parent et al. 1992b).

2.14 IMMUNOLOGICAL

Data on the potential immunological effects of acrolein in humans are extremely limited. A human controlled exposure study found no differences in inflammatory markers in the serum (IL-6) and sputum (IL-6, IL-8) of volunteers exposed to 0.11 ppm for 2 hours (Dwivedi et al. 2015).

No histological changes have been reported in immune organs following inhalation exposure to acrolein in animals. No histopathological changes were noted in the spleens of rats exposed to 44–305 ppm acrolein for 30 minutes (Skog 1950) and exposure to 5 ppm acrolein for 3 days did not result in an inflammatory response in the lung of mice (Kasahara et al. 2008). In mice exposed to acrolein for 6 hours/day, 5 days/week, for 12 weeks, there were multiple changes in circulating blood immune cells (Conklin et al 2017b). These changes include decreased granulocytes and CD8+ T cells at 1 ppm, a dose-related decrease in CD 11b+ monocytes, and decreased CD19+ B-cells at both doses, but not dose related. Changes in natural killer and CD4+ T-cells were observed at the low dose, but not the high dose. A significant 20% reduction in spleen weight was reported for exposure of rats to 3 ppm intermittently for 3 weeks, but the effect was not apparent when normalized to final body weight (Leach et al 1987). No changes in spleen weights or histopathology were observed in rodent intermediate- and chronic-duration inhalation studies with concentrations up to 5 ppm (Conklin et al. 2017b; Feron and Kruysse 1977; Feron et al. 1978; Kutzman et al. 1984; Matsumoto et al. 2021; NTP 1981). Relative thymus weights were decreased in rats exposed to 4.9 ppm for 13 weeks, but the study authors considered the effect to be associated with reduced body weight gain rather than a result of treatment (Feron et al. 1978). No differences in thymus weight were observed in similarly exposed hamsters, and no associated histopathology was found in any species (Feron et al. 1978).

Decreased thymus weights, thymocyte atrophy and necrosis, and lymphoid follicular cell depletion in the spleen were observed in rats gavaged with 10 mg/kg/day for 14 weeks (Auerbach et al. 2008; NTP 2006a). Atrophy and necrosis in the thymus, necrosis in the mandibular and mesenteric lymph nodes, and depletion of the lymphoid follicle in the spleen were seen in mice gavaged with 20 mg/kg/day. In contrast, histopathological examination of the immunological system (i.e., spleen, thymus, lymph nodes) revealed no effects after acute-duration oral exposure to acrolein in rats (Sakata et al. 1989), intermediate-duration exposure in rats (Parent et al. 1992c), or chronic-duration exposure in rats (Parent et al. 1992a), mice (Parent et al. 1991a), or dogs (Parent et al. 1992b). Sakata et al. (1989) was not included in Table 2-2 or plotted in Figure 2-3 because a control group was not included.

Several studies have evaluated the effects of acrolein exposure on immune function or inflammatory response, particularly in the respiratory system, although the results have not been conclusive. A single 3-hour inhalation exposure of 0.09 ppm in mice had no impact on bactericidal activity in response to *Klebsiella pneumoniae*, although repeated exposures over 5 days resulted in lower removal by alveolar macrophages (Aranyi et al. 1986). In rats exposed to acrolein concentrations up to 3 ppm for 6 hours/day, 5 days/week for 3 weeks, no effect was observed on macrophage function in response to *K. pneumoniae* (Sherwood et al. 1986). Clearance of intrapulmonary *Staphylococcus aureus* was reduced in mice following acrolein exposure to ≥3 ppm for 8 hours; this impairment was exacerbated in mice pre-infected with Influenza A virus (Astry and Jakab 1983). Acrolein exposure (5 ppm for 6 hours/day for 3 days) in conjunction with instillation of lipopolysaccharide (LPS) (*Escherichia coli*) did not alter the inflammatory response in mice induced by LPS alone (Kasahara et al. 2008). Rats exposed to 0.55 ppm for 10–26 days (but not 60–180 days) had significantly lower numbers of alveolar macrophages, and additional respiratory challenge with *Salmonella enteritidis* revealed that acrolein-exposed animals were more susceptible to bacterial-induced mortality (Bouley et al. 1975). In contrast, rats exposed to 3 ppm acrolein for 3 weeks were not more susceptible to mortality following intravenous (i.v.) exposure to *Listeria monocytogenes* (Leach et al. 1987).

Mixed results have been observed in the nasal or bronchoalveolar lavage fluid (BALF) parameters in rodents sensitized and/or challenged with ovalbumin (OVA) in conjunction with acrolein exposure. Inflammatory cells (neutrophils and macrophages) were increased in the bronchoalveolar fluid of mice exposed to 5 ppm acrolein for 10 minutes, and this increase was even greater (and included eosinophils) in OVA-sensitized mice (Kim et al. 2019). Mice exposed to 5 ppm acrolein for 4 days showed a suppressed inflammatory response in the nose and lungs, measured as a decrease in inflammatory cell

infiltrates and IL-12p40 levels, compared to challenge only (Spiess et al. 2013), while another study found an increase in neutrophils in mice exposed to 5 ppm for 2 weeks (O'Brien et al. 2016). Suppression of the inflammatory response, measured as a reduction in airway IL-33, IL-25, and IL-1α levels, was also observed in mice challenged with the airborne allergen house dust mite (Danyal et al. 2016).

Mechanisms. The mechanisms of acrolein effects are discussed in detail in Section 2.21, Mechanisms of Toxicity. Acrolein's effect on the immune system is expected to be mediated by its effects on immune signaling proteins. In a review of acrolein mechanisms, Moghe et al. (2015) proposed that acrolein could suppress immune responses by inhibiting macrophage function through inhibition of NF-κB, by alkylation of immune signaling proteins, or by tipping the balance of inflammatory mediators in favor of anti-inflammatory responses. For example, *in vitro* studies using human T cells showed that acrolein could directly alkylate amino acids in NF-κB, leading to reduced binding to proinflammatory mediators (IL-2, IL-10, TNFα, granulocyte-macrophage colony stimulating factor [GMCSF], and IFN-γ) (Moghe et al. 2015). The effects of acrolein on the immune system may depend upon dose and/or exposure duration. Moghe et al. (2015) postulated that acute, high-level exposures were more likely to suppress the immune response, while prolonged, low-level exposures would increase inflammation. Additional information on the evidence for acrolein-induced inflammation is presented in Section 2.21.

2.15 NEUROLOGICAL

Few studies have evaluated the potential neurological effects of acrolein exposure in humans. An aquatic pesticide worker was diagnosed with lateral medullary syndrome and experienced dysphagia and facial droop following exposure to an unknown amount of acrolein, while three additional workers also reported headaches (CDC 2013). In a case-control study, no associations were observed between the urinary acrolein metabolite, 3-HPMA, and attention-deficit hyperactivity disorder in a group of children in Taiwan (Waits et al. 2022).

Nonspecific inflammatory changes were reported in the brains of rats, dogs, monkeys, and guinea pigs after a continuous 90-day exposure to 1.8 ppm acrolein (Lyon et al. 1970); however, the nature and severity of these lesions was not described. No histopathological changes were noted in the brains of rats exposed to 44–305 ppm acrolein for 30 minutes (Skog 1950). Increased relative brain weights have frequently been observed following intermediate- and chronic-duration inhalation exposure in rats and hamsters at concentrations ≥1.4 ppm (Feron and Kruysse 1977; Feron et al. 1978; Kutzman et al. 1984;

NTP 1981), but only at exposure levels at which body weights were decreased. No differences in brain weights were observed in similarly exposed rabbits (Feron et al. 1978), and no associated histopathology was found in any species. Neurobehavioral tests have shown mixed results following inhalation exposure to acrolein. Rats exposed to 0.3 ppm acrolein for 4 days showed altered pain thresholds and spent longer times in corners (Kunkler et al. 2018), while no differences in behavioral measurements (exploratory behavior and locomotive activity) were observed in rats exposed up to 4 ppm for 62 days (Kutzman et al. 1984). Feron et al. (1978) reported clinical signs of toxicity in animals exposed to ≥1.4 ppm for 13 weeks, including hyperactivity followed by somnolence in rats and hamsters and sneezing in rabbits. At 4.9 ppm, additional signs included eyes closed in all animals, salivation and nasal discharge in hamsters, occasional breathing difficulty in rabbits, and piloerection in rats. Many or all of these clinical signs may be attributable to respiratory irritation/inflammation and subsequent hypoxia induced by acrolein.

Neurobehavioral tests in rats and mice following acute- and intermediate-duration oral exposures to acrolein concentrations ≥2.5 mg/kg/day have found decreased response to tail pinch and loss of elevation reflexes/poor body tone (Sprince et al. 1979), decreased rotarod latency (Chen et al. 2019), and increased escape latency in the Morris water maze test (Huang et al. 2013). Histopathological examination in one study revealed neuronal loss and inflammation in the hippocampus in rats gavaged for 8 weeks at 2.5 mg/kg/day (Huang et al. 2013), (the other two neurobehavioral studies examined the brain for histopathology). Histopathological examination of the neurological system (i.e., brain, spinal cord, nerves) revealed no effects after intermediate-duration oral exposure to acrolein in rats or mice (Auerbach et al. 2008; NTP 2006a; Parent et al. 1992c) or chronic-duration exposure in rats (Parent et al. 1992a), mice (Parent et al. 1991a), or dogs (Parent et al. 1992b).

2.16 REPRODUCTIVE

No studies were located regarding reproductive effects in humans after exposure to acrolein by any route.

No evidence of reproductive toxicity has been found in animals exposed to acrolein by inhalation. Reproductive fitness, measured as the number of pregnant rats, corpora lutea, number of viable fetuses, and preimplantation loss, was not affected by intermediate-duration inhalation exposure to acrolein (Bouley et al. 1975; NTP 1981). Increased relative testis and ovary weights (≤15–20%) have been reported in rats and hamsters exposed to acrolein concentrations of 0.55 and 4.9 ppm, but these changes occurred in the context of reduced body weights (Bouley et al. 1975; Feron et al. 1978). No differences

were observed in similarly exposed mice or rabbits, and no associated histopathology or alterations to sperm quality have been found in any species (Feron and Kruysse 1977; Feron et al. 1978; Matsumoto et al. 2021; NTP 1981).

Similarly, no evidence of reproductive toxicity has been found in animals following oral exposure to acrolein. Reproductive performance was not affected in 2 generations of rats gavaged up to 7.2 mg/kg/day acrolein (Parent et al. 1992c). No differences in premature deliveries or spontaneous abortions were observed in rabbits gavaged with up to 2 mg/kg/day on GDs 7–19 (Parent et al. 1993). Histopathological examination of the reproductive system (i.e., testes, ovaries, epididymides, uterus, cervix) revealed no effects after intermediate-duration oral exposure to acrolein in rats or mice (Auerbach et al. 2008; NTP 2006a; Parent et al. 1992c) or chronic-duration exposure in rats (Parent et al. 1992a), mice (Parent et al. 1991a), or dogs (Parent et al. 1992b).

2.17 DEVELOPMENTAL

No studies were located regarding developmental effects in humans following exposure to acrolein from any route.

Only a single study was identified that evaluated developmental effects in animals after inhalation exposure to acrolein. No effects on fetal number or body weight were observed in male and female rats exposed continuously for 26 days (3 days prior to mating and presumed GDs 0–22) to 0.55 ppm (Bouley et al. 1975).

Alterations in fetal weight and skeletal abnormalities have been observed following oral exposure to acrolein in animals. Decreased pup weight (7% at postnatal day [PND] 21 in F1 generation) was observed in a 2-generation study in rats gavaged with 6 mg/kg/day (Parent et al. 1992c). Increased skeletal anomalies, including incomplete ossification of the skull, vertebrae, metacarpals, and metatarsals, were seen in rat fetuses when dams were gavaged with 10 mg/kg/day acrolein on GDs 7–19 (EPA 1983). However, in both of these studies, maternal toxicity was also observed at the dose level that adverse effects were seen in pups. No other evidence of developmental toxicity, such as number of implantations, gestation length, resorptions, or live fetuses per litter, were observed in rats or rabbits gavaged with up to 10 mg/kg/day during gestation (EPA 1983; Parent et al. 1992c, 1993).

2.18 OTHER NONCANCER

Human data on other noncancer effects related to acrolein exposure are limited. In a population-based study, associations were observed between urinary acrolein metabolites and the prevalence of diabetes and insulin resistance (Feroe et al. 2016).

Animal studies have identified potential metabolic effects following inhalation or oral exposure to acrolein. Body temperature was decreased in mice exposed to 250 ppm acrolein for 30 minutes (Conklin et al. 2017a). Glucose tolerance was altered in rats exposed nose-only to 4 ppm acrolein over 1 or 2 days (Snow et al. 2017). In contrast, no differences in blood glucose, insulin, or glucose tolerance were observed in mice exposed by inhalation to 1 ppm acrolein for 12 weeks (Conklin et al. 2017b). Following oral exposure, blood glucose and insulin were increased in mice gavaged with 2.5 mg/kg/day for 4 weeks, resulting in impaired glucose tolerance (Wang et al. 2021).

2.19 CANCER

IARC (2021) reviewed six epidemiology studies that evaluated the relationship between exposure to acrolein and cancer (one cohort study, two case-control studies, and three nested case-control studies). These studies were considered uninformative, because they were either mechanistic in nature or had poor study design and exposure assessment.

Mixed results have been observed in animal studies evaluating the carcinogenic effects of acrolein inhalation. Feron and Kruysse (1977) exposed hamsters to 4.0 ppm acrolein for 52 weeks and found no evidence of respiratory tract tumors or tumors in other tissues and organs, although epithelial hyperplasia and metaplasia were observed in the nasal cavity. However, this study is considered to be of too short duration to determine carcinogenicity, and the maximum tolerable dose (MTD) of acrolein may not have been achieved in this study. In a more recent study by Matsumoto et al. (2021), increased incidence of nasal tumors was observed in female rats (rhabdomyomas, 8%) and female mice (adenomas, 32%) exposed to 2 and 1.6 ppm acrolein, respectively, for up to 2 years, although similar results were not observed in male rats or male mice. There is no clear mode of action that would lead to the observed sex-based differences.

Questionable evidence of the carcinogenicity of acrolein in animals is provided by a few long-term oral studies. Lijinsky and Reuber (1987) reported a cancer bioassay in which groups of rats were given

acrolein in the drinking water at concentrations up to 36 mg/kg/day for 104–124 weeks. This study had several limitations including issues with stability of the acrolein solutions (reported loss of 18% after 6 days at 5°C, 27% loss after 3 days at 22°C), water consumption was not measured/reported, and treatments had to be stopped due to the animals' refusal to drink the solution. The only indication of a carcinogenic effect of acrolein was the incidence of neoplasms of the adrenal cortex in high-dose female rats (5/20 adenomas, 2/20 hyperplastic nodules). Additional oral studies have failed to detect significant cancer incidence in animals. Gavage treatment of rats with up to 2.5 mg/kg/day for 102 weeks failed to produce tumor incidences, including adrenal tumors, which were significantly different from controls (Parent et al. 1992a). Extensive histopathological examination did not reveal any carcinogenic effects in mice (Parent et al. 1991a) or dogs (Parent et al. 1992b) after oral exposure to 4.5 or 2 mg/kg/day acrolein, respectively, for 12–18 months. Because of the disparate results of the Lijinsky and Reuber (1987) and Parent et al. (1991a, 1992a) studies, an independent pathology working group (PWG) re-evaluated the Lijinsky and Reuber tumor data (cited in Parent et al. 1992a). The PWG concluded that the incidence of cortical tumors in treated females was within the limits of historical controls and were of no biological significance for adrenal cancer from acrolein exposure.

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

Mechanisms. IARC (2021) provided a comprehensive review of the cancer mechanistic data on acrolein structured around the 10 key characteristics of carcinogenicity (Smith et al. 2016). In their review, IARC (2021) emphasized acrolein's electrophilicity and capacity to bind both deoxyribonucleic acid (DNA) and proteins; its genotoxicity and ability to alter DNA repair; its ability to induce oxidative stress and inflammation; its suppression of immune responses; and its ability to alter cell proliferation. The study authors did not provide any specific links between the mechanistic data and the tumors seen in animal studies of acrolein carcinogenicity; however, the observation of nasal tumors in rats and mice exposed to acrolein by inhalation (Matsumoto et al. 2021) is consistent with the greater uptake of acrolein in the upper respiratory tract (see Section 3.1) and the evidence for oxidative stress, inflammation, and altered cell proliferation (hyperplasia, metaplasia, and dysplasia) in the nasal cavity of rats exposed by inhalation

(IARC 2021). Further information on the molecular mechanisms of acrolein toxicity and carcinogenicity is provided in Section 2.20 (Genotoxicity) and Section 2.21 (Mechanisms of Toxicity).

2.20 GENOTOXICITY

No studies were located regarding the genotoxic effects of acrolein in humans or animals following inhalation, oral, or dermal exposure. Acrolein was found to be non-mutagenic *in vivo,* as judged by the dominant lethal assay in the mouse (Epstein et al. 1972), the micronucleus assay in mice peripheral blood (NTP 2006a), and the sex-linked recessive lethal test in *Drosophila* (Zimmering et al. 1985).

The *in vitro* genotoxicity of acrolein has been investigated in prokaryotic and eukaryotic organisms and in mammalian cell systems (Table 2-8). In prokaryotic cells, the overall evidence, indicates that acrolein is weakly mutagenic without activating systems and non-mutagenic in the presence of activating systems in *Salmonella typhimurium* and *Escherichia coli* (see Table 2-8 for references). In the yeast, *Saccharomyces cerevisiae*, acrolein was not mutagenic without activating systems (Izard 1973).

Table 2-8. Genotoxicity of Acrolein *In Vitro*

		Results		
		Activation		
Species (test system)	Endpoint	With	Without	Reference
Prokaryotic organisms				
Salmonella typhimurium	Reverse mutation	–	–	Andersen et al. 1972
S. typhimurium	Reverse mutation	–	–	Florin et al. 1980
S. typhimurium	Reverse mutation	–	–	Loquet et al. 1981
S. typhimurium	Reverse mutation	–	–	Bignami et al. 1977
S. typhimurium	Reverse mutation	–	(+)	Lijinsky and Andrews 1980
S. typhimurium	Reverse mutation	–	+	Lutz et al. 1982
S. typhimurium	Reverse mutation	–	+	Eder et al. 1982
S. typhimurium	Reverse mutation	–	–	Basu and Marnett 1984
S. typhimurium	Reverse mutation	ND		Bartsch et al. 1980
S. typhimurium	Reverse mutation	ND	(+)	Khudoley et al. 1987
S. typhimurium TA1535, TA1537, TA1538	Reverse mutation	–	–	Parent et al. 1996b
S. typhimurium TA98	Reverse mutation	–	(+)	Parent et al. 1996b
S. typhimurium TA100	Reverse mutation	+	+	Parent et al. 1996b

Table 2-8. Genotoxicity of Acrolein *In Vitro*

Species (test system)	Endpoint	Results		Reference
		Activation		
		With	Without	
S. typhimurium	Reverse mutation	ND	+	Marnett et al. 1985
S. typhimurium	Reverse mutation	ND	+	Foiles et al. 1989
S. typhimurium (vapor assay in sealed desiccator)	Reverse mutation	–	–	NTP 2006a
S. typhimurium (preincubation) TA98, TA1535, TA1538	Reverse mutation	–	–	NTP 2006a
S. typhimurium (preincubation) TA100	Reverse mutation	(+)	–	NTP 2006a
S. typhimurium TA1535	Reverse mutation	–	(+)	Waegemaekers and Bensink 1984
Escherichia coli PQ37	Reverse mutation	–	–	von der Hude et al. 1988
E. coli K-12/343/133	Reverse mutation	–	ND	Ellenberger and Mohn 1977
E. coli WP2uvrA	Reverse mutation	–	(+)	Parent et al. 1996b
E. coli WPuvrA	Reverse mutation	ND	(+)	Hemminki et al. 1980
E. coli WPuvrA	Reverse mutation	ND	+	Bilimoria 1975
E. coli AB1157	Reverse mutation	–	ND	VanderVeen et al. 2001
Non-mammalian eukaryotic cells				
Saccharomyces cerevisiae	Gene mutation	ND	–	Izard 1973
S. cerevisiae MB1072-2B	Chromosomal aberrations	ND	–	Fleer and Brendel 1982
Mammalian cells				
Human fibroblasts (normal)	Gene mutation	No data	–	Curren et al. 1988
Human fibroblasts (cells deficient in DNA repair)	Gene mutation	No data	+	Curren et al. 1988
Human fibroblast	Gene mutation	ND	+	Kawanishi et al. 1998
Human fibroblast	Gene mutation	ND	–	Kim et al. 2007
Mouse embryonic fibroblast	Gene mutation	ND	–	Kim et al. 2007
Chinese hamster ovary cells	Gene mutation	–	–	Parent et al. 1991b
Chinese hamster V79 cells	Gene mutation	ND	+	Smith et al. 1990
Human myeloid cells K562	DNA damage	ND	+	Crook et al. 1986
Human bronchial cells	DNA damage	ND	+	Grafstrom et al. 1988
Human pulmonary epithelial cell (A549)	DNA damage	ND	+	Wang et al. 2017
Human lung fibroblast (MRC-5)	DNA damage	ND	+	Wang et al. 2017
Human bronchial cells	Impaired DNA repair	ND	+	Krokan et al. 1985

Table 2-8. Genotoxicity of Acrolein *In Vitro*

Species (test system)	Endpoint	Results		Reference
		Activation		
		With	Without	
Human bladder cells (UROtsa)	Impaired DNA repair	ND	+	Lee et al. 2014
Human bronchial epithelial	Impaired DNA repair	ND	+	Wang et al. 2012
Human lung fibroblast	Impaired DNA repair	ND	+	Wang et al. 2012
Human hepatoma line (HepG2)	DNA strand breaks	ND	+	Li et al. 2008
Leydig cells	DNA strand breaks	ND	+	Yildizbayrak et al. 2020
Human Pulmonary epithelial cells	DNA strand breaks	ND	+	Zhang et al. 2018
Bronchial epithelial cells (BEAS-2B)	DNA strand breaks	ND	+	Zhang et al. 2020a
Chinese hamster ovary cells	DNA strand breaks	+	+	Au et al. 1980
Chinese hamster ovary cells	Sister chromatid exchange	+	+	Au et al. 1980
Chinese hamster ovary cells	Sister chromatid exchange	–	+	NTP 2006a
Chinese hamster ovary cells	Chromosomal aberrations	–	–	NTP 2006a
Human epithelial cell line (HT-29)	DNA adduct	ND	+	Pan et al. 2012
Human bronchial epithelial	DNA adduct	ND	+	Wang et al. 2012
Human lung fibroblast	DNA adduct	ND	+	Wang et al. 2012
Mouse embryonic fibroblast	DNA adduct	ND	+	Kim et al. 2007
Acellular systems				
Calf-thymus DNA	DNA adduct	ND	+	Kozekov et al. 2010
Calf-thymus DNA	DNA adduct	ND	+	Pawłowicz and Kronberg 2008
Calf-thymus DNA	DNA adduct	ND	+	Pawlowicz et al. 2006

+ = positive results; (+) = weakly positive results; – = negative results; DNA = deoxyribonucleic acid; ND = not determined

In mammalian cells, acrolein exposure resulted in DNA damage and adduct formation and impaired DNA repair in the absence of activating systems (Table 2-8). Acrolein was found to be non-mutagenic to normal human fibroblasts, mouse embryonic fibroblasts, and Chinese hamster ovary cells (Curren et al. 1988; Kim et al. 2007; Parent et al. 1991b) in culture; however, positive mutagenic responses were observed in fibroblasts with a deficient DNA repair system (Curren et al. 1988). DNA base substitutions and intra-strand cross-links were observed in human fibroblasts containing shuttle vector plasmids bearing the *supF* marker gene (Kawanishi et al. 1998). Acrolein exposure reduced DNA repair capabilities in human bronchial cells, bladder cells, and lung fibroblasts (Krokan et al. 1985; Lee et al.

2014; Wang et al. 2012). Acrolein inhibited the activity of DNA polymerase as well as DNA and ribonucleic acid (RNA) synthesis in rat liver cell nuclei (Crook et al. 1986; Grafstrom et al. 1988; Krokan et al. 1985) and is a potent inhibitor of the DNA repair enzyme, 0_6-methylguanine-DNA methyl transferase. Acrolein induced chromosome breakage and sister-chromatid exchange in Chinese hamster ovary cells (Au et al. 1980). DNA damage was seen in human myeloid cells, pulmonary epithelial cells, bronchial epithelial cells, Leydig cells, and lung fibroblasts in culture following acrolein exposure (Crook et al. 1986; Grafstrom et al. 1988; Li et al. 2008; Wang et al. 2017; Yildizbayrak et al. 2020; Zhang et al. 2018, 2020a). The mechanism by which acrolein induces genotoxicity in mammalian cells is not known, but it has been shown that acrolein can form adducts with DNA, such as alpha-hydroxypropano-2'deoxyguanosine and gamma-hydroxypropano-2'-deoxyguanosine in mouse embryonic fibroblast cells (Kim et al. 2007), human epithelial cells (Pan et al. 2012), human bronchial epithelia and lung fibroblasts (Tang et al. 2011), and calf-thymus DNA (Kozekov et al. 2010; Pawłowicz and Kronberg 2008; Pawlowicz et al. 2006). Yang et al. (2002) showed that acrolein adduction to DNA may be insignificant for the introduction of miscoding errors, as translesion DNA synthesis was high and miscoding incidence was <1% in human HeLa and xeroderma pigmentosum cells. The same inability of acrolein DNA adducts to cause miscoding was observed in *E. coli* as well (VanderVeen et al. 2001). Because of the limited number of *in vivo* tests, there is insufficient evidence to predict that acrolein poses a genotoxic threat to humans.

Overall, *in vitro* data showed weak mutagenic potential of acrolein in bacterial and mammalian cells without metabolic activation (Table 2-8). Acrolein produces DNA adducts and DNA damage and inhibits DNA repair in mammalian cells (Table 2-8). The mechanism of these changes is not clear but may involve downregulation of Werner's syndrome protein (WRN). This protein has been shown to be involved in DNA repair, telomere maintenance, and cellular senescence (Szekely et al. 2005). Jang et al. (2014) exposed normal human lung fibroblasts (NHLFs) *in vitro* to acrolein and observed a downregulation of WRN protein and an increase in acrolein-induced telomere attrition and cellular senescence.

2.21 MECHANISMS OF TOXICITY

The mechanisms of acrolein toxicity have been extensively reviewed (IARC 2021; Moghe et al. 2015); the discussion here is based on these reviews. Many of the toxic effects of acrolein result from the same molecular initiating event: irreversible binding to cellular proteins and macromolecules. As a highly reactive electrophile, acrolein readily interacts (through Michael addition and/or Schiff base cross-

linking) with biological nucleophiles including the sulfhydryl group of cysteine, amino group of lysine, and imidazole group of histidine (Moghe et al. 2015). These amino acid targets are incorporated into a wide variety of proteins that are important for enzyme catalysis, redox signaling, cytoskeletal components, reactive oxygen species sensing, cellular buffering, and other cellular processes. Adduction of these proteins alters their functioning, leading to cellular-level perturbations including mitochondrial dysfunction, disrupted signal transduction, oxidative stress, inflammation, endoplasmic reticulum (ER) stress, and damage to membrane integrity or cellular structure. Protein modification by acrolein may also alter physiological responses to other toxicants by irreversibly altering xenobiotic-metabolizing enzymes such as arylamine N-acetyltransferases. Because of the wide range of cellular functions affected by acrolein protein adduction, this chemical can damage virtually any organ; however, because it is so reactive, its systemic distribution is often limited and its toxic effects tend to be most severe in the tissues acrolein first contacts (e.g., respiratory tract after inhalation exposure, gastrointestinal tract after oral exposure, and skin after dermal exposure).

Oxidative Stress. In laboratory rodents exposed to acrolein by inhalation, gavage, and/or intraperitoneal injection, glutathione depletion has been seen in the liver, nasal cavity, tracheobronchial mucosa, and lungs (IARC 2021). At low exposure levels, cellular thiol-containing antioxidants such as glutathione may bind to and detoxify acrolein; however, as acrolein dose increases and glutathione is depleted, oxidative stress and tissue damage ensues. Additional evidence for acrolein-induced oxidative stress in exposed rodents includes decreased total antioxidant capacity and increased lipid peroxidation (measured as levels of 8-isoprostane or thiobarbituric acid [TBARS]) in the spleen and thymus of rats and livers of mice exposed to acrolein (IARC 2021). Acrolein both induces and results from lipid peroxidation; in fact, lipid peroxidation is considered to be the major source of endogenous acrolein production (Burcham 2017). *In vitro* studies provide support for the association between acrolein exposure and oxidative stress. Depletion of glutathione and antioxidant enzymes (superoxide dismutase and glutathione peroxidase) was observed in human retinal epithelial cells incubated with acrolein; increased generation of oxygen radical was observed in exposed bovine pulmonary arterial endothelial cells; and supplementation of cell medium with antioxidants mitigated the toxicity of acrolein on liver cells (IARC 2021; Moghe et al. 2015).

Endoplasmic Reticulum Stress. ER stress is believed to play a role in several diseases, including neurodegenerative, cardiovascular, respiratory, and liver diseases, as well as cancer (Moghe et al. 2015). The cellular response to ER stress is the unfolded protein response (UPR), a complex signal transduction pathway aimed at reducing the load of unfolded proteins and restoring or maintaining cell function. Under chronic ER stress conditions, apoptosis is triggered. Acrolein adduction of proteins is expected to

cause ER stress, and both ER stress and the UPR have been observed *in vitro* in endothelial cells, hepatocytes, and Swiss 3T3 cells incubated with acrolein. Further, intraperitoneal injection of rats with acrolein was shown to induce ER stress and apoptosis in the lungs, as well as emphysematous changes in the lung (Moghe et al. 2015).

Mitochondrial Dysfunction. An important function of mitochondria is initiating cell signaling pathways leading to apoptosis. Depending on the dose and cell system, acrolein may induce or inhibit apoptosis. In human neuroblastoma cells and A549 cells, acrolein induced caspase-dependent and caspase-independent apoptosis (respectively), while in murine proB lymphocytes and B lymphoblastoid SKW6.4 cells acrolein exposure resulted in alkylation of caspase active sites and inhibition of apoptosis (Moghe et al. 2015). In addition to interfering with apoptotic pathways, acrolein exposure may interfere with cellular respiration. Exposure of rat liver mitochondria to acrolein resulted in dose-dependent inhibition of pyruvate dehydrogenase, alpha-ketoglutarate dehydrogenase, and complexes I and II, important components of the electron transport chain and cellular respiration (Moghe et al. 2015).

Perturbation of Signal Transduction. As with its other effects, acrolein's impact on signal transduction depends on the cell system tested and the exposure conditions. Acrolein exposure of cultured cells has resulted in activation or inactivation of protein kinases and phosphatases that regulate many cellular functions, including protein tyrosine phosphatase-1B; phosphatase PP2A; serine phosphatase; tyrosine phosphatase; and mitogen activated protein kinases (MAPKs) such as extracellular signal-regulated kinase (ERK1/2) and c-Jun N-terminal kinase (JNK) (Moghe et al. 2015). *In vivo* data to support the role of impaired signal transduction in acrolein-induced toxicity are lacking.

Impaired Membrane Structure and/or Function. Protein modification can also lead to disruptions in cell membrane integrity and function. In experiments using *ex vivo* spinal cords, exposure to acrolein resulted in increased cell membrane permeability, measured as permeation of ethidium bromide, horseradish peroxidase, and lactate dehydrogenase (LDH) levels (Moghe et al. 2015). Both *in vivo* and *in vitro* experiments showed that acrolein adducts disrupt proteins involved in presynaptic membrane neurotransmitter uptake and release. Additional evidence comes from studies showing that acrolein exposure induced structural changes in Sertoli cells (including F-actin microfilament aggregation), erythrocytes (membrane phospholipid scrambling), and bronchiolar lung cell monolayers (hyperphosphorylation of keratin-8 and ubiquitination of intermediate filaments). In animal models of multiple sclerosis and spinal cord injury, neuronal membrane and myelin damage have been correlated

with acrolein levels (Moghe et al. 2015); however, it is unclear whether acrolein induced or resulted from the damage.

Inflammation. Numerous *in vivo* bioassays have shown inflammation or increased markers of inflammation (for example, TNFα, IL-6, and IL-8), in the respiratory tract (nasal tissue, lungs, and BALF) of rats and mice exposed to acrolein by inhalation (IARC 2021). These findings are supported by an *in vivo* study in which increased levels of proinflammatory cytokines (IL-1α, IL-1β, IL-6, TNF, and IFN-γ, among others) were detected in the BALF of mice exposed to acrolein by oropharyngeal aspiration (IARC 2021; Moghe et al. 2015). *In vitro* experiments in a variety of mammalian airway cell types (human and/or rat epithelial cells, smooth muscle cells, macrophages, and fibroblasts), demonstrated that acrolein exposure activates NF-κB and upregulates proinflammatory cytokines such as IL-8 (Moghe et al. 2015). In a mast cell analog test system (RBL-2H3 cells), *in vitro* acrolein exposure resulted in degranulation (exocytosis of cytoplasmic granule contents), a process that releases a multitude of inflammatory mediators (Moghe et al. 2015).

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

3.1 TOXICOKINETICS

Aldehydes, including acrolein, are generated via endogenous processes (Burcham 2017). Acrolein can be produced endogenously by the following processes: (1) oxidation of methionine followed by Strecker degradation to methional sulfoxide, which can then decompose forming acrolein; (2) myeloperoxidase-catalyzed oxidation of threonine; (3) oxidation of cell function-regulating polyamines (spermine and spermidine); and (4) lipid peroxidation (Burcham 2017). The primary process producing endogenous acrolein is believed to be lipid peroxidation, in which unsaturated lipids undergo autocatalytic degradation (oxidation followed by beta cleavage of alkoxyl radical to form acrolein and other electrophiles) (Burcham 2017). Endogenous production of acrolein complicates the interpretation of toxicokinetic studies of acrolein, particularly in humans.

Human studies of acrolein with information on absorption, distribution, metabolism, and excretion are limited. Acrolein toxicokinetics have been studied in a small number of studies in dogs and rodents, with most quantitative data derived from studies conducted in rodents. An overview of these data is presented below.

- Studies in animals indicate that acrolein is absorbed in the respiratory tract, primarily the upper respiratory tract, following inhalation exposure. Human and animal studies demonstrate that acrolein is absorbed from the gastrointestinal tract following oral exposure.
- Animal studies indicate distribution of acrolein after inhalation and oral exposure is limited due to the strong reactivity of acrolein with tissues at the exposure site. Acrolein is a highly reactive electrophile that reacts readily with sulfhydryl groups from proteins and amino acids.
- The main metabolic pathway is through acrolein conjugation with reduced glutathione (GSH) followed by enzyme-catalyzed conversion to mercapturic acid products for urinary excretion. The major urinary products of this pathway are 3-HPMA and CEMA. Minor metabolic pathways are postulated to yield glyceraldehyde and malonic acid.
- Acrolein is not excreted unchanged. Acrolein metabolites are excreted primarily in the urine and exhaled air following oral or inhalation exposure; small quantities are excreted in feces.

3.1.1 Absorption

No studies were located regarding the rate and extent of absorption in humans after inhalation exposure to acrolein. The collection of such data would be problematic, as acrolein is highly reactive with any nucleophilic binding site that it encounters during exposure by any route.

Animal data demonstrate that inhalation absorption of acrolein occurs readily at local sites. Struve et al. (2008) isolated the upper respiratory tract of anesthetized rats to measure the uptake of inhaled acrolein in this region (percent difference between concentration in air before entering the rat nose and the concentration exiting the trachea). At acrolein concentrations of 0.6–3.6 ppm for up to 80 minutes and a constant (unidirectional) airflow rate of 100 mL/minute, uptake efficiency estimates declined with exposure concentration from >90% at 0.6 ppm to ~55% at 3.6 ppm. After the airflow rate was increased from 100 to 300 mL/minute, small decreases in uptake efficiency were seen, with the same concentration-related decrease (85% at 0.6 ppm to 35% at 3.6 ppm) (Struve et al. 2008). When measured over time, efficiency of uptake at 3.6 ppm exposure decreased for the first 12–24 minutes and then remained relatively constant over the remainder of the 80-minute exposure period (Struve et al. 2008). Pre-exposure to acrolein resulted in higher uptake efficiency in the upper respiratory tract: groups of rats pre-exposed to 0.6 or 1.8 ppm acrolein for 6 hours/day, 5 days/week for 14 days had higher uptake efficiency than naïve counterparts (Struve et al. 2008). These experiments demonstrated that at low ppm concentrations, the upper respiratory tract efficiently removes a substantial portion of inhaled acrolein before it reaches the lower respiratory tract, and that higher exposure concentrations lead to greater exposures to the lower respiratory tract. Similar results were obtained in an earlier study in rats using a comparable design (Morris 1996); absorption in the upper respiratory tract of rats did not reach steady state in 40 minutes and was found to be inversely correlated with concentration and respiration rate. Likewise, when the isolated upper respiratory tract of mice was exposed to 1.1 ppm acrolein at a flow rate of 25 mL/minute, the uptake efficiency was estimated to be >92% (Morris et al. 2003). In anesthetized mongrel dogs exposed to concentrations of 172–262 ppm acrolein for 1–3 minutes, retention was independent of the respiratory rate (Egle 1972). At ventilation rates of 6–20 respirations/minute, 80–85% of the inhaled acrolein was retained in the entire respiratory tract, with 75–80% localized in the upper respiratory tract.

While no studies were located of absorption in humans after measured oral doses of acrolein, acrolein absorption was demonstrated in 19 humans by analysis of the urinary metabolite, 3-HPMA; the serum acrolein-protein conjugate [Nε-(3-formyl-3,4-dehydropiperidino)lysine (Acr-FDP)]; and buccal cell

acrolein DNA adducts [α- and γhydroxy-1,N2-cyclic propano-2′-deoxyguanosine (α-OH-Acr-dG and γ-OH-Acr-dG)] up to 24 hours following ingestion of fried fast foods (Wang et al. 2019). Levels of urinary 3-HPMA increased after fast food consumption and generally peaked 12 hours post ingestion; thereafter, the concentrations began decreasing, reaching near-baseline concentrations after 24 hours. At all timepoints after exposure, buccal cell acrolein DNA adducts were increased, while serum protein adducts were unchanged from pre-exposure levels (Wang et al. 2019).

Parent et al. (1996a) administered gavage doses of 2.5 or 15 mg/kg [2,3-^{14}C] acrolein to male and female Sprague-Dawley rats. Doses of 2.5 mg/kg were extensively absorbed, as only 12–15% of the initial dose was found in the feces. In the high-dose group, 28–31% of the initial dose was found in the feces.

No studies were located regarding absorption of acrolein in humans after dermal exposure. In cases of accidental dermal exposure, effects were restricted to the exposed region of the body, presumably because of the high reactivity of acrolein. In an *in vitro* study of dermal permeation, human dermis was exposed to acrolein vapor (153 ppm) in static Franz diffusion cells exposing a surface area of 0.64 cm^2 for up to 30 minutes (Thredgold et al. 2020). Estimates of dermal penetration (measured by analysis of receptor fluid) and absorption (measured by analysis of skin tissue after exposure) were negligible (0.480 and 0.887 μg/cm^2, respectively).

Limited information is available regarding dermal absorption of acrolein in animals. The percutaneous LD_{50} for rabbits ranged from 160 to 1,000 mg/kg, depending on the acrolein concentration and vehicle (water or mineral spirits) (Albin 1962). LD_{50} values for acrolein administered in mineral spirits are lower than those in which water served as the vehicle, likely because of the greater skin permeability of mineral spirits.

3.1.2 Distribution

Acrolein is highly reactive electrophile. Because it readily reacts with biological nucleophiles (proteins, DNA, glutathione), distribution is primarily local at the site of entry with limited systemic distribution.

No studies were located regarding distribution of acrolein in humans or animals after inhalation exposure. Studies regarding absorption in animals exposed by inhalation demonstrated uptake in respiratory tract tissues, but did not indicate whether systemic distribution occurred (Egle 1972; Morris 1996; Morris et al.

2003; Struve et al. 2008). Urinary metabolites of acrolein were detected in mice exposed to 0.5–1 ppm acrolein for 6 hours, suggesting that systemic absorption occurred (Conklin et al. 2017b).

No studies were located regarding distribution of acrolein in humans after oral exposure; however, following voluntary ingestion of fried fast food, the increased concentration of the acrolein urinary metabolite, 3-HPMA, suggested some systemic distribution, while increased acrolein DNA adducts in buccal cells indicated local distribution in the oral cavity (Wang et al. 2019).

In a study conducted by Draminski et al. (1983), the acrolein conjugated metabolite, S-carboxyethyl-mercapturic acid, was identified in the urine of rats after oral administration of a single dose of 10 mg/kg of acrolein, suggesting distribution of acrolein to the liver and kidney, where conjugation most likely occurred. Parent et al. (1996a) detected radioactivity in the kidney, spleen, lungs, blood, liver, fat, adrenals, and ovaries at similar levels in rats sacrificed 168 hours after oral administration of 2.5 mg/kg [2,3-^{14}C]acrolein. Radioactivity in blood and tissue represented approximately 1% of the dose, indicating limited systemic distribution. After i.v. administration of the same dose, radioactivity levels in the kidneys, spleen, lungs, blood, and adrenal glands were between 2- and 100-fold higher compared with oral administration (Parent et al. 1996a).

No studies were located regarding distribution of acrolein in humans or animals after dermal exposure.

3.1.3 Metabolism

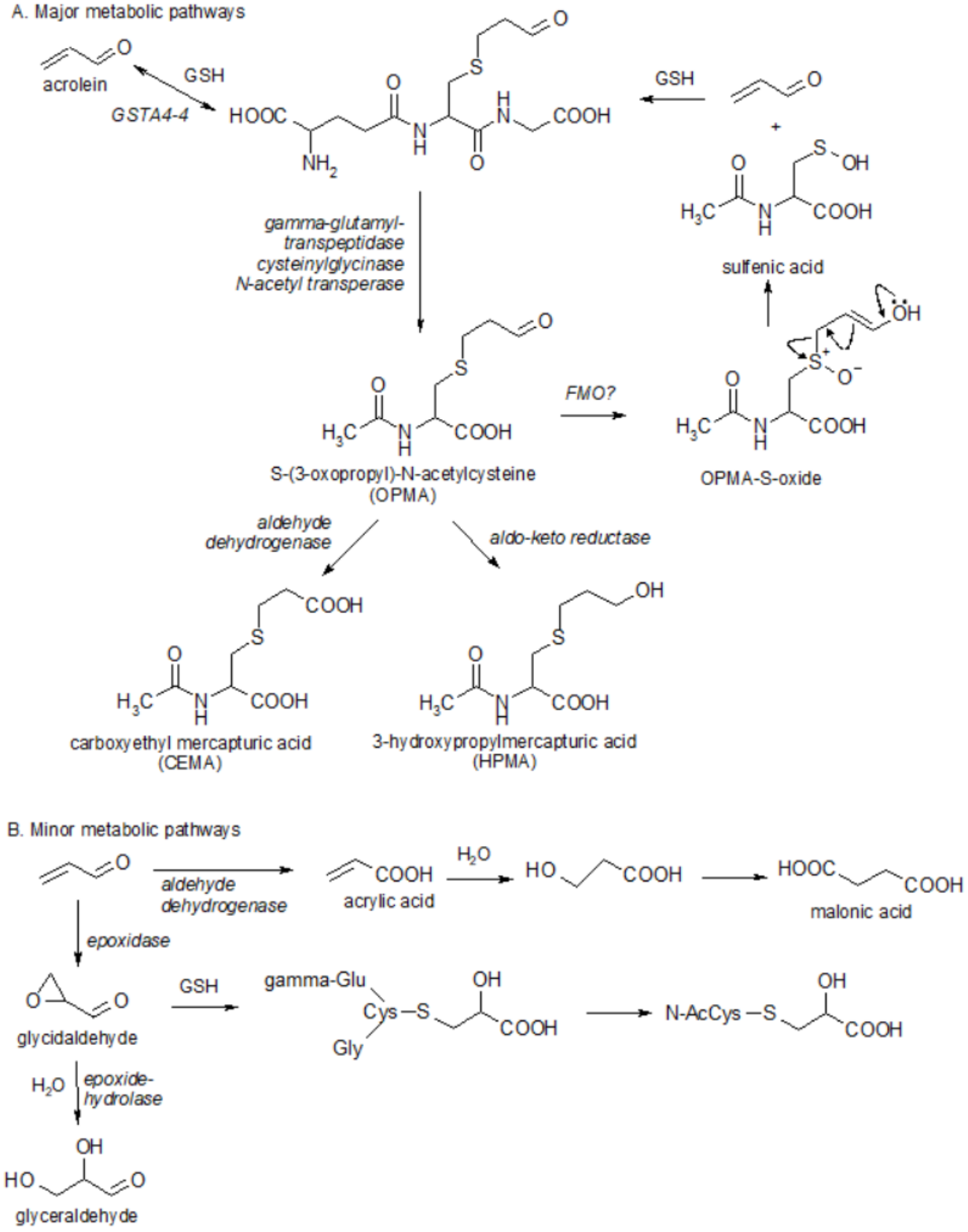
Acrolein metabolism is attributed to conjugation reactions. The primary reaction involves the electrophilic site of acrolein reacting directly with the cysteinyl thiol (-SH) of proteins (lysine and histidine) and nonproteins (glutathione), and this reaction may be nonenzymatic or catalyzed by glutathione-S-transferase (Esterbauer et al. 1975; Parent et al. 1998). In experiments in non-biological, cell-free systems, acrolein formed thiol ethers rapidly (within seconds) in reactions with glutathione or cysteine (Esterbauer et al. 1975, 1976). In *in vitro* experiments using cultured human bronchial cells, human mucoepidermoid pulmonary carcinoma cells, and isolated cell preparations from rat liver and kidneys, acrolein formed conjugates with glutathione and/or thioredoxin and with amino acids including lysine, histidine, cysteine, and N-acetylcysteine (Dawson et al. 1984; Dupbukt et al. 1987; Gurtoo et al. 1981; Xiong et al. 2021, Yang et al. 2004; Zitting and Heinonen 1980). Glutathione depletion in these cells was also reported (Xiong et al. 2021). Glutathione depletion has also been reported after *in vivo* exposure to acrolein (Arumugam et al. 1999a, 1999b; Lam et al. 1985; Struve et al. 2008). For example,

in rats exposed by inhalation, dose-related depletion of glutathione in the nasal respiratory and olfactory mucosa was seen after exposure to 0.1–3.6 ppm of acrolein for 1.5–3 hours (Lam et al. 1985; Struve et al. 2008).

Based on experimental results in rat liver and lung preparations (Patel et al. 1980) as well as *in vivo* studies in rats exposed by oral or i.v. administration (Parent et al. 1998) or subcutaneously (Kaye 1973), Stevens and Maier (2008) developed a metabolic scheme for acrolein (Figure 3-1). As shown in the figure, the major pathway begins with glutathione conjugation (either nonenzymatic or catalyzed by glutathione-S-transferase) in the liver. The glycine and gamma-glutamic acid residues are then enzymatically cleaved via cysteinylglycinase and gamma-glutamyl transferase (GGT), respectively, and the cysteine conjugate that results is metabolized by N-acetyl transferase to yield S-(3-oxopropyl) mercapturic acid (OPMA). OPMA may be reduced by aldo-keto reductase to 3-HPMA or oxidized via aldehyde dehydrogenase to CEMA. These reactions compete for the aldehydic site and result in the major and minor urinary metabolites, respectively. OPMA may also be oxidized by a flavin-containing monooxygenase (FMO) to yield OPMA-S-oxide, which can release acrolein to form sulfenic acid. Two minor pathways have also been proposed. The first involves the epoxidation of acrolein to glycidaldehyde and subsequent glutathione conjugation and conversion to N-acetyl-S-2-hydroxyethylcysteine, which is excreted in urine. Glycidaldehyde may also be metabolized to glyceraldehyde by epoxide hydrolase. In the second minor pathway, acrolein is metabolized by aldehyde dehydrogenase to acrylic acid which may subsequently converted to malonic acid.

Much of the information supporting the metabolic scheme presented above was based on toxicokinetic studies performed by Parent et al. (1996a, 1998) using male and female Sprague-Dawley rats exposed by gavage or i.v. administration to ^{14}C-acrolein. After a single i.v. or oral dose of 2.5 mg/kg, four and six metabolites (respectively) were identified, as shown in Table 3-1. The study authors suggested that the finding of significant quantities of oxalic acid (an oxidation product of malonic acid) after oral administration, but not i.v. administration, might be attributable to metabolism catalyzed by gut microbes (Parent et al. 1998).

Figure 3-1. Metabolism of Acrolein



Source: Stevens and Maier (2008) © 2008 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim

Table 3-1. Metabolite Levels (Percent Sample Radioactivity) in Urine of Rats after Intravenous or Oral Dosing with 2.5 mg/kg Acrolein

	Intravenous (peak levels, 4–8 hours after dosing)[a]		Oral (peak levels, 0–4 hours after dosing)[a]	
Metabolite	Male	Female	Male	Female
3-HPMA	73.3%	74.4%	38.3%	41.2%
Oxalic acid	ND	ND	34.9%	32.9%
CEMA	5.6%	8.3%	11.7%	11.7%
N-Acetyl-S-2-carboxy-2-hydroxyethylcysteine	8.0%	5.5%	9.5%	7.8%
3-Hydroxypropionic acid	11.1%	10.8%	5.6%	6.5%
Malonic acid	ND	ND	Trace	Trace

[a]Values expressed as the percentage of initial sample radioactivity.

3-HPMA = 3-hydroxypropylmercapturic acid; CEMA = N-acetyl-S-(2-carboxyethyl)-L-cysteine; ND = not detected

Source: Parent et al. 1998

After both i.v. and oral dosing with 2.5 mg/kg acrolein, urinary excretion of metabolites was complete by 24 hours post dosing. Parent et al. (1998) exposed additional groups of animals to repeated oral doses of 2.5 mg/kg or a single dose of 15 mg/kg to evaluate the effects on metabolism. After a single high oral dose of 15 mg/kg, metabolites did not appear in the urine until 4–8 hours after dosing and continued to occur at measurable levels beyond 24 hours post dosing. The distribution of metabolites was similar after low and high oral doses as well as after repeated oral exposure (14 daily doses of unlabeled acrolein followed by a single dose of radiolabeled acrolein). In addition, there were no clear sex-related differences in metabolite distribution or excretion rates.

Studies in human smokers (Alwis et al. 2012; Carmella et al. 2007) and in animals (Alarcon 1976; Conklin et al. 2017b; Kaye 1973) support the identification of 3-HPMA as the major urinary metabolite of acrolein. Mice exposed to 0.5–1 ppm acrolein for 6 hours exhibited 2–3-fold increases in urinary levels of 3-HPMA (Conklin et al. 2017b). Similarly, 3-HPMA was identified in the urine of rats after a subcutaneous dose of acrolein (Alarcon 1976; Kaye 1973).

3.1.4 Excretion

No studies were located regarding excretion of acrolein or metabolites after inhalation or dermal exposure in humans or animals, or in humans after oral exposure.

The primary routes of acrolein excretion after oral and i.v. exposure are via urinary metabolites and exhaled carbon dioxide, with lesser amounts excreted in the feces. Available data suggest that urinary and fecal excretion after oral exposure is somewhat dose-dependent, and that there are no sex differences in excretory patterns. Parent et al. (1996a) found that in rats administered a dose of 2.5 mg/kg [2,3-^{14}C]acrolein via gavage, 30–31% of the initial dose was expired as CO_2, while 52–63% was found in the urine and 12–15% was found in the feces. Rats dosed with 15 mg/kg [2,3-^{14}C]acrolein exhibited similar expiration of the initial dose as CO_2, but had a higher fraction of the initial dose going to feces (28–31%) and a lower fraction going to urine (37–41%) (Parent et al. 1996a). Six metabolites of [2,3-^{14}C]acrolein were identified in the urinary fraction of the 2.5 mg/kg group: N-acetyl-S-2-carboxyethylcysteine; N-acetyl-S-2-hydropropylcysteine; N-acetyl-S-2-hydroxyethylcysteine; 3-hydroxypropionic acid; malonic acid; and oxalic acid (Parent et al. 1998). Analysis for metabolites in feces revealed no detectable metabolites. Draminski et al. (1983) reported the presence of the acrolein metabolite, S-carboxyethylmercapturic acid, in the urine of rats after administration of a single oral dose of 10 mg/kg of acrolein. The percentage of the dose recovered as the metabolite in the urine was not determined.

Rats administered 2.5 mg/kg [2,3-^{14}C]acrolein intravenously expired 26–27% of the initial dose as CO_2, which is lower, but not significantly different, from the amount expired by animals orally exposed to the same dose (Parent et al. 1996a). In this study, intravenously administered [2,3-^{14}C]acrolein was predominantly eliminated in the urine (67–69%), with a small fraction found in the feces (1–2%).

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

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

high dose to low dose, route to route, and various exposure scenarios and to study pollutant mixtures (El-Masri et al. 2004). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic endpoints (Clewell 1995).

Research on PBPK models of acrolein have focused on simulating characteristics of the anatomy and physiology of the rodent and human respiratory tract that are thought to contribute to interspecies differences in dose-response relationships for nasal cavity lesions. Important features of acrolein toxicity and kinetics that are relevant to interspecies extrapolation include: (1) necrotic lesions of the nasal respiratory and olfactory epithelia (Dorman et al. 2008); (2) first-pass extraction of acrolein by nasal cavity tissues which decreases as the inhalation exposure concentration increases (Struve et al. 2008); and (3) saturable metabolic clearance of acrolein that contributes to dose-dependent extraction of acrolein in the respiratory tract (Patel et al. 1980; Struve et al. 2008).

Several models have been developed to simulate the kinetics uptake and metabolism of acrolein in the rodent and human respiratory tract (Asgharian et al. 2012; Schroeter et al. 2008; Xi et al. 2018). These models are described in detail in the following discussion because they provide a means to simulate the nasal cavity kinetics of acrolein in rats and humans for supporting interspecies dosimetry extrapolation (Schroeter et al. 2008).

Schroeter et al. (2008) Model

Description. Schroeter et al. (2008) developed a model to simulate the kinetics of inhaled acrolein in rats and humans. The core of the model is a computational fluid dynamics (CFD) model of the nasal cavity. The three-dimensional model was mapped to identify tissues representing the squamous epithelium, respiratory epithelium, and olfactory epithelium (see Figure 1 of Schroeter et al. 2008). Each tissue compartment is represented by layered sub-compartments that provide a diffusion pathway for acrolein in a surface mucus layer, epithelial layer, and submucosa. Inhaled acrolein deposits in the surface mucus layer and then diffuses to deeper sub-compartments where it is cleared by metabolism and absorption to blood. Transfer (flux, pg/cm^2 second) of acrolein from air to epithelial tissue is assumed to occur by diffusion, governed by the concentration in air at the mucus surface (pg/cm^3), an air-phase diffusion coefficient (cm^2/second), and a tissue/air partition coefficient. Exchanges between nasal tissue sub-compartments are also assumed to occur by diffusion governed by a diffusion coefficient and the concentration gradient between sub-compartments. Metabolism clearance of acrolein is simulated as a

first-order process (k, second^{-1}) combined with a saturable processes (V_{max}, K_M), with parameter values assigned to the epithelial and submucosal layers of squamous epithelium, respiratory epithelium, and olfactory epithelium. The disposition of metabolites is not simulated. Absorption to blood from the submucosal layer was simulated as a flow-limited sink with transfer governed by the concentration in the submucosal layer and blood flow to the submucosa.

Parameter Estimates and Calibration. Parameter values for rats and humans are presented in Tables 1 and 2 of Schroeter et al. (2008). Values for nasal cavity physiological parameters (air flow, blood flow, sub-compartment thickness) were adopted from previously published nasal cavity models (Bogdanffy et al. 1999; Frederick et al. 1998; Morris 1996; Morris et al. 1993; Plowchalk et al. 1997). The CFD models were constructed from magnetic resonance imaging of rat and human nasal cavities (Kimbell et al. 1997; Subramaniam et al. 1998). Air flow and air acrolein concentration in the nasal passages were calculated at approximately 150,000 locations (nodal points) in the three-dimensional model by solving a Navier-Stokes equation for a viscous incompressible fluid. An air-phase mass transfer coefficient was calculated at each nodal point assuming equilibrium conditions in which extraction from air was equal to uptake into tissue (Equations 1 and 2 from Schroeter et al. 2008). The air-phase mass transfer coefficient was calculated as the product of the diffusivity of acrolein in tissue (cm^2/second) and the tissue/air partition coefficient divided by the tissue depth. Values for the tissue-phase diffusion coefficient and tissue/air partition coefficient were based on values for formaldehyde measured in skin with adjustments for differences in the diffusivity of acrolein and formaldehyde in water and the water/air partition coefficients for the two chemicals (Kimbell et al. 2001; Loden 1986; RAIS 2023). Parameters for metabolism of acrolein in the nasal cavity of the rat were calibrated to achieve good fit to observations on nasal extraction of acrolein in rats (Morris 1996; Struve et al. 2008). The optimized value for the rat V_{max} was scaled to the human based on the human/rat ratio of the combined respiratory and olfactory surface areas (12.5). The rat value for the first-order metabolism rate coefficient was scaled to the human with a human/rat factor (0.4).

A sensitivity analysis of the model showed that predictions of the average flux of acrolein in olfactory tissues (used for interspecies dosimetry extrapolation) was most sensitive to changes in the metabolism V_{max}, the air/tissue partition coefficient and nasal tissue depth. Predictions showed low sensitivity to the values assigned the first-order metabolism rate coefficient, metabolism K_M, nasal blood flow, or mass transfer rates to the squamous epithelium.

Evaluation. After calibration of the metabolism parameters, the model predicted the overall dose-dependent and air flow-dependent nasal extraction fraction of acrolein in rats exposed to concentrations ranging from 1 to 9 ppm and flow rates ranging from 100 to 443 mL/minute (Morris 1996; Struve et al. 2008). In general, the predicted concentrations were within 20% of observations (shown in Figure 3 of Schroeter et al. 2008). Schroeter et al. (2008) did not report evaluations of the model against observations that were not included in calibrating model parameters.

Applications to Dosimetry. The model was used to predict regional nasal tissue acrolein doses from acrolein exposures in rats and humans (Schroeter et al. 2008). The model predicted a nonlinear decrease in the nasal extraction fraction over an exposure concentration range of 0.1–3.6 ppm. Nasal extraction fraction in the rat was predicted to be 2–3 times higher than in the human. The model predicted higher flux of acrolein into tissues in the anterior region of the nasal cavity compared to the posterior region, consistent with removal of acrolein from the inhaled air in the anterior region. Schroeter at al. (2008) predicted acrolein flux in respiratory and olfactory epithelia in regions of the nasal cavity where lesions were observed in rats exposed to 0.6–1.8 ppm (6 hours/day, 5 days/week) acrolein for periods of up to 65 days (Dorman et al. 2008). Consistent with higher incidences of nasal lesions at the 1.8 ppm exposure level, the model predicted higher tissue flux at the 1.8 ppm exposure level. In general, at the 1.8 ppm exposure level, higher tissue flux was predicted for regions of the nasal cavity that had higher lesion incidences.

Schroeter et al. (2008) applied the model to an interspecies dosimetry extrapolation of olfactory tissue lesions observed in the Dorman et al. (2008) study. Based on the Dorman et al. (2008) study, 0.6 and 1.9 ppm were identified as a NOAEL and LOAEL, respectively. The lowest flux predicted in olfactory tissues in nasal cavity regions that showed elevated lesion incidence (72 pg/cm^2 second) was used to represent the internal dose metric for the extrapolation to humans. This value was lower than the highest flux predicted for the NOAEL (191 pg/cm^2 second). The human model was used to predict fluxes at all nodal points in the olfactory regions of the human CFD model and the 99th percentile value was used to estimate the human equivalent concentration (HEC). The HEC was defined as the exposure that resulted in a 99th percentile flux in olfactory tissues equal to the rat internal dose metric (72 pg/cm^2 second). The HEC for continuous exposure was estimated to be 8 ppb.

Asgharian et al. (2012) Model

Description. Asgharian et al. (2012) developed a model to simulate the kinetics of reactive gases (acetaldehyde, acrolein, formaldehyde) in the human lung. The model simulates the uptake, metabolism, and absorption of acrolein at each airway generation (branching) number in a model of the thoracic and pulmonary regions of the human lung. The upper respiratory tract is not simulated. The model simulates the disposition of acrolein during the entire breathing cycle, which includes inhalation, pause, and exhalation phases. Inhaled acrolein deposits in the airway walls where it is cleared by metabolism and absorption to blood. Air flow in the lung is assumed to be uniform with the average laminar parabolic velocity. Transfer (flux, μg/cm^2 second) of acrolein from air to tissue is assumed to occur by diffusion, governed by the concentration in air at the mucus surface (pg/cm^3), an air-phase diffusion coefficient (cm^2/sec), and a tissue/air partition coefficient. A mass transfer coefficient (cm/second) that accounts for air phase and tissue phase mass transfer was calculated for the air-tissue equilibrium condition. Transfer within the tissue layer from airway wall to blood is assumed to occur by diffusion governed by a tissue-phase diffusion coefficient (cm^2/second), with the concentration at the tissue-blood interface assumed to be zero, reflecting complete clearance of acrolein by metabolism and absorption. Loss of acrolein vapor during the pause and exhalation phases of the breathing cycle is also simulated as a diffusion process governed by the air-phase diffusion coefficient and the concentration in air. Metabolism clearance of acrolein was simulated as a first-order process (k, second^{-1}) combined with a saturable process (V_{max}, K_M), and is assumed to occur in all regions of the lung. Disposition of metabolites is not simulated.

Parameter Estimates and Calibration. Parameter values for the acrolein model are presented in Table 1 of Asgharian et al. (2012). Values for the air-phase and tissue-phase diffusion coefficients, and metabolism parameters were from Schroeter et al. (2008). Airflow and concentrations of acrolein in each airway of the respiratory tract were estimated by solving a Navier-Stokes equation for a viscus incompressible fluid in a branching generation model of the human lung. Mass transfer coefficients were derived for the inhalation, pause, and exhalation phases of the breathing cycle (Asgharian et al. 2011). The concentration of acrolein in tissues was calculated from the reaction diffusion equation reported in Schroeter et al. (2008).

Asgharian et al. (2012) compared predictions from the formaldehyde model to predictions made with other reported models and with observations made during acetaldehyde exposures (Egle 1970; Overton et al. 2001). Evaluations of the acrolein model against observations were not reported.

Applications to Dosimetry. The model was used to predict regional airway (branching generation number) wall flux (rate of loss of acrolein from air to the airway walls) in the thoracic and pulmonary regions of human lung and tracheal tissue concentrations during inhalation of acrolein vapor (Asgharian et al. 2011). Flux was predicted to increase with increasing airflow, peaking at airway branch generations 8–10 when at rest (6.7/L minute) and at airway branch generations 17–18 during heavy exercise (55.3 L/minute). Acrolein concentrations in tracheal tissue were predicted to penetrate only to a depth of 80 µm and be higher at the end of the inspiratory phase of the breathing cycle compared to the end of the breathing cycle. The model predicted a nonlinear increase in tracheal tissue concentrations as the exposure concentration increased, consistent with a lack of strong reaction within the lung tissue, slow diffusion, and vapor release from the tissue back into the air stream (Asgharian et al. 2011, 2012).

Xi et al. (2018) Model

Description. Xi et al. (2018) developed a model to simulate the kinetics of acrolein in the respiratory tract of the rat. The model uses a CFD model of the respiratory tract that includes the nasal cavity, trachea, and lungs extending to the ninth airway bifurcation. The CFD model accounts for regions of turbulent and laminar air flow and deposition of acrolein aerosol droplets (see Figure 1 of Xi et al. 2018). Exposure was simulated as an aerosol of varying droplet diameters (0.48–8 nm) to simulate molecular aggregation of acrolein and water molecules. The tissue model includes two compartments representing the combined mucus and epithelial layer and a vascularized submucosa layer. Transfer (flux, pg/cm^2 second) of acrolein from air to epithelial tissue is assumed to occur by diffusion, governed by the concentration in air at the mucus surface (pg/cm^3), an air-phase mass transfer coefficient (cm/second), and a tissue/air partition coefficient. Acrolein in the epithelial layer is transferred to the submucosa where it is absorbed. Metabolism clearance of acrolein was simulated as a first order process (k, second^{-1}) combined with a saturable processes (V_{max}, K_M), with parameter values assigned to the epithelial and submucosal layers of squamous epithelium, respiratory epithelium, and olfactory epithelium. The disposition of metabolites is not simulated. The model assumes that acrolein that is not metabolized is completely absorbed to blood.

Parameter Estimates and Calibration. The CFD model was based on magnetic imaging of the lung of a 9–10-week-old Sprague-Dawley rat (Corley et al. 2012). A model of laminar and tubule flow in the rat respiratory tract was used to simulate air flow at 3.8 million nodal points of the CFD model (Kim et al. 2014; Li et al. 2017). The change in diameter of airway aerosol droplets resulting from molecular aggregation with water during passage through the airways was simulated using a molecular dynamic

model (Xi et al. 2018). Equations used to calculate transfer of acrolein to tissue were from previously reported models (Schroeter et al. 2008; Tian and Longest 2010a). Parameters for the two-layered model of the respiratory tract tissue were from Tian and Longest (2010a, 2010b). Parameters for diffusion and metabolism in respiratory tract tissue were from previously reported models (Schroeter et al. 2008; Tian and Longest 2010b).

Model predictions were compared to acrolein deposition fractions observed in rats (Struve et al. 2008). The model predicted that molecular aggregation contributed to a decrease in deposition fraction with increasing exposure concentration; however, it could not completely explain the observed decrease in deposition fraction, consistent with saturable metabolism being a major contributor.

Applications to Dosimetry. The model predicted a size dependence on regional deposition fractions, with the largest fraction deposited in the nose. Deposition in the nasal region decreased for approximately 75% for droplet sizes <1 nm to approximately 30% for 8-nm droplets. The size-dependent decrease in deposition in the nose resulted in a size-dependent increase in deposition in the trachea (see Figure 2 of Xi et al. 2018). Regional deposition was also found to be dependent on vapor diffusivity, with increasing deposition in the trachea relative to the nasal cavity, with decreasing diffusivity (see Figure 2 of Xi et al. 2018).

3.1.6 Animal-to-Human Extrapolations

The irritant properties of acrolein have been reported in both human and animal studies. *In vivo* studies in animals and *in vitro* studies in human and animal cell cultures have reported the common mechanisms of action of cellular thiol reactivity and glutathione depletion (Arumugam et al. 1999a, 1999b; Beauchamp et al. 1985; Nardini et al. 2002). Acrolein exposure levels were very comparable for the appearance of cellular changes in nasal epithelium of animals (Cassee et al. 1996a) and onset of nasal irritation in humans (Weber-Tschopp et al. 1977). Therefore, it is reasonable to extrapolate animal health effects to human health risk resulting from acrolein exposure.

3.2 CHILDREN AND OTHER POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal

exposure during gestation and lactation. Children may be more or less susceptible than adults to health effects from exposure to hazardous substances and the relationship may change with developmental age.

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

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

Since point-of-contact irritation is the principal toxic action of acrolein, children are not likely to be more susceptible to acrolein's effects at the tissue level. Despite uncertainties in age-related differences in lung architecture, surface area, and ventilation rates, simple dosimetry modeling of a category 1 gas, such as acrolein, does not suggest significant differences in early juvenile and adult internal inhalation exposure (Ginsberg et al. 2005). It is not known if there are age-related differences in the pharmacokinetics of acrolein. The amount of ingested acrolein available for gastrointestinal irritation would be the same for children and adults. While children may have a higher inhalation rate (per mass) than adults (NRC 1993), it is unknown whether they would continue to breathe more airborne acrolein than adults. While adults have been shown to reduce their respiration rate by as much as 20% in the presence of airborne acrolein (Weber-Tschopp et al. 1977), it is not known if children will react in the same or similar manner. Animal studies have shown offspring of acrolein-exposed mothers to have reduced body weights and skeletal deformities (EPA 1983; Parent et al. 1992c). However, these effects occurred at high oral doses that were fatal to the mothers.

In general, individuals whose respiratory function is compromised, such as those with emphysema, or individuals with allergic airway disease such as rhinitis and/or allergic asthma, will be at a higher risk of developing adverse respiratory responses when exposed to a strong respiratory irritant such as acrolein. This was demonstrated in animals in which allergic airway-diseased mice were more responsive than non-diseased mice to acute respiratory irritant effects of 0.3 ppm acrolein (Morris et al. 2003).

3.3 BIOMARKERS OF EXPOSURE AND EFFECT

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

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

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

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

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

3.3.1 Biomarkers of Exposure

Identification of a specific and reliable biomarker of acrolein exposure has proved to be challenging. Urinary excretion of 3-HPMA, a product of the conjugation of acrolein with glutathione, has been proposed as a biomarker of acrolein exposure. However, it has been reported that other compounds are also metabolized to 3-HPMA, including allylamine (Boor et al. 1987), allyl halides (Kaye and Young 1972), and allyl alcohol, allyl formate, allyl nitrate, and allyl propionate (Kaye 1973), so urinary 3-HPMA is not a specific biomarker for acrolein exposure. In addition, urinary 3-HPMA levels do not provide a means of distinguishing between exogenous and endogenous acrolein.

Alwis et al. (2012) developed a method to examine urinary metabolites of volatile organic compounds (VOCs), including 3-HPMA and CEMA as specific metabolites of acrolein. To validate the method, they compared urinary levels of 3-HPMA and CEMA in smokers and nonsmokers. Higher 3-HPMA and CEMA levels were detected in the urine of tobacco smokers, and there was a significant correlation between these urinary metabolites and serum cotinine (a biomarker for tobacco intake), supporting the use of 3-HPMA and CEMA as markers of exposure to acrolein (Alwis et al. 2012). Chen et al. (2019) evaluated the stability of urinary levels of 3-HPMA as a biomarker of acrolein exposure from cigarette smoke. Urine samples were collected over the course of 20 weeks from a group of smokers supplied with research cigarettes (Chen et al. 2019). The results indicated that 3-HPMA excretion was "fairly" stable in smokers (with steady intake) by repeated measures correlation. The longitudinal consistency intra-class correlation coefficient (ICC) for 3-HPMA was 0.46. The "fair" performance of this metabolite was attributed to the fact that acrolein exposure from sources other than cigarette smoke was likely to have affected the correlation.

Data in animals also show a relationship between acrolein exposure and urinary 3-HPMA. In mice, exposure to 0.5 or 1 ppm acrolein for 6 hours resulted in 2–3-fold increases in urinary levels of creatinine-adjusted 3-HPMA (Conklin et al. 2017a). Zheng et al. (2013) showed that when rats were injected (intraperitoneal or intraspinal) with acrolein, urinary levels of 3-HPMA were elevated in a dose-dependent manner. This effect was inhibited when rats were co-administered acrolein scavengers (hydralazine or phenelzine), supporting the supposition that 3-HPMA in the urine was a specific biomarker for acrolein and correlated with exposure.

Recently, a method was developed for measuring acrolein concentrations in serum (Imazato et al. 2015). In the study, acrolein in serum from humans with no known exposure was measured at levels ranging

from 2.2 to 5.15 μM. As with urinary metabolite levels, serum measurements of acrolein do not provide a method for differentiation between endogenous and exogenous acrolein.

3.3.2 Biomarkers of Effect

Available biomarkers of acrolein effects cannot distinguish between exogenous and endogenous acrolein sources. Acrolein interacts with DNA to form mutagenic adducts including the exocyclic acrolein-deoxyguanosine adduct, AdG (Chen and Lin 2009; Liu et al. 2005). It has been proposed that these adducts could be used as specific biomarkers of DNA damage induced by acrolein (Chen and Lin 2011). Methods to detect these specific adducts in human saliva (Chen and Lin 2011), placenta (Chen and Lin 2009), and human lymphocytes (Chen and Lin 2009; Yin et al. 2013) have been developed. In addition, Wang et al. (2019) observed increased buccal cell acrolein-DNA adducts in humans up to 24 hours after they consumed fried fast foods (a known source of acrolein exposure).

Acrolein-lysine adducts have been proposed for use as urinary biomarkers of oxidative stress/oxidative damage (Moghe et al. 2015). It is important to note, however, that these acrolein adducts have also been proposed as biomarkers for a wide variety of disease states ranging from Alzheimer's disease (Yoshida et al. 2023) to osteoporosis (Herr et al. 2021).

3.4 INTERACTIONS WITH OTHER CHEMICALS

Acrolein inhalation was shown to alter the uptake of acetone from the upper respiratory tract of rats and mice under co-exposure conditions (Morris 1996; Morris et al. 2003). Acrolein exposure produced an increase in the uptake of acetone (up to 2-fold) and prevented acetone from achieving steady-state absorption (Morris 1996; Morris et al. 2003).

Ansari et al. (1988) showed that acrolein enhances the inhibitory effect that certain industrial chemicals, such as styrene and 1,2-dichloroethane, have on the α-l-proteinase inhibitor of human plasma *in vitro*. A decrease in the activity of the α-l-proteinase inhibitor may result in an increase in the activity of the lung enzyme neutrophil elastase, which can lead to the development of emphysema.

Acrolein has been shown to increase the pentobarbital- and hexobarbital-induced sleeping time in rats (Jaeger and Murphy 1973). The mechanism, according to the study authors, could include changes in the absorption and distribution of the barbiturates. The mechanism may involve a covalent reaction between

acrolein and cytochrome P450, leading to inactivation of P450 and prolonged action of the barbiturates (Lame and Segall 1987).

Acrolein forms adducts with thiols such as glutathione, cysteine, N-acetylcysteine, and others. These reactions protect tissues and cells from the cytotoxic effects of acrolein or acrolein-releasing substances (Brock et al. 1981; Chaviano et al. 1985; Dawson et al. 1984; Gurtoo et al. 1981; Ohno and Ormstad 1985; Whitehouse and Beck 1975). However, at higher acrolein exposure levels, depletion of glutathione renders tissues susceptible to damage from other endogenous and exogenous sources of oxidative stress.

Exposure of mice for 10 minutes to mixtures of sulfur dioxide and acrolein showed that either irritant can alter or block the effect of the other (Kane and Alarie 1979). Furthermore, when the mice were exposed to mixtures, recovery was much slower than when exposed to the individual chemicals. The study authors postulated that a bisulfite-acrolein adduct may be formed. When exposure ceased, this adduct would release acrolein, thus preventing immediate recovery.

Kane and Alarie (1978) exposed mice to mixtures of acrolein and formaldehyde and showed that the respiratory response to mixtures was less pronounced than the response to either chemical alone. However, *in vitro* studies using human bronchial epithelial BEAS-2B cells demonstrated that co-exposure to formaldehyde and acrolein resulted in synergistic effects on cytotoxicity and measures of oxidative stress (Zhang et al. 2019), apoptosis (Zhang et al. 2020b), and DNA damage (Zhang et al. 2020a, 2020b). Similarly, Zhang et al. (2018) reported synergistic effects of formaldehyde and acrolein on measures of cytotoxicity, DNA damage, and micronuclei in human lung carcinoma A549 cells.

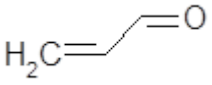
Human subjects exposed to side-stream smoke containing acrolein reported a higher degree of annoyance than a different group of subjects exposed to the same concentration of acrolein alone, suggesting that other smoke constituents contribute to irritant effects (Weber-Tschopp 1977).

CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

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

Table 4-1. Chemical Identity of Acrolein

Characteristic	Information	Reference
Chemical name	Acrolein	
Synonym(s) and registered trade name(s)	Acraldehyde, acrylic aldehyde, acrylaldehyde, allyl aldehyde, ethylene aldehyde, 2-propenal, propenaldehyde, Aqualin, Biocide, Crolean, MAGNACIDE B®, MAGNACIDE H®, Slimicide	NLM 2023; RTECS 2019
Chemical formula	C_3H_4O	NLM 2023
SMILES	C=CC=O	NLM 2023
Chemical structure		
CAS Registry Number	107-02-8	NLM 2023

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

4.2 PHYSICAL AND CHEMICAL PROPERTIES

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

Table 4-2. Physical and Chemical Properties of Acrolein

Property	Information	Reference
Molecular weight	56.06	O'Neil 2013
Color	Colorless or yellowish	Lewis 1997
Physical state	Liquid	Lewis 1997
Melting point	-87.8 °C	NLM 2023
Boiling point	52.3 °C	NLM 2023
Density at 20°C	0.840 g/cm^3	NLM 2023
Odor	Disagreeable, choking odor, pungent	Lewis 1997; O'Neil 2013
Odor threshold:		
Water	0.11 ppm	Amoore and Hautala 1983
Air	0.16 ppm	Amoore and Hautala 1983
Taste threshold	No data	
Solubility:		
Water at 25°C	2.12x10^5 mg/L	Seidell 1941
Organic solvents	Miscible with lower alcohols, ketones, benzene, diethyl ether, and other common organic solvents	Tomlin 2003
Partition coefficients:		
Log K_{ow}	-0.01	Hansch and Leo 1995
K_{oc}	24 (estimated)[a]	Lyman 1982
Vapor pressure at 25°C	274 mmHg	Daubert and Danner 1987
Henry's law constant at 25°C	1.22x10^{-4} atm-m^3/mol	Gaffney et al. 1987
Autoignition temperature	220 °C	NLM 2023
Flashpoint	-18 °C (open cup) -26 °C (closed cup)	NLM 2023; O'Neil 2013
Flammability limits	2.8–31 volume %	NLM 2023
Conversion factors		
Air	1 ppm (v/v)=2.3 mg/m^3 1 mg/m^3=0.43 ppm (v/v)	Verschueren 2001

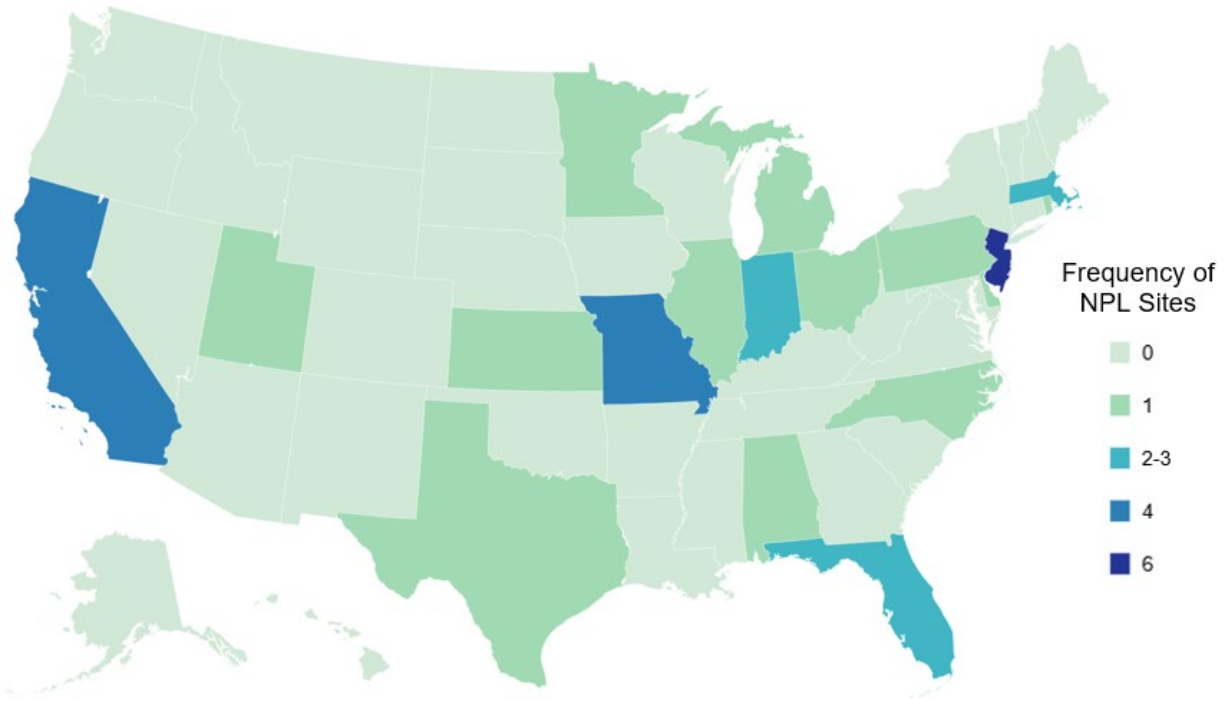
[a]K_{oc} value was estimated using the measured log K_{ow} (-0.01) and a linear regression equation described in Lyman (1982).

CHAPTER 5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Acrolein has been identified in at least 33 of the 1,868 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (ATSDR 2022a). However, the number of sites in which acrolein has been evaluated is not known. The number of sites in each state is shown in Figure 5-1.

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



Source: ATSDR 2022a

- The main route of acrolein exposure for the general population stems from indoor air; smoking (cigarettes, e-cigarettes, marijuana), cooking with oils and fats, and building materials all contribute to acrolein levels in the air.
- Ingestion of some foods and beverages and consumption of contaminated drinking water can also be routes of exposure.
- Acrolein is released to the environment in emissions from manufacturing and use facilities, combustion processes (including automobile emissions and smoke from any type of fire), degradation of other pollutants, and direct release.
- Acrolein is a reactive compound and is unstable in the environment.

- Acrolein is not persistent in the atmosphere and reacts with hydroxyl radicals, with a half-life of 15–20 hours.
- Acrolein can be removed from water and soil by volatilization, abiotic, and biodegradation processes.

Acrolein may be released to the environment in emissions and effluents from its manufacturing and use facilities, in emissions from combustion processes (including cigarette smoking and combustion of petrochemical fuels), from direct application to water and wastewater as a slimicide and aquatic herbicide, as a photooxidation product of various hydrocarbon pollutants found in air (including propylene and 1,3-butadiene), and from land disposal of some organic waste materials. Acrolein is a reactive compound and is unstable in the environment.

In ambient air, the primary removal mechanism for acrolein is predicted to be reaction with photo-chemically generated hydroxyl radicals (half-life, 15–20 hours). Products of this reaction include carbon monoxide, formaldehyde, and glycolaldehyde. In the presence of nitrogen oxides, peroxynitrate and nitric acid are also formed. Small amounts of acrolein may also be removed from the atmosphere in precipitation. Insufficient data are available to predict the fate of acrolein in indoor air. In water, small amounts of acrolein may be removed by volatilization (half-life, 23 hours from a model river 1 m deep), aerobic biodegradation, or reversible hydration to β-hydroxypropionaldehyde, which subsequently biodegrades. Based on the reactivity of acrolein, it is expected that removal of acrolein from water through the binding of the chemical to dissolved and suspended organics will become increasingly important as the concentration of the organics in water increases. However, information on this removal process could not be located.

Half-lives of <1–3 days for small amounts of acrolein in surface water have been observed. When highly concentrated amounts of acrolein are released or spilled into water, this compound may polymerize by oxidation or hydration processes. In soil, acrolein is expected to be subject to removal through volatilization, abiotic and biotic degradation processes, and possibly irreversible binding to soil components. This compound can be highly mobile in soil; however, this movement is expected to be attenuated by the removal processes given above.

Data regarding the monitoring of acrolein are available for ambient and indoor air. Data from the EPA National Air Quality System (AQS) show the most recent mean acrolein concentrations in ambient air in the United States ranging between 0.062 and 0.591 ppbv (ppb based on volume) (EPA 2023a). For indoor air, acrolein concentrations range from <0.02 to 43 $\mu g/m^3$ (<0.02–18 ppbv), with the higher

concentrations in this range typically being obtained from indoor environments where the combustion of tobacco products occurs (Chan et al. 2016; Seaman et al. 2007; Weber et al. 1979).

No current data indicate that acrolein is a contaminant of drinking water supplies in the United States. Acrolein was found in drinking water stored in polyethylene cisterns in Brazil (de Oliveira Moura et al. 2019). The Water Quality Portal (WQP) database data indicate that acrolein occurs at a low frequency in wastewater streams, ambient surface water, and groundwater in the United States (WQP 2023). Acrolein is intentionally introduced into irrigation canals and other waterways to control underwater plants and other aquatic life. No current information on the quantities of acrolein that are released into waterways as a pesticide are available.

Acrolein is a gaseous constituent of cigarette smoke and has been detected at levels equivalent to 3–220 μg per cigarette. Acrolein is formed when fats are heated to high temperatures. It has also been found in foods and food products such as raw cocoa beans, volatiles from cooked mackerel and white bread, and vegetable oils, wine, whiskey, and lager beer. Acrolein concentrations in food are typically under 40 μg/g, with most concentrations at ≤1 μg/g (WHO 2002). Acrolein can be produced endogenously as a product of lipid peroxidation (Uchida et al. 1998a, 1998b) and can form protein adducts that have been implicated in atherosclerosis and Alzheimer's disease.

Monitoring data indicate that the general population may be exposed to acrolein through inhalation of contaminated air and ingestion of certain foods. Because of the lack of recent, comprehensive monitoring data, the average daily intake of acrolein through the consumption of food and drinking water, and the relative importance of each of these sources of exposure, cannot be adequately determined. However, based on the assumption that all foods contain maximal reported levels of acrolein, an exposure of around 1 mg/person/day (17 g/kg body weight/day) may be estimated (Guth et al. 2013). Estimating the typical level of exposure to acrolein is complicated because acrolein is a common component of tobacco smoke, and there is wide variation among individuals regarding the frequency and level of exposure to tobacco smoke. Even so, estimates of acrolein exposure in both the general population and for nonsmokers living with a resident smoker are available. A study from Canada (Environment Canada 2000) suggests that the general population is exposed to an average acrolein concentration of 1.3 $\mu g/m^3$, with a median value of 0.6 $\mu g/m^3$ from outdoor and indoor air. Based on this average acrolein exposure and an inhalation volume of 20 m^3, it can be estimated that the average adult inhales 26 μg acrolein/day. Nazaroff and Singer (2004) estimated that the daily average inhalation intakes of acrolein through environmental tobacco smoke (ETS) over the lifetime of a nonsmoker are 22–50 μg/day for males and 16–36 μg/day for females.

These exposure levels for nonsmokers in a household with ETS are approximately 2.2–3.7 times higher than residents living within a household without ETS.

There is potential for exposure to acrolein in many occupational settings as the result of its varied uses and its formation during the combustion and pyrolysis of materials such as wood, petrochemical fuels, and plastics. As a result, it would be difficult to list all occupations in which work-related exposure to acrolein occurs. Occupational exposure can occur via inhalation and dermal contact.

5.2 PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.2.1 Production

Acrolein was first produced commercially in the 1930s through the vapor-phase condensation of acetaldehyde and formaldehyde (Etzkorn et al. 2002). A second method was developed in the 1940s, which involved the vapor-phase oxidation of propylene; however, this method was not used at first due to the poor performance of cuprous oxide catalysts. During the 1960s, propylene oxidation was greatly enhanced by the introduction of bismuth molybdate-based catalysts and has since become the primary method used for the commercial production of acrolein. Acrylic acid and carbon oxides are the major byproducts produced during this reaction. Minor byproducts are acetaldehyde, acetic acid, formaldehyde, and polyacrolein.

The national aggregate production volume of acrolein was between 250 million and <500 million pounds annually in the years 2016–2019, for five reporting companies (Arkema Inc; Baker Hughes, Inc; Evonik Corp; Halliburton; The Dow Chemical Company); specific information is not available based on confidential business information (CBI) (EPA 2022a).

Table 5-1 summarizes information on companies that reported the production, import, or use of acrolein for the Toxics Release Inventory in 2021 (TRI21 2023). The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list.

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

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AL	2	0	999,999	1, 3, 5, 6
CA	1	100,000	999,999	9
GA	1	1,000	9,999	1, 5
IA	28	0	99,999	1, 5, 9, 12, 13, 14
IL	11	0	99,999	1, 5, 12, 13, 14
IN	8	100	999,999	1, 5, 9, 13, 14
KS	7	0	9,999	1, 4, 5, 12, 13, 14
LA	2	100	999,999	1, 3, 4, 5, 6, 13, 14
MI	4	100	9,999	1, 5, 9, 13, 14
MN	8	0	99,999	1, 5, 9, 13, 14
MO	1	100	999	1, 5, 13, 14
NC	2	100	9,999	1, 5
ND	3	100	9,999	1, 5, 9, 13, 14
NE	15	0	99,999	1, 5, 9, 13, 14
NY	1	1,000	9,999	1, 13
OH	5	100	9,999	1, 5, 12, 13, 14
OK	1	0	99	1, 5
OR	1	100	999	1, 5, 13, 14
PA	1	100	999	1, 4, 13, 14
SC	2	0	99	1, 5
SD	6	100	99,999	1, 5, 9, 13, 14
TN	1	1,000	9,999	1, 5, 13, 14
TX	18	0	999,999	1, 3, 5, 6, 7, 12, 13, 14
VA	1	0	99	1, 5
WI	2	0	999	1, 5, 13, 14

[a]Post office state abbreviations used.
[b]Amounts on site reported by facilities in each state.
[c]Activities/uses:

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

Source: TRI21 2023 (Data are from 2021)

Acrolein is also produced within the body by the metabolism of other substances, such as allyl acetate, allyl alcohol, cyclophosphamide, and ifosfamide (Auerbach et al. 2008; Sakata et al. 1989).

5.2.2 Import/Export

The Baker Hughes Corporation reported that 630,960 pounds of acrolein were exported in 2019; however, the four other manufacturers declared these data as CBI or no exports (EPA 2022a). All five domestic chemical companies reporting to the CDR declared zero imports or that information as CBI in 2019 (EPA 2022a).

5.2.3 Use

The largest single use for acrolein is as an intermediate in the manufacture of acrylic acid, most of which is converted to its lower alkyl esters (IARC 2021). Acrolein is also used as an herbicide (trade name Magnacide H) and biocide (trade name Magnacide B) (NPIRS 2023). It is used as an herbicide in irrigation waters and drainage ditches to control algae and aquatic weeds, and as a biocide to control mollusks in recirculating process water systems; as a slimicide in the paper industry; as a biocide in oil wells and liquid petrochemical fuels; in the cross-linking of protein collagen in leather tanning; as a tissue fixative in histological samples; in the manufacture of colloidal forms of metals; in the production of perfumes; as a warning agent in methyl chloride refrigerant; and as an intermediate in the manufacture of methionine and its hydroxyl analogue, glutaraldehyde, allyl alcohol, pyridines, and tetrahydrobenz-aldehyde (Arntz et al. 2012; Etzkorn et al. 2002; Hess et al. 1978; IARC 2021; Lewis 1997; NPIRS 2023; O'Neil 2013; Windholz et al. 1983). Isolated, refined acrolein is used mainly as a biocide and as an intermediate in the production of methionine, which is a protein supplement used in animal feed (Arntz et al. 2012; IARC 2021). Due to its pungent odor, acrolein was once added as a warning agent to methyl chloride refrigerant, which is no longer manufactured or used (IARC 2021). Acrolein has been used to make synthetic glycerol, acrolein polymers, polyurethane, and polyester resins (Lewis 1997). It has also been used in military poison gas mixtures (IARC 2021).

5.2.4 Disposal

Prior to implementing land disposal of waste residues (including waste sludge), environmental regulatory agencies should be consulted for guidance on acceptable disposal practices. Acrolein may be subject to explosive self-polymerization: discharge carefully into water; add excess 10% sodium bisulfite solution; dilute product with excess water and discharge into an oxidation pond; or transport without dilution to an incineration plant (WHO 1991). Materials containing small amounts of acrolein may be disposed of by neutralization (if needed), followed by secondary biological treatment or by submerged combustion (to

concentrate the waste) followed by incineration (Hess et al. 1978). On-site combustion is an option for disposal if the spill site is in a very remote, inaccessible area, and there is danger of subsequent discharge if other methods of disposal are attempted.

Acrolein has been identified as a hazardous waste by the EPA, and the disposal of this compound is regulated under RCRA. Specific information regarding federal regulations concerning disposal of hazardous wastes through land treatment, landfilling, incineration, thermal treatment, chemical/physical/biological treatment, underground injection, and deep-sea injection are provided in the Code of Federal Regulations (40 CFR 190–399). Release of acrolein in wastewater is regulated under the Clean Water Act by the National Pollutant Discharge Elimination System (NPDES).

Information regarding effluent guidelines and standards for acrolein may be found in 40 CFR 122, 40 CFR 125, 40 CFR 268, 40 CFR 413, 40 CFR 423, and 40 CFR 433 (EPA 2022b, 2022c, 2022d, 2022e, 2022f, 2022g).

Pursuant to RCRA Section 3004(g)(5), EPA has proposed to restrict the land disposal of acrolein (EPA 1989). Acrolein may be land disposed only if prior treatment standards have been met, or if disposal occurs in units that satisfy the statutory no migration standard (EPA 1989). Proper guidelines and standards are outlined in the Federal Register (EPA 1989).

5.3 RELEASES TO THE ENVIRONMENT

The Toxics Release Inventory (TRI) data should be used with caution because only certain types of facilities are required to report (EPA 2022i). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ ≥10 full-time employees; if their facility's North American Industry Classification System (NAICS) codes is covered under EPCRA Section 313 or is a federal facility; and if their facility manufactures (defined to include importing) or processes any TRI chemical in excess of 25,000 pounds, or otherwise uses any TRI chemical in excess of 10,000 pounds, in a calendar year (EPA 2022i).

5.3.1 Air

Estimated releases of 330,370 pounds (~149.85 metric tons) of acrolein to the atmosphere from 135 domestic manufacturing and processing facilities in 2021, accounted for about 97% of the estimated total

environmental releases from facilities required to report to the TRI (TRI21 2023). These releases are summarized in Table 5-2.

Table 5-2. Releases to the Environment from Facilities that Produce, Process, or Use Acrolein[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
AL	2	1,250	0	0	0	0	1,250	0	1,250
CA	1	3	0	0	0	5	3	5	8
CO	2	0	0	0	0	0	0	0	0
GA	1	7,928	0	0	0	0	7,928	0	7,928
IL	9	14,098	87	0	0	0	14,098	87	14,185
IN	8	11,884	0	0	0	0	11,884	0	11,884
IA	27	128,322	634	0	1	0	128,900	57	128,957
KS	7	22,012	0	0	0	0	22,012	0	22,012
LA	2	1,549	1	0	0	0	1,550	0	1,550
MI	4	7,627	0	0	0	0	7,627	0	7,627
MN	8	12,172	0	0	0	0	12,172	0	12,172
MO	2	1,721	0	0	0	0	1,721	0	1,721
NE	15	51,921	0	0	5	0	51,926	0	51,926
NY	1	3,543	0	0	0	0	3,543	0	3,543
NC	2	14,826	4	0	0	80	14,830	80	14,910
ND	3	5,844	0	0	0	0	5,844	0	5,844
OH	5	6,948	0	7,028	0	0	13,976	0	13,976
OK	1	1,373	0	0	0	0	1,373	0	1,373
OR	1	281	0	0	0	0	281	0	281
PA	1	2,011	0	0	0	0	2,011	0	2,011
SC	2	2,020	0	0	0	0	2,020	0	2,020
SD	6	11,852	0	0	0	0	11,852	0	11,852
TN	1	3,601	0	0	0	0	3,601	0	3,601
TX	20	2,936	582	3,022	0	0	5,958	582	6,540
VA	1	12,987	0	0	0	0	12,987	0	12,987

Table 5-2. Releases to the Environment from Facilities that Produce, Process, or Use Acrolein[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
WI	3	1,661	0	0	0	0	1,661	0	1,661
Total	135	330,370	1,307	10,050	6	85	341,008	811	341,819

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

RF = reporting facilities; UI = underground injection

Source: TRI21 2023 (Data are from 2021)

Potential sources of atmospheric release of acrolein include emissions from facilities involved in the manufacture or use of products containing acrolein; volatilization from treated waters and contaminated waste streams; formation as a photooxidation product of various hydrocarbon pollutants such as propylene, 1,3-butadiene, and other dienes; emissions from combustion processes; and use in petroleum operations (DOI 1994; Ghilarducci and Tjeerdema 1995; Graedel et al. 1978; Maldotti et al. 1980; WHO 1991, 2002).

Specific combustion sources include exhaust gas from engines powered by gasoline, diesel or other petrochemical fuels, power plants, burning vegetation (i.e., forest fires), combustion of cellulose materials such as wood, cotton, tobacco, and marijuana, and combustion of polyethylene plastics (EPA 1998a; 1998b; Hodgkin et al. 1982; Jonsson et al. 1985; Lipari et al. 1984; Spada et al. 2008; WHO 1991, 2002). Acrolein is also a pyrolysis product of polyethylene, animal fats and vegetable oils, cellophane, plastics, and paraffin wax (Boettner and Ball 1980; Chiang et al. 2022; EPA 1980; Potts et al. 1978; Tanne 1983; Wharton 1978). The concentrations of acrolein in emissions from various combustion and pyrolysis processes are listed in Table 5-3.

Table 5-3. Acrolein in Emissions from Combustion

Source	Concentration	References
Auto exhaust gas		
Gasoline engine	Not detected to 27.7 ppm (detection limit 0.01 ppm); 0–7.79% of total aldehydes, excluding acetone	IARC 2021; Lipari and Swarin 1982; Nishikawa et al. 1987a; Seizinger and Dimitriades 1972; Sigsby et al. 1987; Zweidinger et al. 1988
Gasoline engine	0.16 mg/L gasoline	Grosjean et al. 2001
	0.01–0.26 mg/mile	Baldauf et al. 2005
Diesel engine	2.26 mg/L diesel fuel	Grosjean et al. 2001
Diesel engine	0.05–0.3 ppm	IARC 2021; Seizinger and Dimitriades 1972
Ethanol engine	Not detected (detection limit 0.01 ppm)	Lipari and Swarin 1982
Cigarette smoke	3–220 µg/cigarette	Dong et al. 2000; Guerin et al. 1987; Hoffmann et al. 1975; Horton and Guerin 1974; Lau et al. 1997; Magin 1980; Manning et al. 1983
	1.6–22 µg/cigarette with carbon filter	Thweatt et al. 2007
Marijuana smoke	92–145 µg/cigarette	Hoffmann et al. 1975; Horton and Guerin 1974
e-cigarette vapor	<9.28–9,180 ng/puff	Belushkin et al. 2020; Gillman et al. 2020
Smoke		
Wood	50 ppm	Einhorn 1975
Cotton	60 ppm	
Kerosene	<1 ppm	
Emissions from woodburning fireplaces	21–132 mg/kg wood 20–103 mg/kg wood	Lipari et al. 1984 EPA 1993
Softwood	46.90 mg/kg wood	McDonald et al. 2000
Hardwood	91.23 mg/kg wood	
Hardwood, wood stove	45.54 mg/kg wood	
Emissions from power plants		
Coal-fueled	0.002 pounds of aldehydes/ 1,000 pounds of fuel	Natusch 1978
Gas-fueled	0.2 pounds of aldehydes/1,000 pounds of fuel	
Oil-fueled	0.1 pounds of aldehydes/1,000 pounds of fuel	
Pyrolysis of polyvinyl chloride food-wrap film during hot wire cutting	27–151 ng/cut	Boettner and Ball 1980

Table 5-3. Acrolein in Emissions from Combustion

Source	Concentration	References
Emissions from the combustion of polyethylene foam	2–23 ppm	Potts et al. 1978
Pyrolysis of polyethylene foam	76–180 ppm	Potts et al. 1978
15 cm above heated cooking oil	2.5–30 mg/m^3	EPA 1980
Emissions from burning candle	0.18 µg/kg	Lau et al. 1997

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

Table 5-4. Acrolein Emissions to the Air Based on 2017 National Emissions Inventory (NEI)

Emission sector	Pounds emitted
Bulk gasoline terminals	201
Fires, prescribed fires	47,288,355
Fires, wildfires	90,147,017
Fuel combustion, commercial/institutional, biomass	40,794
Fuel combustion, commercial/institutional, coal	378
Fuel combustion, commercial/institutional, natural gas	41,834
Fuel combustion, commercial/institutional, oil	1,114
Fuel combustion, commercial/institutional, other	1,613
Fuel combustion, electric generation, biomass	207,929
Fuel combustion, electric generation, coal	103,362
Fuel combustion, electric generation, natural gas	61,135
Fuel combustion, electric generation, oil	861
Fuel combustion, electric generation, other	23,726
Fuel combustion, industrial boilers, ICEs, biomass	691,309
Fuel combustion, industrial boilers, ICEs, coal	5,419
Fuel combustion, industrial boilers, ICEs, natural gas	3,699,365

Table 5-4. Acrolein Emissions to the Air Based on 2017 National Emissions Inventory (NEI)

Emission sector	Pounds emitted
Fuel combustion, industrial boilers, ICEs, oil	6,154
Fuel combustion, industrial boilers, ICEs, other	9,827
Fuel combustion, residential, other	0
Fuel combustion, residential, wood	1,841,371
Gas stations	0
Industrial processes, cement manufacturing	32
Industrial processes, chemical manufacturing	195,644
Industrial processes, ferrous metals	6,939
Industrial processes, mining	8
Industrial processes, not elsewhere classified	212,798
Industrial processes, non-ferrous metals	5,707
Industrial processes, oil and gas production	3,238,585
Industrial processes, petroleum refineries	9,935
Industrial processes, pulp and paper	412,298
Industrial processes, storage and transfer	5,904
Miscellaneous non-industrial, not elsewhere classified	147,237
Mobile, aircraft	2,470,330
Mobile, commercial marine vessels	159,792
Mobile, locomotives	837,941
Mobile, non-road equipment, diesel	3,194,566
Mobile, non-road equipment, gasoline	655,099
Mobile, non-road equipment, other	76,384
Mobile, on-road diesel heavy duty vehicles	1,463,230
Mobile, on-road diesel light duty vehicles	532,979
Mobile, on-road gasoline heavy duty vehicles	29,545
Mobile, on-road gasoline light duty vehicles	1,684,985
Solvent, degreasing	270
Solvent, graphic arts	15
Solvent, industrial surface coating and solvent use	8,015
Waste disposal	257,242

ICE = internal combustion engine

Source: EPA 2022h

Formation of acrolein in air is known to occur through photochemical reactions of VOCs that are released from a number of differing source types, including solvent and fuel vapors and automobile exhaust (Ghilarducci and Tjeerdema 1995; Liu et al. 1999a; 1999b). Acrolein has been produced by the

photodegradation of plastic debris (Lomonaco et al. 2020). Seaman et al. (2007) measured the emission of acrolein from building materials used in homes; results are summarized in Table 5-5.

Table 5-5. Acrolein Emissions from Building Material

Source	Concentration
Latex paint	0.35 ng/g of material
Particle board	1.0 ng/g of material
Lumber	
Pine	5.9 ng/g of material
Douglas fir	8.1 ng/g of material
Yellow poplar and red oak	1.0 ng/g of material
Redwood lumber	1.3 ng/g of material

Source: Seaman et al. 2007

The intentional release of acrolein into irrigation channels as an herbicide and molluscicide also results in the volatilization of acrolein into air (DOI 1994; EPA 2003; Ghilarducci and Tjeerdema 1995). In the San Joaquin Valley of California, it was reported that 194,668 pounds (97.3 tons) of acrolein were emitted into the air from agricultural uses of the pesticide in 2001, which amounted to 1.4% of the total pesticide emissions from this region (CEPA 2002).

Another source of acrolein is through the emissions from dairy silages and other feedstuffs (Malkina et al. 2011). Acrolein was released into the air from a cowshed, oxidation pond, and solid-liquid separation tank on a large dairy farm (Guo et al. 2019). When deep-frying using palm, soybean, or olive oil, acrolein was released at rates of 73.4–674 μg/m^3 (Chiang et al. 2022).

5.3.2 Water

Estimated releases of 1,307 pounds (~0.59 metric tons) of acrolein to surface water from 135 domestic manufacturing and processing facilities in 2021, accounted for < 1% of the estimated total environmental releases from facilities required to report to the TRI (TRI21 2023). This estimate includes releases to wastewater treatment and publicly owned treatment works (POTWs) (TRI21 2023). These releases are summarized in Table 5-2.

Acrolein may be released to water in effluents from its manufacturing plants and use facilities (see Section 5.2.3 for specific information regarding uses) and from its direct application to water as a broad-

range biocide in irrigation canals, cooling towers, water treatment basins, and process water circuits (DOI 1994; EPA 2003; Ghilarducci and Tjeerdema 1995; IARC 2021; Lue-Hing et al. 1981; Nordone et al. 1996a, 1996b; WHO 1991; WSSA 1983).

Acrolein in effluent concentrations from seven types of potable water reuse systems were reported as <0.010–0.333 µg/L (Marron et al. 2020).

The amount of acrolein released from industrial operations to publicly owned treatment works (POTWs) in U.S. waters in 1986 was estimated to be 1,645,600 pounds/year (823 tons/year) (EPA 1991). However, it was reported that a large portion of the acrolein received by POTWs is removed before discharge in effluent streams, with 5% released to surface waters, 0–5% to air, and 10% to sludge (EPA 1991).

Data on the release of acrolein into water as a consequence of its use as a pesticide are available only for the state of California. It is reported that usage of acrolein in California declined from 328,238 pounds (164 tons) in 1999 to 290,180 pounds (145 tons) and 233,928 pounds (117 tons) in 2000 and 2001, respectively (EPA 2003). The predominant use of acrolein is as an aquatic herbicide with releases into rights-of-way (i.e., irrigation canals) and other water areas amounting to 326,767 pounds (163 tons), 297,320 pounds (149 tons), and 239,362 pounds (120 tons) in 1999, 2000, and 2001, respectively. The decrease in acrolein usage is due to changes in the permitting process required prior to acrolein treatment of irrigation canals instituted in 2001. No current information is available on the usage of acrolein after the permitting process changed.

5.3.3 Soil

Estimated releases of 6 pounds (~0.0027 metric tons) of acrolein to soil from 135 domestic manufacturing and processing facilities in 2021, accounted for < 1% of the estimated total environmental releases from facilities required to report to the TRI (TRI21 2023). An additional 10,050 pounds (~4.56 metric tons), constituting about 3% of the total environmental emissions, were released via underground injection (TRI21 2023). These releases are summarized in Table 5-2.

The occurrence of acrolein in soil at one hazardous waste site in the United States and leachate from several municipal landfills provides evidence that this compound has been released to soil as the result of land disposal of some organic wastes (ATSDR 2022a; TRI21 2023). No data were located regarding the amount of acrolein released to soil.

5.4 ENVIRONMENTAL FATE

5.4.1 Transport and Partitioning

Air. Acrolein is relatively unstable in the atmosphere; therefore, transport within the atmosphere is expected to be limited. The relatively high vapor pressure of acrolein (274 mm Hg at 25°C [Daubert and Danner 1987]) suggests that this compound will not partition from the vapor phase to particulates in the atmosphere. Occurrence of acrolein in rainwater (Grosjean and Wright 1983; Nishikawa et al. 1987b) indicates that this compound may be removed from the atmosphere by washout.

Water. Volatilization is expected to be a significant removal process for any acrolein released to surface waters (Nordone et al. 1996a, 1996b). Based on a measured Henry's law constant of 1.22×10^{-4} atm-m^3/mol at 25 °C (Gaffney et al. 1987), the volatilization half-life from a model river 1 m deep, flowing 1 m/second with a wind speed of 3 m/second, was estimated to be 23 hours using the method of Thomas (1982).

Sediment and Soil. Using a linear regression equation based on log octanol/water partition coefficient (K_{ow}) data (Lyman 1982), an adsorption coefficient (K_{oc}) of 24 was estimated, which suggests that adsorption of acrolein to suspended solids and sediments in water would not be significant. This does not take into account the reactivity of acrolein, which could lead to the removal of acrolein from water through chemical binding of the compound to dissolved or suspended organics in water and sediments. The relatively low estimated K_{oc} value suggests that acrolein will be highly mobile in soil and that this compound has the potential to leach (Swann et al. 1983). The relatively high vapor pressure of acrolein and its volatility from water suggest that this compound will evaporate rapidly from soil surfaces and that volatilization is probably a major removal process from soil. Degradation processes and volatilization, however, are expected to significantly retard movement of acrolein through soil.

Other Media. Veith et al. (1980) measured a bioconcentration factor (BCF) of 344 for acrolein in bluegill sunfish; however, this may be an overestimate, since total ^{14}C was measured in the fish, which may have resulted in the measurement of acrolein metabolites. A BCF of 0.6 was estimated for acrolein using a linear regression equation based on a log K_{ow} of -0.01 (Bysshe 1982; Hansch and Leo 1995). These BCFs, as well as the relatively high water solubility of this compound, suggest that acrolein does not bioconcentrate significantly in aquatic organisms. Acrolein did not accumulate in leaf lettuce after

both single and multiple applications in irrigation water at a concentration of 75 ppm (Nordone et al. 1997). Acrolein residues in the lettuce fell to 0% within 53 days following the initial application.

5.4.2 Transformation and Degradation

Air. The dominant removal process for acrolein in ambient air is predicted to be a reaction with photochemically generated hydroxyl radicals in the troposphere. The atmospheric half-life for acrolein is estimated to be 15–20 hours, based on experimentally determined hydroxyl radical reaction rate constants ranging between 1.90×10^{-11} and 2.53×10^{-11} cm^3/molecules-second at 25–26°C and an average ambient hydroxyl radical concentration of 5.0×10^5 molecules/cm^3 (Atkinson 1985). Acrolein reacts with hydroxyl radicals as both an olefin and an aldehyde (Grosjean 1990). Products of this reaction include carbon monoxide, formaldehyde, glyoxal, and glycolaldehyde. In the presence of nitrogen oxides, products include peroxynitrate, acryloylperoxy nitrate, nitric acid, glycidaldehyde, malonaldehyde, and β-hydroxypropionaldehyde (Edney et al. 1986; Grosjean 1990; Liu et al. 1999b; Salgado et al. 2008).

Direct photolysis in the ambient atmosphere occurs but is expected to be of minor importance. Gardner et al. (1987) reported that the quantum yields for irradiation of acrolein at low air pressures were 0.0066 at 313 nm and 0.0044 at 334 nm. The study authors used a computer analysis of their photodissociation data to estimate the half-life of acrolein to be 10 days in the lower troposphere and <5 days in the upper troposphere.

Experimental data indicate that reaction of acrolein with ozone ($k=2.8 \times 10^{-19}$ cm^3/molecules-second at 25°C; half-life, 59 days) or nitrate radicals ($k=5.9 \pm 2.8 \times 10^{-16}$ cm^3/molecules-second at 25°C; half-life, 16 days) in the troposphere would be too slow to be environmentally significant (Atkinson 1985; Atkinson et al. 1987). However, Salgado et al. (2008) measured a faster reaction rate with the nitrate radical of 3.30×10^{-15} cm^3/molecules-second at 25°C; this rate results in a lifetime of 168 hours (7 days), which corresponds to a half-life of 116 hours. The fate of acrolein in indoor air is expected to be different from its fate in outdoor air because of differences in the concentrations of oxidants in indoor air compared to outdoor air and the possibility of other mechanisms of removal.

Water. Low concentrations of acrolein may degrade in natural water by either aerobic biodegradation or reversible hydration to β-hydroxypropionaldehyde, which subsequently undergoes aerobic biodegradation (Bowmer and Higgins 1976; EPA 1979; Ghilarducci and Tjeerdema 1995; Tabak et al. 1981). Acrolein at a concentration of 5–10 mg/L was completely degraded in 7–10 days in a static culture flask screening

procedure (Tabak et al. 1981). Acrolein applied to surface waters at application rates suggested for herbicidal use can persist up to 6 days (WSSA 1983). Bowmer and Higgins (1976) measured acrolein removal in both laboratory water and in field experiments using irrigation channels. Their studies suggested that the degradation of the hydration product of acrolein, β-hydroxypropionaldehyde, occurs after the concentration of acrolein falls below 2–3 ppm. The degradation of β-hydroxypropionaldehyde was also preceded by a 100-hour lag period, suggesting that biodegradation was occurring through the action of acclimated cultures.

In buffered laboratory water, acrolein reached equilibrium with its degradation products (predominantly β-hydroxypropionaldehyde) in approximately 300 hours; in irrigation channels, acrolein removal was complete. Half-lives were reportedly <1–3 days in surface water, but values were for the combined effect of degradation and volatilization (Bowmer and Higgins 1976; Bowmer et al. 1974). Kissel et al. (1978) measured acrolein removal in buffered laboratory water and natural river water using both chemical analysis methods and bioassays. Complete hydrolysis (which, according to the study authors, includes hydration to β-hydroxypropionaldehyde) occurred within 150, 120–180, and 5–40 hours in buffered solutions at 22°C and pH 5, 7, and 9, respectively. Based on fish kill bioassays in natural river water at pH 8.1, >93% degradation of acrolein occurred within 6 days. The half-lives of acrolein in aerobic test systems that were treated at an application rate of 15 mg/L were 9.5 hours in water and 7.6 hours in sediment (Smith et al. 1995). The half-lives of acrolein in anaerobic test systems treated at the same rate were 10.3 hours in water and approximately 10 days in sediment. Degradation products included β-hydroxypropionaldehyde, acrylic acid, allyl alcohol, propanol, 3-hydroxypropionic acid, propionic acid, glyceric acid, and oxalic acid, which indicate that hydrolysis, oxidation, and reduction contributed to the degradation of acrolein during this study.

Marron et al. (2020) studied acrolein in potable water reuse systems. The second-order rate constant of acrolein with aquatic hydroxyl radical was 7.0×10^9/moles-second; this indicates that it would not be a significate route of removal.

The decay rate constants for acrolein applied to irrigation canals have been reported to be similar (0.14–0.21) regardless of the difference in time-concentration regimens (100 µg/L for 48 hours to 15,000 µg/L for several hours) (DOI 1994). The half-life of acrolein, applied at a flow rate of 3,964 L/second to achieve 15 ppm for 1 hour, was 10.2 hours in a weedy canal and 7.3 hours in a non-weedy canal (Nordone et al. 1996b; USGS 1998). The concentration of acrolein was 25 µg/L in samples from the Columbia River collected 65 km from where it was applied at a concentration of 125 µg/L (DOI 1994).

Nordone et al. (1996a) studied the dissipation of acrolein applied to agriculture canals with flow rates of 142, 283, and 453 L/second to achieve target concentrations of 7.5, 11.6, and 10.4 ppm, respectively. The study authors concluded that typical application of acrolein as an aquatic herbicide in agricultural canals does not result in the introduction of acrolein into natural receiving waters 2.7 km downstream.

The ultraviolet (UV) spectrum of acrolein in hexane shows moderate absorption of UV light in the environmentally significant range (wavelengths >290), suggesting that acrolein might undergo photolysis in natural waters; however, hydration of acrolein destroys the chromophores that absorb UV light (EPA 1979), and the equilibrium appears to be far on the side of the hydration product. Thus, the potential for direct photolysis of acrolein in natural waters is probably slight. Oxidation of small amounts of acrolein in natural waters would not be environmentally significant; however, highly concentrated acrolein solutions (i.e., spills) may be polymerized by oxidation or hydration processes (EPA 1979). Insufficient data are available regarding anaerobic biodegradation to establish the significance of this process as a removal mechanism or to determine the rate at which such a process would proceed. This information would be particularly useful in determining the fate of acrolein under conditions frequently encountered in groundwater and in landfills.

Based on the reactivity and nucleophilicity of acrolein, it is expected that acrolein has the potential to react with dissolved and suspended organics in water. This removal process would become increasingly important for determining the fate of acrolein in water as the concentration of organics in water increased. However, no studies have been conducted to describe this possible route for removal of acrolein from water.

Sediment and Soil. Experimental data specifically pertaining to the degradation or transformation of acrolein in soil were not located. Results of studies in aquatic systems suggest that acrolein, at low concentrations, may be subject to aerobic biodegradation in soil or transformation via hydration followed by aerobic biodegradation of the hydrated product.

Since acrolein is a very reactive compound, abiotic processes, such as oxidation or conjugation with organic matter in soils, may be the most important degradation processes. However, no information could be located for these possible acrolein reaction pathways in soil.

5.5 LEVELS IN THE ENVIRONMENT

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

Table 5-6 shows the lowest limits of detections achieved by analytical analysis in various environmental media. An overview summary of the range of concentrations detected in environmental media is presented in Table 5-7.

Table 5-6. Lowest Limit of Detection Based on Standards[a]

Media	Detection limit	Reference
Air	0.012 µg/m^3	Cahill (2010)
Drinking water	0.7 µg/L	EPA (1984)
Surface water and groundwater	0.7 µg/L	EPA (1984)
Soil	43 µg/kg	WQP (2023)
Sediment	2.1 µg/kg	WQP (2023)
Urine[b]	13 µg/L	CDC (2021)

[a]Detection limits based on using appropriate preparation and analytics. These limits may not be possible in all situations.
[b]Metabolite: 3-hydroxypropyl mercapturic acid.

Table 5-7. Summary of Environmental Levels of Acrolein

Media	Low	High	For more information
Outdoor air (µg/m^3)	<0.02	0.985	Section 5.5.1
Indoor air (µg/m^3)	<LOD	57.63	Section 5.5.1
Surface water (µg/L)	<LOD	7.5	Section 5.5.2
Groundwater (µg/L)	<LOD	12,000	Section 5.5.2
Food (µg/kg or L)	0.25	198,100	Section 5.5.4

LOD = limit of detection

Detections of acrolein in air, water, and soil at NPL sites are summarized in Table 5-8.

Table 5-8. Acrolein Levels in Water, Soil, and Air of National Priorities List (NPL) Sites

Medium	Median[a]	Geometric mean[a]	Geometric standard deviation[a]	Number of quantitative measurements	NPL sites
Water (ppb)[b]	NA	NA	NA	2	2
Soil (ppb)[b]	NA	NA	NA	2	1
Air (ppbv)	3.1	2.76	5.32	7	5

[a]Concentrations found in ATSDR site documents from 1981 to 2022 for 1,868 NPL sites (ATSDR 2022a). Maximum concentrations were abstracted for types of environmental media for which exposure is likely. Pathways do not necessarily involve exposure or levels of concern.
[b]There were not enough data found to calculate the median, mean, and standard deviations for these values.

5.5.1 Air

The atmospheric concentrations of acrolein have been measured in several locations, and the most comprehensive monitoring studies are discussed below. Data for 2015–2022 obtained from EPA's Air Quality System (AQS) database are presented in Table 5-9 (EPA 2023a). Data for 2022 show average concentrations of acrolein at various monitoring stations ranging from 0.062 to 0.591 ppbv (0.14–1.36 µg/m^3), with maximum values of 1.27 ppbv (2.91 µg/m^3). Data obtained for 2019 show similar average concentrations for acrolein, ranging from 0.060 to 0.482 ppbv (0.14–1.11 µg/m^3) with a maximum value of 1.21 ppbv (2.77 µg/m^3). Higher average concentrations of 0.071–1.028 ppbv (0.16–2.36 µg/m^3) for acrolein, with a maximum value of 11.1 ppbv (25.45 µg/m^3), were found for 2016. The National Air Toxics Monitoring Program (EPA) reported peak concentrations for acrolein of <1 ppbv (2.3 µg/m^3) at 12 monitoring sites, with 1 site reporting a peak concentration of 1–5 ppbv (2.3–11.46 µg/m^3) (Mohamed et al. 2002). These data were obtained in 1996 at 13 monitoring sites in New Jersey, Louisiana, Texas, and Vermont. Following the Norfolk Southern train derailment in East Palestine, Ohio on February 3, 2023, atmospheric samples obtained on February 20–21, 2023 showed acrolein levels in East Palestine up to 6 times higher than rural background concentrations near Pittsburgh, Pennsylvania (Oladeji et al. 2023). EPA sampling data from February to March 2023 showed a maximum concentration of approximately 0.35 ppbv (0.81 µg/m^3) obtained on February 9, 2023 (EPA 2023b).

Table 5-9. Summary of Annual Concentration of Acrolein (ppbv) Measured in Ambient Air at Locations Across the United States[a,b]

Year	Number of monitoring locations	Number of samples	Lowest arithmetic mean at all locations	Average arithmetic mean at all locations	Highest arithmetic mean at all locations	Maximum concentration
2015	29	1,703	0.049	0.255	0.657	8.9
2016	49	2,650	0.071	0.321	1.028	11.1
2017	66	3,418	0.053	0.276	0.653	4.6
2018	61	3,336	0.037	0.228	0.498	1.7
2019	56	2,907	0.060	0.206	0.482	1.21
2020	60	3,478	0.081	0.192	0.469	4.83
2021	77	5,755	0.053	0.213	0.545	2.56
2022	61	1,702	0.062	0.224	0.591	1.27

[a]Values were originally reported in parts per billion carbon (ppbC) and converted to ppbv.
[b]24-hour sampling period.

Source: EPA 2023a

Background acrolein concentrations were estimated at <0.02 μg/m^3 based on data from the National Air Toxics Trends Sites network for 2001–2002 (McCarthy et al. 2006). Acrolein levels in congested areas of Camden, New Jersey were 0.1–5.5 μg/m^3 in a study conducted in 2004–2006 (Lioy et al. 2011). Logue et al. (2010) studied air pollutant concentrations at four sites in Pennsylvania from 2006 to 2008 and found acrolein arithmetic mean concentrations of 0.07–0.23 μg/m^3.

A concentration of acrolein in ambient air in California has been estimated to average 0.36 μg/m^3 (0.16 ppb) and is based on emissions and census tract data obtained in 1999 (Morello-Frosch et al. 2000). The concentration of acrolein was determined at 39 sites representing coastal, remote, intermediate, and urban areas of California in 2013 (Cahill 2014). Corresponding concentrations were <0.041–0.130 μg/m^3 (10 coastal sites), <0.041–0.160 μg/m^3 (10 remote sites), <0.041–0.110 μg/m^3 (8 intermediate sites), and 0.046–0.410 μg/m^3 (11 urban sites) (Cahill 2014). In the 2007 Harbor Community Monitoring Study (HCMS), a saturation monitoring campaign in the communities adjacent to the Ports of Los Angeles and Long Beach, California, mean acrolein concentrations of 0.01 and 0.03 ppbv (0.023 and 0.069 μg/m^3) were detected during the summer and winter, respectively (Mason et al. 2011). Acrolein ambient air concentrations in Roseville, California near several high-traffic roads showed fluctuations throughout the day peaking between 6 pm and midnight (Spada et al. 2008). The mean summer and winter time concentrations were 0.158 and 0.012–0.028 μg/m^3, respectively. The California Air Resources Board's Monitoring and Laboratory Division routinely determined acrolein concentrations at the same site and

recorded mean concentrations of 0.985 μg/m^3 in 2005 and 1.240 μg/m^3 in 2006 (Spada et al. 2008). Ambient air concentrations of acrolein at the Oakland-San Francisco Bay Bridge Toll Plaza obtained in April 2001 showed differing concentrations between morning and evening measurements. Acrolein concentrations ranged from 0.096 to 0.140 μg/m^3 (0.041–0.060 ppb) during the morning commute, which were lower than the concentrations of 0.031–0.047 and 0.058–0.079 μg/m^3 (0.013–0.020 and 0.025–0.034 ppb) during two evening monitoring periods taken on consecutive days (Destaillats et al. 2002).

Acrolein levels in a tire smoke plume were 17.8 times higher than background levels when measured 300 m from an uncontrolled burn at a landfill in Iowa City, Iowa (Singh et al. 2015). Acrolein concentrations in the air near industrial fires are summarized in Table 5-10 (Griffiths et al. 2022).

Table 5-10. Acrolein Concentrations (ppm) at Ground Level During Industrial Fires

Primary burning material	Number of observations	Minimum to maximum	Median	Mean (SD)
Tires and tire crumble	3,706	0.00–1.46	0.56	0.53 (0.34)
Dry mixed recyclables	5,274	0.00–66.60	0.29	0.85 (1.55)
Timber and wood products	2,443	0.00–51.20	0.52	0.61 (1.93)
WEEE	100	0.00–0.94	0.35	0.36 (0.25)
Residual mixed wastes	2,178	0.00–9.04	0.46	0.66 (0.70)
Chemical manufacture	282	0.00–0.77	0.10	0.17 (0.19)

SD = standard deviation; WEEE = waste electrical and electronic equipment

Source: Griffiths et al. 2022

Acrolein concentrations in wildfire smoke are summarized in Table 5-11; the highest concentrations are found in actively forming smoke and dissipate as the smoke ages (O'Dell et al. 2020).

Table 5-11. Concentration of Acrolein (μg/m^3) Measured in Fresh and Aged Western U.S. Wildfire Smoke

Smoke type[a]	Number of observations	Percent detected (%)	Median	25th percentile	75th percentile
Young	344	100	0.0124	0.0092	0.0166
Medium	462	100	0.0051	0.003	0.0071

Table 5-11. Concentration of Acrolein (µg/m^3) Measured in Fresh and Aged Western U.S. Wildfire Smoke

Smoke type[a]	Number of observations	Percent detected (%)	Median	25th percentile	75th percentile
Old	83	55.4	0.0001	0	0.0004
Extra old	11	45.5	0	0	0.0003

[a]Designated young if 2-methylfuran >0.7 ppt; medium if 2-methylfuran was not elevated but acrolein was >7.4 ppt; and old if 2-methylfuran and acrolein were not elevated, but acrylonitrile was >2.9 ppt.

Source: O'Dell et al. 2020

Acrolein has been detected in indoor air and its concentrations are summarized in Table 5-12. The concentrations of acrolein range from 0.85 to 12.2 µg/m^3 in residential homes (Highsmith and Zweidinger 1988; Seaman et al. 2007). Acrolein concentrations are found to be typically higher in indoor air when comparing paired indoor/outdoor samples taken at a site (Seaman et al. 2007; Scheepers et al. 2017). Yin et al. (2021) studied carbonyl compounds concentrations in airliner cabins and found acrolein in conjunction with acetone at average concentrations of 20.7 µg/m^3. A review of ATSDR public health assessments for sites that evaluated soil vapor intrusion identified three sites with indoor air acrolein concentrations ranging from 6.4 to 30 µg/m^3 (ATSDR 2004a, 2004b, 2005; Burk and Zarus 2013).

Table 5-12. Acrolein Concentrations in Indoor Air

Type of building	Concentration	Location	References
Residential	0.36–1.95 ppbv (0.85–4.62 µg/m^3)[a]	Raleigh, North Carolina	Highsmith and Zweidinger 1988
Residential Semi-rural	3.5-12.2 µg/m^3 7.35 µg/m^3 (average)	Yolo County, California	Seaman et al. 2007
Residential Suburban	2.1–6.1 µg/m^3 3.5 µg/m^3 (average)	Placer County, California	
Residential Urban	2.5–6.5 µg/m^3 4.2 µg/m^3 (average)	Los Angeles County, California	
Restaurants	8–18 ppb (19–43 µg/m^3)[a]	Zürich, Switzerland	Weber et al. 1979
Hospital		Radboudumc, The Netherlands	Scheepers et al. 2017
Helicopter platform[b]	0.15–0.17 µg/m^3		
Dentistry building[b]	0.24–0.32 µg/m^3		
Kindergarten[b]	0.17–0.19 µg/m^3		
Hospital	0.1–18.1 µg/m^3	Rennes, France	Bessonneau et al. 2013

Table 5-12. Acrolein Concentrations in Indoor Air

Type of building	Concentration	Location	References
Grocery stores	1.7–26 µg/m^3	North Coast, Central Valley, South Coast, California	Chan et al. 2016
Hardware/furniture stores	0.02–3.9 µg/m^3		
Apparel stores	3.0 µg/m^3		
Student lounge			
Nonsmoking	0.8–1.6 µg/m^3	Bounds Green, United Kingdom	Williams et al. 1996
Smoking	6.4 µg/m^3		
Tavern	21–24 µg/m^3	Research Triangle Park, North Carolina	Löfroth et al. 1989
Airline cabin	<LOD–57.63 µg/m^3	28 at 1–4-hour flights; 5 at 4–10-hour flights; 23 at 10–14-hour flights	Yin et al. 2021

[a]Converted measurement in ppbv to µg/m^3, assuming an ambient temperature of 20°C and an atmospheric pressure of 1,013 mbars.
[b]7th floor at helicopter pad; front desk in dentistry building; first floor office in kindergarten.

LOD = limit of detection; ppbv = parts per billion by volume

5.5.2 Water

According to the WQP database, from 2005 to 2019, acrolein has been detected in 20% of 69 surface water samples at average concentrations of 0.97–4.44 µg/L (WQP 2023). For groundwater sample data, acrolein was found in ~76% of 2,052 samples for the years 2005–2009; the average concentration was reported as 135.79 µg/L. Acrolein was not detected in 178 groundwater samples reported for 2010–2023 (WQP 2023).

Acrolein is a chemical that is on the EPA contaminant candidate list for study in the Unregulated Contaminant Monitoring Rule (UCMR), which collects drinking water data on substances that are suspected to be present in drinking water but do not have health-based standards set under the Safe Drinking Water Act (SDWA) (EPA 2019). The latest round of monitoring did not include acrolein as one of the chemicals chosen for study. Acrolein was found in drinking water stored in polyethylene cisterns in Brazil at concentrations of <3–115 µg/L; 75% were above the potability limit (de Oliveira Moura et al. 2019). Other data regarding drinking water were not located.

5.5.3 Sediment and Soil

Acrolein was not detected in five soil samples reported in the WQP database from 2005 to 2009; no soil samples for acrolein were reported for the years 2010–2023 (WQP 2023). In sediment samples, acrolein was found at a maximum of 1.9 µg/kg in 8 of 105 sediment samples reported for 2005–2014. No sediment sample data was reported for 2015–2023 (WQP 2023). Acrolein was identified in sediment/ soil/water samples collected from Love Canal in Niagara Falls, New York (Hauser and Bromberg 1982); however, no quantitative data were available.

5.5.4 Other Media

Acrolein can be produced in endogenously as a product of lipid peroxidation (Uchida et al. 1998a, 1998b) and can form protein adducts that have been implicated in atherosclerosis (Uchida et al. 1998b) and Alzheimer's disease (Calingasan et al. 1999). As shown in Table 5-13, acrolein has been found in a variety of foods, including fruits, vegetables, baked or fried foods and alcoholic beverages (Jiang et al. 2022). In wine making, acrolein concentrations in initial grapes were reported at 45.8–49.8 µg/L and resulting musk levels were 41.1–46.8 µg/L. At the end of fermentation and in the final wine, acrolein levels were below the detection limit of 0.6 µg/L (Ferreira et al. 2018). Feron et al. (1991) reported concentrations of acrolein of <0.01–0.05 ppm in various fruits and up to 0.59 ppm in cabbage, carrots, potatoes, and tomatoes. The acrolein concentrations in heated fats and oils and in the headspace above these materials increase with increasing cooking temperature (Casella and Contursi 2004). For example, peanut oil heated for 2 hours at 110, 145, and 200°C resulted in the production of acrolein at concentrations of 0.2, 2.7, and 24 µM, respectively. In comparison to other oils, peanut oil was found to have the lowest production of acrolein after 2 hours of heating at 145°C, with higher concentrations found in sunflower (2.9 µM), corn oil (4.3 µM), and olive oil (9.3 µM) when heated under the same conditions (Casella and Contursi 2004). Sufficient data are not available to establish the level of acrolein typically encountered in these foods.

Table 5-13. Acrolein Content in Foods and Beverages

Food	Content (µg/kg or L)	Food	Content (µg/kg or L)
Fruits	10–50	Roasted cocoa beans	0.25–0.45
Vegetables	590	Fish oil	200–1,600
Cheese	1,000	Frying oils	7,400–198,100
Doughnuts	14.1–16.9	Frying fats	56,500

Table 5-13. Acrolein Content in Foods and Beverages

Food	Content (µg/kg or L)	Food	Content (µg/kg or L)
Codfish fillet	100	Cognacs	1,420–1,500
Sour dough	1,472	Scotch whiskey	670–11,100
Bread	161	Sparkling wine	20.3–33.4
French fries	14.8–19.9	Red wine	1.0–1.5
Potato chips	16.3–23.3	Cider	2,600–31,800
Frying cassava	1.7–10.2	Beer	<2.5–5.4
Frying pork sausage	~2–6		

Source: Jiang et al. 2022

Acrolein is a gaseous constituent of tobacco and marijuana smoke, occurring in both mainstream and side-stream smoke (Ayer and Yeager 1982; Hoffmann et al. 1975; Holzer et al. 1976; Rylander 1974; Weber-Tschopp et al. 1977). The level of acrolein in side-stream smoke has been found to be notably higher (12 times higher) than in mainstream smoke (Triebig and Zober 1984). The amount of acrolein emitted in tobacco smoke varies depending upon the kind of cigarette, smoking conditions, puff volume, puff rate, nature, and type of tobacco, as well as a number of other extraneous factors (Holzer et al. 1976). Smoke from various cigarettes has been found to contain 3–220 µg acrolein per cigarette (Dodson 1994; Hoffmann et al. 1975; Horton and Guerin 1974; Magin 1980; Manning et al. 1983). Smoke from a marijuana cigarette was also found to contain 92–145 µg/cigarette (Hoffmann et al. 1975; Horton and Guerin 1974). Studies performed to determine the concentration of acrolein in smoke-filled rooms (Rylander 1974; Triebig and Zober 1984; Weber-Tschopp et al. 1977) indicate that the concentration of acrolein in indoor air is highly dependent upon such factors as the number of cigarettes smoked, rate at which the cigarettes are smoked, size of the room, number of people in the room, and type of ventilation. Acrolein levels measured in various settings where people were smoking are: cafe, 30–100 ppb; train, 10–120 ppb; car with three smokers (windows open), 30 ppb (average); car with three smokers (windows closed), 300 ppb (average); restaurant, 3–13 ppb; tavern, 5–18 ppb; and cafeteria, l–10 ppb (Triebig and Zober 1984). Thirdhand smoke, defined as tobacco smoke residues lingering in the indoor environment, levels of acrolein were 127.9, 7.0, and 2.4 µg/m^3 in the room 20 minutes, 2 hours, and 8 hours after smoking was discontinued, respectively (Sleiman et al. 2014).

Electronic cigarettes (e-cig) have been determined to be a source of acrolein exposure (Belushkin et al. 2020; Chen et al. 2023; Dawkins et al. 2018; Gillman et al. 2020). Belushkin et al. (2020) studied 34 devices using 57 e-liquids manufactured in 2012, 2017, and 2018 from the United Kingdom, Poland, France, South Africa, and Canada. Emitted acrolein levels were <9.28–2,160 ng/puff in closed systems

and 31.6–9,180 ng/puff in open systems. In another study, it was found that acrolein levels did not differ based on power levels of the e-cig device or nicotine content of the liquid (Dawkins et al. 2018). The formation of acrolein in e-cig aerosols in enhanced by the presence of triacetin (Vreeke et al. 2018).

5.6 GENERAL POPULATION EXPOSURE

The general population may be exposed to acrolein through inhalation of contaminated air, inhalation of cigarette smoke, and through ingestion of certain foods. Widespread exposure occurs due to the formation of acrolein during the cooking of fats. Primary factors influencing the level of exposure to acrolein via inhalation are location (urban versus rural), duration and frequency of exposure to tobacco smoke, concentration of tobacco smoke, duration and frequency of exposure to high concentrations of vehicle exhaust (e.g., in parking garages, in heavy traffic), occupational exposure, and downwind distance of residence or work site relative to stationary point sources. Primary factors influencing the level of exposure to acrolein via ingestion are diet and volume of intake, which is typically related to age and sex.

Acrolein may volatilize from water; thus, there is potential for inhalation exposure during showering and bathing. ATSDR's three-compartment Shower and Household-Use Exposure (SHOWER) model predicts air concentrations in the shower stall, bathroom, and main house throughout the day by estimating the contribution from showering or bathing and the contribution from other water sources in the house, such as the dishwasher, clothes washer, and faucets. This information, along with human activity patterns, is used to calculate a daily time weighted average exposure concentrations via inhalation exposure and from dermal uptake from skin contact. ATSDR's SHOWER model is available by sending a request to showermodel@cdc.gov. Using air and water levels discussed in Sections 5.5.1 and 5.5.2, reasonable maximum exposure (RME) levels for acrolein were calculated for different exposure groups (Table 5-14).

Table 5-14. Reasonable Maximum Exposure of Acrolein for Daily Inhalation Dose and Administered Dermal Dose in µg/kg/day for the Target Person

Exposure group	Inhalation (µg/m^3)	Dermal (µg/kg/day)
Birth–<1 year	1.2	0.0048
1–<2 years	1.2	0.0044
2–<6 years	1.2	0.0038
6–<11 years	1.2	0.0031
11–<16 years	1.2	0.0025
16–<21 years	1.2	0.0023

Table 5-14. Reasonable Maximum Exposure of Acrolein for Daily Inhalation Dose and Administered Dermal Dose in µg/kg/day for the Target Person

Exposure group	Inhalation (µg/m^3)	Dermal (µg/kg/day)
Adult	1.2	0.0023
Pregnant and breastfeeding women	1.2	0.0023

Source: ATSDR 2022b

Probabilistic estimates of 24-hour time-weighted concentrations of acrolein in air have been used to assess human exposures to acrolein in the Canadian population (Environment Canada 2000; WHO 2002). Mean and median estimates of acrolein concentration of 1.3 and 0.6 µg/m^3 (0.56 and 0.26 ppb), respectively, were derived, with a 95% percentile value of 5.0 µg/m^3 (2.1 ppb). The estimate used measured data on acrolein concentrations obtained between 1989 and 1996 for outdoor air in rural, suburban, and urban sites and indoor air measurements taken in 40 homes between 1991 and 1993. The exposure estimate assumed both a mean time of 3 hours spent outdoors and that the general population was exposed to concentrations of acrolein similar to those in indoor air of their homes. Based on the mean estimate for acrolein concentration and an inhalation volume of 20 m^3 of air per day, it was estimated that an average adult will inhale 26 µg acrolein/day (Environment Canada 2000). Because of the limited data regarding acrolein levels in foods, a reliable assessment of the acrolein exposure through foods is not possible at present. However, based on the assumption that all foods contain maximal reported levels of acrolein, an exposure of around 1 mg/person/day (17 g/kg body weight/day) may be estimated (Guth et al. 2013).

Levels of the acrolein metabolite, 3-hydroxypropyl mercapturic acid (3-HPMA), were measured in individuals before and after consumption of self-prepared and commercially available potato crisps (Watzek et al. 2012). Levels of 3-HPMA increased reaching a maximum at 4–6 hours, with a half-life of 9-12 hours. Wang et al. (2019) examined the levels of 3-HPMA in urinary samples and serum acrolein-protein conjugates (Acr-FDP) before and after the consumption of fried foods. Urinary 3-HPMA levels increased 2 hours after consumption of fried food, with an elimination half-life of 10 hours. Concentrations decreased, approaching baseline level after 24 hours. Acr-FDP levels in plasma were slightly, but not significantly, increased 2, 6, or 24 hours after consuming fried food (Wang et al. 2019).

ETS, including primary, secondhand, and thirdhand smoke, is a major source of acrolein exposure for many individuals in the general population. Nazaroff and Singer (2004) estimated that in 2000, between 31 and 53 million nonsmokers in the United States were exposed to acrolein concentrations in indoor air,

ranging from 1.6 to 3.6 μg/m^3 in households where ETS is generated by one or more individuals residing in the same household. Between 15 and 25 million of the affected number of nonsmokers are adults. Based on the lifetime average for the volume of inspired air of 14 m^3/day for males and 10 m^3/day for females, it is estimated that the inhalation intake of acrolein through inspiration of ETS over a lifetime is 22–50 μg/day for males and 16–36 μg/day for females. Assuming that the exposure data obtained from the Canadian study (Environment Canada 2000) discussed above are representative of exposures of residents in the United States to acrolein in households without ETS, then it is estimated that the inhalation intake of acrolein for nonsmokers exposed to ETS in the residence is 2.2–3.8 times greater for both males and females than in households without ETS. This comparison is based on inhalation intakes of acrolein for males and females in non-ETS households of 18 and 13 μg/day, respectively, that are based on an estimated mean acrolein concentration in air of 1.6 μg/L taken from the Canadian study (Environment Canada 2000) and on the average daily inhalation volumes of air for males and females given by Nazaroff and Singer (2004). National Health and Nutrition Examination Survey (NHANES) data from 2005 to 2006 reported that urinary levels of 3-HPMA and CEMA were higher among tobacco smokers (cigarette, cigar, and pipe users) compared to non-tobacco users (Alwis et al. 2015).

There is potential for exposure to acrolein in many occupational settings as the result of its varied uses and its formation during the combustion and pyrolysis of materials such as wood, petrochemical fuels, and plastics. As a result, it would be difficult to list all occupations in which work-related exposure to acrolein occurs. Some of these occupations include those involved in the production of acrylates, methionine, perfumes, plastics, refrigerants, rubber, or textile resins (Ghilarducci and Tjeerdema 1995).

Acrolein has been detected in workplace air at a number of locations (Feng et al. 2022b; NIOSH 1982, 1983, 1986). Acrolein concentrations of 0.057–0.085 ppm were detected during system testing conducted as part of a submarine overhaul in Portsmouth Naval Shipyard in Portsmouth, New Hampshire (NIOSH 1986). NIOSH (1983) reported >0.0044–0.18 ppm acrolein in the wire line department of Rubbermaid Inc. in Wooster, Ohio, and NIOSH (1982) reported >0.06 ppm in molding areas of Gerlinger Casting Corporation in Salem, Oregon. A year-long air monitoring program in a petroleum refinery named acrolein as the largest contributor to the hazard index (Feng et al. 2022b).

The concentrations of acrolein were 0.01 mg/m^3 (0.004 ppm) in the air of a food factory, 0.59, 0.31, 0.15, 0.16, and 0.06 mg/m^3 (0.25, 0.13, 0.064, 0.069, and 0.026 ppm) in the air of five restaurant kitchens, and 0.02 mg/m^3 (0.009 ppm) in the air of two bakeries (Vainiotalo and Matveinen 1993). Henriks-Eckerman

et al. (1990) reported that acrolein was emitted from coated steel plates heated to 350°C. This indicates that workers involved in welding or heating painted metal may be exposed to acrolein

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Those segments of the general population with potentially high exposure to acrolein from exogenic sources include people who come in frequent or prolonged contact with tobacco or marijuana smoke, people who are occupationally exposed, and people who live or work near dense traffic areas, in smoggy areas (e.g., Los Angeles), or downwind from stationary point sources or may have been exposed to high levels from accidental releases. Acrolein uptake from cigarette smoke for individuals working in bars and taverns that allow indoor smoking can range from 15 to 1,830 µg/day, based on an 8-hour shift, a respiration volume of 20 m^3 air/day, and a concentration range of acrolein in air of 2.3–275 µg/m^3 (IARC 1995). With the passage of legislation prohibiting smoking indoors, it is expected that these exposure levels would now be much lower. Individuals who work or reside near irrigation canals and other bodies of water that are undergoing treatment with acrolein to eliminate unwanted plants or aquatic life are at risk for exposure to acrolein. Individuals living near some landfills and other waste sites may be exposed to acrolein in ambient air or drinking water.

Firefighters are at high risk of exposure to acrolein when battling house fires, wildfires, and industrial fires (Fent et al. 2022; Griffiths et al. 2022; O'Dell et al. 2020). Navarro et al. (2021) monitored 81 firefighters in different job tasks while fighting wildfires; the minimum and maximum acrolein exposure levels were 0.6 and 13.8 ppb (1.38 and 31.64 µg/m^3), respectively. The highest levels were for direct suppression workers (Navarro et al. 2021). The concentrations of the acrolein metabolite, 3-HPMA, measured in urine samples pre- and post-firefighting are presented in Table 5-15 (Fent et al. 2022). Attack firefighters have the position of advancing hose lines and suppressing all active fires, while search and rescue conduct forcible entry and enter burning buildings. Student and instructors were exposed to burning pallets of straw, oriented strand board fires, and simulated smoke and electronic flames; all of these exercises were performed in enclosed areas. For the general population, the median concentrations of 3-HPMA are 175 µg/g creatinine for nonsmokers and 508 µg/g creatine for smokers (Fent et al. 2022).

Table 5-15. 3-HPMA Concentration (µg/g creatinine) in Urine of Firefighters Pre- and Post-Fire Response

	Collection period	Number of samples	Mean	Median	Minimum–maximum
Attack and search firefighters	Pre-fire	48	207	182	68.1–739
	3 hours	48	209	196	92.2–665
Firefighter student	Pre-fire	36	172	146	92.7–403
	3 hours	36	342	211	96.3–1,660
Instructor	Pre-fire	12	231	168	97.7–764
	3 hours	12	439	322	179–1,230

Source: Fent et al. 2022

Patients receiving oxazaphosphorine drugs, such as cyclophosphamide and ifosfamide, for their cancer treatment are at risk for exposure to acrolein, a metabolite of these drugs (Furlanut and Franceschi 2003; Kaijser et al. 1993). For example, patients receiving cyclophosphamide at a dose of 60 mg/kg body weight/day by 1-hour infusion for 2 consecutive days had peak blood acrolein concentrations ranging between 6.2 and 10.2 µM (Ren et al. 1999). The urinary clearance of acrolein from blood during therapy results in concentrations of acrolein in urine ranging from 0.3 to 406.8 nM, depending on urine volume (Takamoto et al. 2004). This range of urinary acrolein concentrations is sufficient to result in acrolein-induced renal toxicities that must be reduced through increasing urine volume during treatment with diuretics or receiving uroprotective drugs during treatment (Kaijser et al. 1993).

CHAPTER 6. ADEQUACY OF THE DATABASE

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

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

6.1 INFORMATION ON HEALTH EFFECTS

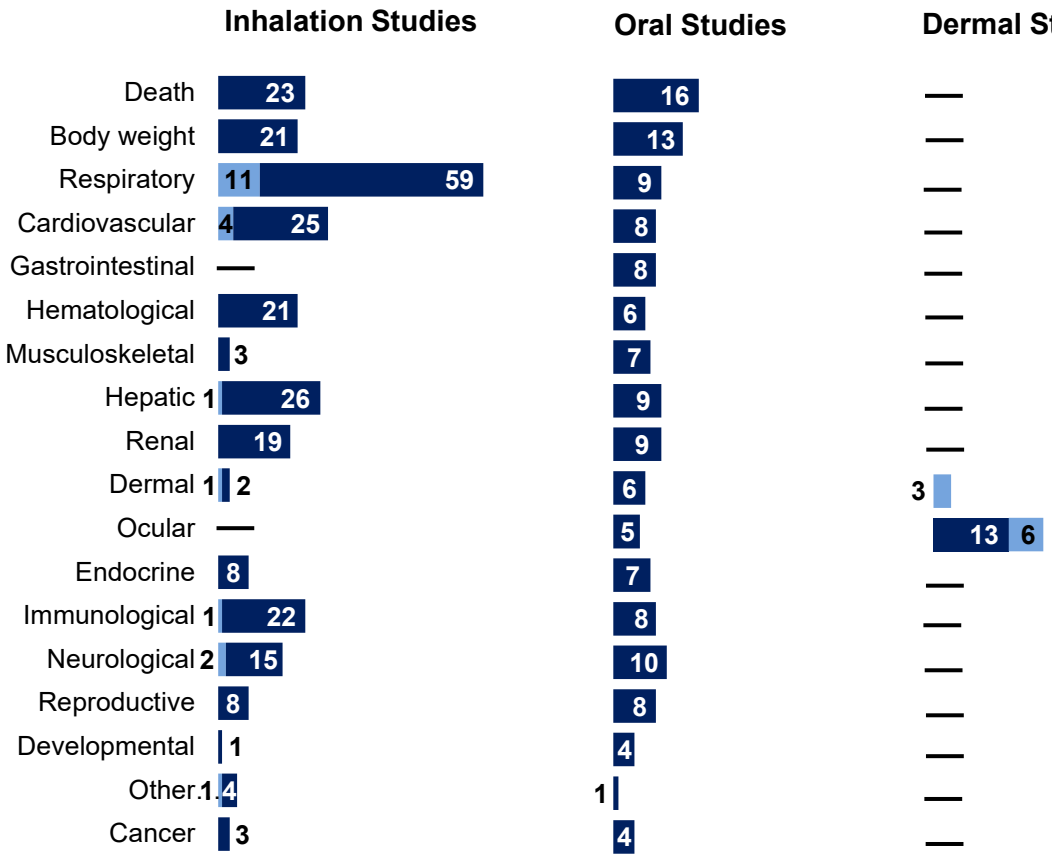
Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to acrolein that are discussed in Chapter 2 are summarized in Figure 6-1. The purpose of this figure is to illustrate the information concerning the health effects of acrolein. The number of human and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

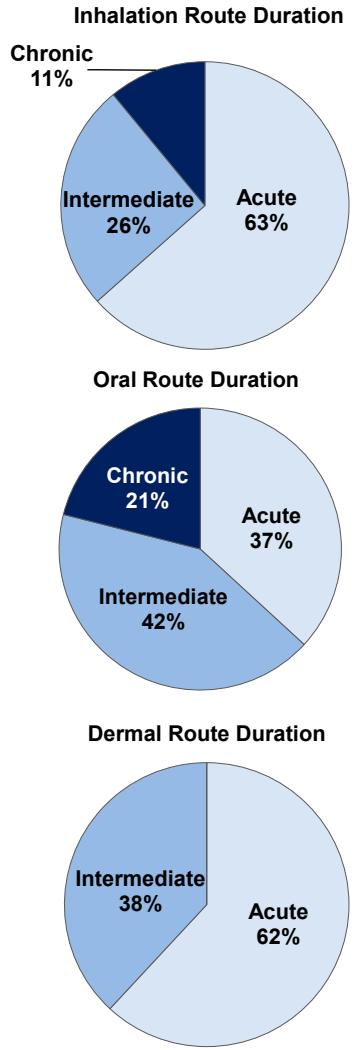
6.2 IDENTIFICATION OF DATA NEEDS

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

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

Potential respiratory effects was the most studied endpoint
The majority of the studies examined inhalation exposure in **animals** (versus **humans**)





*Includes studies discussed in Chapter 2. The number of studies include those finding no effect; most studies examined multiple endpoints.

Acute-Duration MRLs. A provisional acute-duration inhalation MRL was derived for acrolein. The available acute oral database was inadequate for deriving an MRL. Only one study was available where measured effects were seen in the absence of increased mortality (Conklin et al. 2010). The biological significance of the clinical chemistry changes observed in this study is unclear. Acute-duration oral studies that include histological examination of the gastrointestinal tract may provide data regarding sensitive irritant effects that could serve as a basis for an acute-duration oral MRL.

Intermediate-Duration MRLs. A provisional intermediate-duration inhalation MRL was adopted from the provisional chronic-duration inhalation MRL derived for acrolein. Respiratory effects were observed in animals following intermediate-duration exposure; however, due to limitations in these studies (number of animals studied, number of dose groups, limited respiratory endpoints), these studies were not used for derivation of an MRL (Bouley et al. 1975; Dorman et al. 2008). Additional, more comprehensive intermediate-duration inhalation studies would be useful for derivation of an intermediate-duration inhalation MRL. An intermediate-duration oral MRL was derived for acrolein.

Chronic-Duration MRLs. A provisional chronic-duration inhalation MRL was derived for acrolein. The oral database is inadequate to derive a chronic-duration oral MRL. Chronic-duration oral studies were performed in rats, mice, and dogs; however, extensive histopathological examination revealed no effects in any organs (Parent et al. 1991a, 1992a, 1992b). Reduced survival of mice and rats (a frank effect level) was observed at relatively low doses, although no cause of death could be determined. Additional chronic-duration oral studies are unlikely to identify a NOAEL and/or less serious LOAEL that would be useful for derivation a chronic-duration oral MRL.

Health Effects.

Reproductive. No evidence of reproductive toxicity has been found in animal studies by the oral and inhalation route; however, studies evaluating reproductive function following acrolein inhalation are limited. Additional reproductive toxicity studies by the inhalation route would be useful. Reproductive performance was not affected in 2-generation oral rat studies suggesting that no further oral studies are needed.

Developmental. Only a single study evaluated developmental effects in animals after inhalation exposure to acrolein during pregnancy and limited endpoints were examined (i.e., fetal number and body weight only). Oral prenatal and multigeneration studies suggest that developmental effects of acrolein may be dependent on frank maternal toxicity. Further animal

studies providing information on pre- and postnatal developmental toxicity of acrolein after inhalation and oral exposure would be useful.

Immunotoxicity. Information regarding immunological effects of acrolein in humans is limited to a single controlled exposure study examining cytokine levels in serum and sputum. Additional epidemiology studies evaluating possible associations between immune function and acrolein exposure would be useful. Experimental animal studies of immune function and inflammatory responses following acrolein inhalation have yielded mixed results with immune suppression suggested in some, but not all, cases. Studies using a battery of immunotoxicity tests to correlate exposure concentrations with specific endpoints of immune response would be useful.

Genotoxicity. A limited number of *in vivo* genotoxicity studies have been conducted. Further studies in animals would be useful to determine the ability of acrolein to induce chromosomal aberrations after exposure. Cytogenetic analysis of peripheral lymphocytes of workers exposed to acrolein would provide an opportunity to assess its genotoxicity in humans.

Epidemiology and Human Dosimetry Studies. The human studies database for acrolein is limited to a few controlled-exposure studies using human volunteers and a few cross-sectional studies evaluating respiratory effects associated with acrolein exposure. Epidemiology studies correlating the nature and severity of respiratory, immunological, and gastrointestinal endpoints with acrolein exposure intensity and duration are needed.

Biomarkers of Exposure and Effect. Available biomarkers of acrolein exposure (urinary metabolites and serum acrolein) and effect (acrolein-adducted DNA, thiols, and lysine) are not capable of distinguishing between exogenous and endogenous acrolein sources. Because acrolein is produced endogenously by a variety of physiological processes (see Section 3.1) including many disease states, it is unclear whether additional research is likely to yield specific biomarkers that are useful for assessing exogenous exposure.

Absorption, Distribution, Metabolism, and Excretion. There are no data in humans on absorption, distribution, metabolism, or elimination of acrolein under controlled exposure circumstances; however, collection of such data is problematic due to its reactivity and toxicity. Toxicokinetic data are available in animals after inhalation and oral exposure. There are no *in vivo* data on the toxicokinetic behavior of acrolein in animals exposed dermally, and these data would facilitate an understanding of

whether there are route-specific differences. The metabolism of acrolein and excretion of urinary metabolites in rats exposed orally and in *in vitro* systems is relatively well understood, but there are few data available to evaluate whether inhalation leads to different metabolic pathways or kinetics.

Comparative Toxicokinetics. No studies were located regarding comparative toxicokinetics of acrolein *in vivo*. Although similar inhalation effects have been observed in rats and humans (Cassee et al. 1996a; Weber-Tschopp et al. 1977) at comparable exposure levels, the animal species that serves as the best model for extrapolating results to humans remains unknown.

Children's Susceptibility. Although no data are available describing age-related differences in acrolein toxicity, acrolein is expected to affect children by the same mechanisms through which it affects adults. However, data are needed to determine if tissue-specific, age-related differences exist for glutathione levels, possibly resulting in an increased sensitivity to acrolein, particularly for respiratory effects. Children with asthma and reactive airway dysfunction may exhibit effects at levels different than adults with similar sensitivities (Annesi-Maesano et al. 2012; Kuang et al. 2021).

Physical and Chemical Properties. Physical and chemical property data are essential for estimating the partitioning of a chemical in the environment. Physical and chemical property data are available for acrolein and are sufficient for estimating the environmental fate of acrolein (Amoore and Hautala 1983; Daubert and Danner 1987; Gaffney et al. 1987; Hansch and Leo 1995; Lewis 1997; NLM 2023; O'Neil 2013; Seidell 1941; Tomlin 2003; Verschueren 2001).

Production, Import/Export, Use, Release, and Disposal. Data regarding the production methods for acrolein, production facilities, use, and disposal are adequate (Etzkorn et al. 2002). Data regarding current gross estimates of production volumes and capacities are available (EPA 2022a). Production data may be difficult to obtain since many companies desire to maintain their confidentiality. There is limited information regarding import/export of acrolein and reporting is considered CBI (EPA 2022a). Data regarding release of acrolein into air are available for mobile and stationary sources (CEPA 2002; EPA 1998a, 2022h; WHO 2002). Acrolein has been released to the air by the photodegradation of plastic debris and emissions from dairy silages and other feedstuffs (Lomonaco et al. 2020; Malkina et al. 2011). Limited data are available on the release of acrolein to publicly owned treatment works (POTWs) and the release of acrolein as a pesticide to irrigation waters in California (EPA 1991, 2003), but no data could be located on release of acrolein to soil. Use, release, and disposal information is useful for determining where environmental exposure to acrolein may be high. Determining the percentage of acrolein used as a

captive intermediate (i.e., consumed in closed processes in which the compound is not isolated) rather than as an isolated, refined product is important in estimating the amount of release to the environment from stationary, non-combustion-related sources. An estimate of the amount of acrolein released from stationary sources would be useful in establishing the relative importance of each source of acrolein. Even with the availability of information on the production, use, and disposal of acrolein, the amounts released would be difficult to estimate, since major factors contributing to its occurrence in the environment are its formation as a product of the photochemical degradation of other atmospheric pollutants and its release in emissions from a wide variety of combustion processes.

Environmental Fate. The environmental fate of acrolein in air is well studied (Atkinson 1985; Atkinson et al. 1987; Gardner et al. 1987; Grosjean 1990). Given that acrolein occurs in the atmosphere from both natural and anthropogenic sources (DOI 1994; EPA 1998a; Ghilarducci and Tjeerdema 1995; Graedel et al. 1978; Hodgkin et al. 1982; Jonsson et al. 1985; Lipari et al. 1984; Liu et al. 1999a, 1999b; Maldotti et al. 1980; Spada et al. 2008; WHO 1991, 2002), it would be helpful to have estimates of the relative contributions of these sources to acrolein concentrations in air, especially the contribution of the photochemical production of acrolein. Data on the dissipation and degradation of acrolein in water are available (Bowmer and Higgins 1976; Bowmer et al. 1974; EPA 1979; Ghilarducci and Tjeerdema 1995; Kissel et al. 1978; Marron et al. 2020; Nordone et al. 1996a, 1996b; Smith et al. 1995; Tabak et al. 1981; USGS 1998). No data were located on the removal of acrolein from water through reactions with dissolved and suspended organic matter in water. Studies on this route of removal of acrolein from water would be useful for determining the lifetime of acrolein in waters with high organic content. Measured soil-water partition coefficient data are not available. This information would be helpful for describing the absorption and mobility of acrolein in soil. Experimental data pertaining to the persistence of acrolein in soil and groundwater are lacking. Studies on volatilization from soil surfaces, anaerobic biodegradation in soil and simulated groundwater, and aerobic biodegradation in simulated groundwater would be useful in establishing the likelihood of exposure near hazardous waste disposal sites resulting from volatilization from soil surfaces or from groundwater contamination.

Bioavailability from Environmental Media. No studies were located regarding the bioavailability of acrolein from environmental media. Since acrolein has been detected in ambient air and in food and beverages (ppb levels), it is important to determine if acrolein can be absorbed by humans from environmental samples. However, the chemical structure of acrolein makes it a highly reactive molecule, which presumably is why its effects are, for the most part, restricted to the area of exposure (i.e., respiratory system for inhalation exposure or localized skin damage for dermal exposure). The limited

information available regarding inhalation absorption of acrolein in experimental animals demonstrated uptake in respiratory tract tissues, but did not indicate whether systemic distribution occurred (Egle 1972; Morris 1996; Morris et al. 2003). Virtually no information is available regarding absorption by the gastrointestinal tract or skin; additional studies would be useful in establishing whether acrolein is absorbed through these sites or is retained.

Food Chain Bioaccumulation. Measured and estimated BCF values for acrolein indicate that this compound would not bioaccumulate significantly in fish (Bysshe 1982; Hansch and Leo 1995; Veith et al. 1980). No information was available on the bioaccumulation of acrolein in organisms at other trophic levels in aquatic environments. Monitoring for the accumulation of acrolein in organisms from several trophic levels would be useful in estimating the levels of acrolein to which humans are exposed through dietary intake.

Exposure Levels in Environmental Media. Reliable monitoring data for the levels of acrolein in contaminated media at hazardous waste sites are needed so that the information obtained on levels of acrolein in the environment can be used in combination with the known body burden of acrolein to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Data are available regarding the detection of acrolein in the environment, most notably in ambient air (Cahill 2014; Destaillats et al. 2002; EPA 2023a; Griffiths et al. 2022; Highsmith and Zweidinger 1988; IARC 2021; Lioy et al. 2011; Logue et al. 2010; Mason et al. 2011; McCarthy et al. 2006; Mohamed et al. 2002; Morello-Frosch et al. 2000; Scheepers et al. 2017; Seaman et al. 2007; Singh et al. 2015; Spada et al. 2008; WHO 1991, 2002), and also in water (de Oliveira Moura et al. 2019; WQP 2023), soil, and sediment (Hauser and Bromberg 1982; WQP 2023). Additional information on exposure to acrolein in air in urban areas, rural areas, and near hazardous waste disposal sites, as well as in water (specifically, drinking water supplied from groundwater down gradient from hazardous waste disposal sites and contaminated surface waters) and soil at waste disposal sites would be useful. Monitoring air and water over a 1-year period would provide some indication of seasonal variations.

Exposure Levels in Humans. Data for residential exposure to acrolein are limited to a probabilistic study that provided a 24-hour time-weighted estimate of acrolein concentrations in air and inhalation intake for Canadian residents (Environment Canada 2000) and a study on exposure of nonsmokers in the United States to acrolein in ETS (Nazaroff and Singer 2004). The development of a program for monitoring environmental media would provide information for better estimations of acrolein exposure

levels in humans. Data are not available for intake of acrolein through the diet. Market basket surveys or total diet studies similar to those conducted by the U.S. Food and Drug Administration (FDA) are needed to provide data on typical levels of exposure via dietary intake given the presence of acrolein in a number of foods (Casella and Contursi 2004; Feron et al. 1991; Ferreira et al. 2018; Jiang et al. 2022). Monitoring studies of acrolein concentrations in air are available for a few occupations such as shipyard workers, welders, plastic manufacturers, food service employees, and firefighters (Feng et al. 2022b; Fent et al. 2022; Griffiths et al. 2022; Henriks-Eckerman et al. 1990; IARC 2021; Navarro et al. 2021; NIOSH 1982, 1983, 1986; O'Dell et al. 2020; Vainiotalo and Matveinen 1993). Given the high likelihood of occupational exposures to acrolein as a consequence of its emission from combustion sources and the variability in the frequency and amount of exposure to the compound in various occupational settings, additional monitoring data are needed to provide reliable estimates of average daily intake of acrolein in workers.

Exposures of Children. Data on the exposure of children to acrolein are very limited (Nazaroff and Singer 2004; WHO 2002). For children living in a residence where one or more individuals smokes some form of tobacco product, long-term exposure to acrolein and other compounds in ETS are expected (Nazaroff and Singer 2004; WHO 1999). Lifetime exposures to acrolein in ETS have been estimated for individuals residing with one or more smokers (Nazaroff and Singer 2004); however, there are no data that specifically address the inhalation intake of acrolein from ETS in individuals below the age of 18 years. Information on acrolein concentrations in indoor air is limited for residences in the United States (Highsmith and Zweidinger 1988; Seaman et al. 2007). More data are needed to adequately assess the exposures of children to acrolein generated from indoor combustion sources, especially tobacco and other smoking products. Determination of the average daily intake of acrolein would be complicated by the variability in the frequency and amount of exposure to cigarette smoke and other acrolein sources. Therefore, exposure studies should be structured to assess the temporal variations in acrolein concentrations over a typical day and should also account for seasonal changes in air exchange within a residence (i.e., winter versus summer). It may be possible to use data obtained from NHANES for age-related exposure by controlling for smoking-related exposure. For children who are not exposed to ETS in the home environment, it is expected that the largest exposure to acrolein will be through inhalation of ambient air, especially in urban areas, and through the diet. Therefore, studies that are tailored to assessing exposure of children to acrolein in ambient air would be useful given the tendency for some children to spend more time outdoors than many adults. Also, market basket surveys or total diet studies similar to those conducted by the FDA would be useful for providing data on typical levels of exposure via dietary intake for children.

6.3 ONGOING STUDIES

There are several ongoing studies evaluating the potential adverse effects of acrolein exposure in humans and laboratory animals as well as studies of mechanisms of toxicity (Table 6-1).

Table 6-1. Ongoing Studies on Acrolein

Investigator	Affiliation	Research description	Sponsor
Human studies			
Aherrera, Angela	Johns Hopkins University	Cross-sectional study evaluating biomarkers of exposure and effect in e-cigarette users	NIEHS
Bhatnagar, Aruni	University of Louisville	Cross-sectional study of VOC exposure with cardiometabolic disease	NIEHS
Hatsukami, Dorothy	University of Minnesota	Evaluation of tobacco biomarkers (acrolein metabolites) in biological samples	NCI
Animal and mechanistic studies			
Gordon, Terry	New York University School of Medicine	Cardiopulmonary toxicity of e-cigarettes in a chronic-duration inhalation study in animals	NCI
Hecht, Stephen	University of Minnesota	Acrolein metabolism and excretion with co-administration of watercress (source of 2-phenethyl isothiocyanate)	NCI
Srivastava, Sanjay	University of Louisville	Exposure to aldehyde metabolites of VOCs contribute to cardiometabolic disease as evaluated by endothelial function and insulin resistance through endoplasmic reticulum stress and unfolded protein response in endothelial cells	NIEHS
Srivastava, Sanjay	University of Louisville	Mechanisms (role of MiR-21) of macrophage activation in atherosclerosis from exposure to acrolein in electronic nicotine delivery systems	NHLBI

NCI = National Cancer Institute; NHLBI = National Heart, Lung, and Blood Institute; NIEHS = National Institute of Environmental Health Sciences; VOC = volatile organic compound

Source: National Institute of Health (NIH) RePORTER 2023

CHAPTER 7. REGULATIONS AND GUIDELINES

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

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

Table 7-1. Regulations and Guidelines Applicable to Acrolein

Agency	Description	Information	Reference
	Air		
EPA	RfC	$2x10^{-5}$ mg/m^3 ($1x10^{-5}$ ppm)	IRIS 2003
WHO	Air quality guidelines	No data	WHO 2010
	Water & Food		
EPA	Drinking water standards and health advisories	Not listed	EPA 2018a
	National primary drinking water regulations	Not listed	EPA 2009
	RfD	$5x10^{-4}$ mg/kg/day	IRIS 2003
WHO	Drinking water quality guidelines	No data	WHO 2022
FDA	Food additives permitted for direct addition to food for human consumption	Acrolein used to prepare modified food starch must not exceed 0.6%	FDA 2022
	Cancer		
HHS	Carcinogenicity classification	No data	NTP 2021
EPA	Carcinogenicity classification	Data are inadequate for an assessment of human carcinogenic potential	IRIS 2003
IARC	Carcinogenicity classification	Group 2A[a]	IARC 2021
	Occupational		
OSHA	PEL (8-hour TWA) for general industry, shipyards, and construction	0.1 ppm (0.25 mg/m^3)	OSHA 2021a, 2021b, 2021c
NIOSH	REL (up to 10-hour TWA) STEL (15-minute TWA) IDLH	0.1 ppm (0.25 mg/m^3)[b] 0.3 ppm (0.8 mg/m^3) 2 ppm	NIOSH 2019

Table 7-1. Regulations and Guidelines Applicable to Acrolein

Agency	Description	Information	Reference
	Emergency Criteria		
EPA	AEGLs-air		EPA 2018b
	AEGL 1[c]		
	10-minute, 30-minute, 60-minute, 4-hour, 8-hour	0.030 ppm	
	AEGL 2[c]		
	10-minute	0.44 ppm	
	30-minute	0.18 ppm	
	60-minute	0.10 ppm	
	4-hour	0.10 ppm	
	8-hour	0.10 ppm	
	AEGL 3[c]		
	10-minute	6.2 ppm	
	30-minute	2.5 ppm	
	60-minute	1.4 ppm	
	4-hour	0.48 ppm	
	8-hour	0.27 ppm	
DOE	PACs-air		DOE 2018a
	PAC-1[d]	0.03 ppm	
	PAC-2[d]	0.1 ppm	
	PAC-3[d]	1.4 ppm	

[a]Group 2A: probably carcinogenic to humans.
[b]NIOSH recommends that careful consideration be given to reducing exposures to acrolein due to limited studies that indicate that these substances have chemical reactivity and mutagenicity similar to acetaldehyde and malonaldehyde (NIOSH 2018).
[c]Definitions of AEGL terminology are available from EPA (2018c).
[d]Definitions of PAC terminology are available from DOE (2018b).

AEGL = acute exposure guideline levels; DOE = Department of Energy; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; HHS = Department of Health and Human Services; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PAC = protective action criteria; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; STEL = short-term exposure limit; TWA = time-weighted average; WHO = World Health Organization

CHAPTER 8. REFERENCES

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APPENDIX A. ATSDR MINIMAL RISK LEVEL WORKSHEETS

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

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

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

APPENDIX A

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

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Acrolein
CAS Numbers: 107-02-8
Date: May 2024
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Acute
Provisional MRL: 0.003 ppm (0.007 mg/m^3)
Critical Effect: Nose and throat irritation and decreased respiratory rate
Reference: Weber-Tschopp et al. 1977
Point of Departure: LOAEL = 0.3 ppm
Uncertainty Factor: 100
LSE Graph Key: 2
Species: Human

MRL Summary: A provisional acute-duration inhalation MRL of 0.003 ppm was derived for acrolein based on a LOAEL of 0.3 ppm for nose and throat irritation and reduced respiratory rate in humans exposed to acrolein by inhalation for 1 hour (Weber-Tschopp et al. 1977). The LOAEL was divided by a total uncertainty factor of 100 (10 for human variability and 10 for use of a LOAEL).

Selection of the Critical Effect: Most acute-duration inhalation studies of acrolein focused on effects of the respiratory tract or immune effects in the respiratory tract. The lowest effect levels (≤2 ppm) for acute-duration inhalation studies of acrolein are shown in Table A-1. Effects observed at the lowest exposure concentrations consisted of irritation of the nose and throat and decreased respiratory rate in humans (Weber-Tschopp et al. 1977), nasal lesions in rats (Cassee et al. 1996a), and immune suppression in mice (Aranyi et al. 1986). Aranyi et al. (1986) reported the lowest LOAEL identified for acute-duration inhalation exposure to acrolein based on reduced bactericidal activity of the respiratory tract in mice. Following a 5-day exposure to 0.1 ppm acrolein in mice, alveolar macrophagic clearance of a 3-hour *K. pneumoniae* infection was significantly lower: control and treated mice removed 84% and 77% of bacteria, respectively. Although statistically significant, it is not clear whether this change is adverse and would lead to health consequences from secondary bacterial infections following exposure to acrolein. In addition, immunological findings in acute studies using higher concentrations were mixed. Clearance of intrapulmonary *Staphylococcus aureus* was reduced in mice following acrolein exposure to ≥3 ppm for 8 hours (Astry and Jakab 1983); however, the inflammatory response was not altered in mice exposed to 5 ppm for 6 hours/day for 3 days in conjunction with instillation of LPS (*Escherichia coli*) (Kasahara et al. 2008). Nasal effects, which were consistently observed at low concentrations in humans and experimental animals (see Table A-1), were considered the critical effects for acute-duration exposure to acrolein.

Table A-1. Select NOAEL and LOAEL Values (≤2 ppm) in Animals Following Acute-Duration Inhalation Exposure to Acrolein

		NOAEL/LOAEL (ppm)			
Species	Duration	NOAEL	LOAEL	Effect	Reference
Respiratory					
Human	2 hours	0.11			Dwivedi et al. 2015

Table A-1. Select NOAEL and LOAEL Values (≤2 ppm) in Animals Following Acute-Duration Inhalation Exposure to Acrolein

Species	Duration	NOAEL/LOAEL (ppm) NOAEL	LOAEL	Effect	Reference
Human	1 hour		0.3	Nose and throat irritation (subjective symptoms); decreased respiratory rate	Weber-Tschopp et al. 1977[a]
Rat (Wistar)	3 days 6 hours/day		0.25	Nasal lesions (disarrangement and thickening of the respiratory epithelium, basal cell hyperplasia)	Cassee et al. 1996a
Guinea pig (NS)	2 hours		0.6	Increased respiratory flow resistance and tidal volume, decreased respiration rate	Murphy et al. 1963
Mouse (Swiss-Webster)	10 minutes		1.03	RD_{50}	Steinhagen and Barrow 1984
Mouse (C57BL/6N)	10 minutes		1.3	Decreased respiratory rate and increased expiratory pause and specific airway resistance	Morris et al. 2003
Mouse (B6C3F1)	10 minutes		1.41	RD_{50}	Steinhagen and Barrow 1984
Rat (Wistar)	6 hours	1.4			Cassee et al. 1996a
Mouse (C57BL/6N)	10 minutes		1.59	RD_{50}	Morris et al. 2003
Mouse (Swiss-Webster)	5 days 6 hours/day		1.7	Nasal lesions (ulceration, necrosis, and squamous metaplasia of the respiratory and olfactory epithelium)	Buckley et al. 1984
Mouse (Swiss-Webster)	10 minutes		1.7	RD_{50}	Kane and Alarie 1977
Rat (Wistar)	4 hours		2	Lung lesions (epithelial cell sloughing and mononuclear cells in the bronchioles, hyperemia, emphysema)	Arumugam et al. 1999a
Immunological					
Human	2 hours	0.11			Dwivedi et al. 2015
Mouse (CD)	5 days 3 hours/day		0.1	Decreased resistance to respiratory tract infection	Aranyi et al. 1986

Table A-1. Select NOAEL and LOAEL Values (≤2 ppm) in Animals Following Acute-Duration Inhalation Exposure to Acrolein

Species	Duration	NOAEL/LOAEL (ppm) NOAEL	LOAEL	Effect	Reference
Mouse (CD)	3 hours	0.09			Aranyi et al. 1986

[a]Selected study/endpoint for derivation of acute-duration inhalation MRL.

LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; NS = not specified; RD_{50} = exposure concentration producing a 50% respiratory rate decrease; SLOAEL = serious lowest-observed-adverse-effect level

Selection of the Principal Study: For nasal effects, Weber-Tschopp et al. (1977) and Cassee et al. (1996a) had the lowest LOAELs (see Table A-1). Cassee et al. (1996a) demonstrated nasal lesions in rats; however, the LOAEL (0.25 ppm) was similar to the human LOAEL (0.3 ppm) from Weber-Tschopp et al. (1977). The human data are preferable for the derivation of the MRL, eliminating the introduction of uncertainty from interspecies extrapolation; therefore, Weber-Tschopp et al. (1977) was selected as the principal study. Weber-Tschopp et al. (1977) reported a LOAEL of 0.3 ppm based on nose and throat irritation and reduced respiratory rate. No NOAEL was determined.

Summary of the Principal Study:

Weber-Tschopp A, Fischer T, Gierer R, et al. 1977. [Experimental irritating effects of acrolein on man.] Int Arch Occup Environ Health 40:117-130. (German)

Forty-six college student volunteers (21 men, 25 women) were exposed to 0.3 ppm acrolein for 60 minutes. Groups of three at a time entered into a chamber. Endpoints evaluated include eye, nose, and throat irritation, blink rate, and respiratory rate. At 5-minute intervals during exposure, volunteers described irritation scores for the eyes, nose, and throat using a subjective questionnaire. The scores were as follows: 1 (not at all), 2 (a little), 3 (medium), and 4 (strong). Blink rate was evaluated in two students per group of three. Respiration rate was evaluated in one student per group of three by an extensometer tape recording movements placed below the ribs. The participants served as their own controls before exposure. Results of irritation were increased throughout 0.3-ppm acrolein exposure, with a mean rating of 2 "a little." Irritation symptoms began as early as 10 minutes into the 1-hour exposure. Eye irritation was the most sensitive, followed by nose, and then throat irritation. Blink rate increased quickly with initial 10-minute exposure and continued for the remaining duration. Respiratory rate was reduced by 20% and was significant after 40 minutes. Additional experiments were performed that involved increasing concentrations of acrolein over a 40-minute time frame. Volunteers exposed to increasing levels of acrolein vapors for 40 minutes reported significant nose irritation at 0.26 ppm, throat irritation at 0.43 ppm, and a decrease in respiratory rate (25%) at 0.60 ppm. Nasal irritation was also reported by subjects exposed to 0.6 ppm acrolein for 1.5 minutes, following prior exposure to lower concentrations (0.15, 0.30, and 0.45 ppm; 8-minute recovery between exposures).

Selection of the Point of Departure for the MRL: Nose and throat irritation (subjective symptoms) and reduced respiratory rate occurred at a LOAEL of 0.3 ppm. No NOAEL was determined; therefore, the LOAEL of 0.3 ppm was selected as the point of departure (POD).

Calculations

Adjustment for Intermittent Exposure: Humans were exposed for 1 hour and due to the reversible nature of the effects, no adjustment was made for continuous exposure.

Human Equivalent Concentration: No HEC was derived due to the study subjects being human.

Uncertainty Factor: The LOAEL was divided by a composite uncertainty factor (UF) of 100:

- 10 for use of a LOAEL
- 10 for human variability

This results in the following provisional MRL:

$$provisional\ MRL = \frac{LOAEL}{UFs} = \frac{0.3\ ppm}{(10\ x\ 10)=100} = 0.003\ ppm$$

Other Additional Studies or Pertinent Information that Lend Support to this MRL: The respiratory tract is a well-established target organ of acrolein exposure. In humans, exposure to acrolein was associated with numerous respiratory symptoms as well as altered respiratory function (Wang et al. 2022). An epidemiological study found associations with respiratory irritation symptoms (Sakellaris et al. 2021). Acute-duration studies in rats and mice exposed to acrolein by inhalation consistently showed effects on the nasal olfactory and respiratory epithelium (Buckley et al. 1984; Cassee et al. 1996a; Snow et al. 2017), lung lesions (Arumugam et al. 1999a; Snow et al. 2017), and changes in respiration rate and frequency (Ballantyne et al. 1989; Cassee et al. 1996b; Hazari et al. 2008; Kurhanewicz et al. 2018; Morris et al. 2003; Perez et al. 2013, 2015; Snow et al. 2017;). RD_{50} values indicative of sensory irritation ranged from 4.6 to 9.2 ppm in rats and from 1.03 to 2.9 ppm in mice (Babiuk et al. 1985; Cassee et al. 1996b; Kane and Alarie 1977; Morris et al. 2003; Nielsen et al. 1984; Steinhagen and Barrow 1984). With longer exposure durations, more severe degenerative (necrosis) and regenerative (metaplasia) lesions, as well as inflammatory responses in the respiratory tract, were observed (Costa et al. 1986; Dorman et al. 2008; Feron et al. 1978; Kutzman et al. 1985; Leach et al. 1987; Liu et al. 2019; NTP 1981). The provisional MRL is equivalent to 3 ppb and is higher than the measured ambient air levels, which range from 0.062 to 0.591 ppbv (0.14–1.36 µg/m^3) as determined from EPA's AQS (EPA 2023a) and discussed in Section 5.5.

Agency Contacts (Chemical Managers): Sam Keith

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Acrolein
CAS Numbers: 107-02-8
Date: May 2024
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Intermediate
Provisional MRL: 0.0004 ppm (0.0009 mg/m^3) (based on the chronic-duration inhalation MRL)
Critical Effect: See chronic-duration inhalation MRL
Reference: Matsumoto et al. 2021 (see chronic-duration inhalation MRL)
Point of Departure: See chronic-duration inhalation MRL
Uncertainty Factor: See chronic-duration inhalation MRL
LSE Graph Key: 71
Species: Rat

MRL Summary: The provisional chronic-duration inhalation MRL of 0.0004 ppm, based on a benchmark concentration lower confidence limit (BMCL) of 0.27 ppm for nasal lesions in male rats exposed for 2 years, was adopted as the provisional intermediate-duration inhalation MRL. The BMCL was adjusted for continuous exposure (6 hours/day, 5 days/ week) and converted to a $BMCL_{HEC}$ of 0.012 ppm. The $BMCL_{HEC}$ was divided by a total uncertainty factor of 30 (10 for human variability and 3 for animal to human extrapolation after applying dosimetric adjustment). A derived intermediate-duration inhalation MRL was considered, but the study that it was based on had some limitations (see later discussion). Intermediate-duration inhalation studies provide support for the use of the chronic-duration inhalation MRL for the intermediate duration.

Selection of the Critical Effect: See worksheet for chronic-duration inhalation MRL.

Selection of the Principal Study: See worksheet for chronic-duration inhalation MRL.

Summary of the Principal Study: See worksheet for chronic-duration inhalation MRL.

Selection of the Point of Departure for the MRL: See worksheet for chronic-duration inhalation MRL.

Calculations: See worksheet for chronic-duration inhalation MRL.

Uncertainty Factor: See worksheet for chronic-duration inhalation MRL.

Other Additional Studies or Pertinent Information that Lend Support to this MRL: A number of studies have evaluated the toxicity of acrolein following intermediate-duration inhalation exposure, and the lowest LOAELs for these studies are based on respiratory (Bouley et al. 1975; Conklin et al. 2017b; Dorman et al. 2008; Feron et al. 1978; Kutzman et al. 1985; Lyon et al. 1970) or immunological (Bouley et al. 1975) effects. Of the intermediate-duration studies located, the lowest nasal effect LOAEL was 0.55 ppm for sneezing (nasal irritation) (Bouley et al. 1975). This finding is supportive of nasal irritation effects; however, there were several important study limitations including the use of a single dose, a 26-day exposure duration, and limited respiratory endpoints evaluated (clinical signs and lung weights). The next lowest nasal LOAEL was similar at 0.586 ppm based on histopathological lesions in the nose of male rats (Dorman et al. 2008). Dorman et al. (2008) conducted a comprehensive evaluation of histology of the nasal cavity and respiratory tract following 13 weeks of exposure (three concentrations and a control) to acrolein in groups of 12 male F344 rats. The LOAEL was 0.586 ppm based on nasal lesions and the NOAEL was 0.200 ppm.

Derivation of an intermediate-duration inhalation MRL based on the nasal lesions in the study by Dorman et al. (2008) was considered. The data on nasal lesions were not amenable to benchmark dose (BMD) modeling, because the incidences were 0/12 at 0 and 0.200 ppm and 12/12 at 0.586 and 1.733 ppm. Therefore, a NOAEL/LOAEL approach was used to derive a candidate MRL. The NOAEL was duration-adjusted for exposures of 6 hours/day and 5 days/week, so the $NOAEL_{ADJ}$ was 0.200 ppm x 6 hours/24 hours x 5 days/7 days = 0.036 ppm. The $NOAEL_{HEC}$ was calculated using a regional gas dose ratio (RGDR) of 0.25 resulting in a $NOAEL_{HEC}$ = 0.036 ppm x 0.25 = 0.009 ppm. Using an uncertainty factor of 30 (3 for animal to human extrapolation after dosimetric adjustment and 10 for human variability) results in a value of 0.009 ppm/30 = 0.0003 ppm as the candidate intermediate-duration inhalation MRL.

The provisional chronic-duration inhalation MRL of 0.0004 ppm based on Matsumoto et al. (2021) is nearly identical to the calculated intermediate-duration inhalation MRL of 0.0003 ppm based on Dorman et al. (2008). However, ATSDR has greater confidence in the value based on the Matsumoto et al. (2021) study due to its study design (larger numbers of animals per group and better dose spacing) and because BMD modeling was possible using the data from Matsumoto et al. (2021). Therefore, the chronic-duration MRL of 0.0004 ppm was adopted as the intermediate-duration inhalation MRL. The provisional MRL is equivalent to 0.4 ppb and is within the measured ambient air levels which range from 0.062 to 0.591 ppbv (0.14–1.36 µg/m^3) as determined from EPA's AQS (EPA 2023a) and discussed in Section 5.5.

Agency Contacts (Chemical Managers): Sam Keith

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Acrolein
CAS Numbers: 107-02-8
Date: May 2024
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Chronic
Provisional MRL: 0.0004 ppm (0.0009 mg/m^3)
Critical Effect: Nasal respiratory gland metaplasia
Reference: Matsumoto et al. 2021
Point of Departure: BMCL = 0.27 ppm ($BMCL_{HEC}$ = 0.012 ppm)
Uncertainty Factor: 30
LSE Graph Key: 71
Species: Rat

MRL Summary: A provisional chronic-duration inhalation MRL of 0.0004 ppm was derived for acrolein based on a BMCL of 0.27 ppm for nasal lesions in male rats exposed for 2 years. The BMCL was adjusted for continuous exposure (6 hours/day, 5 days/ week) and converted to a $BMCL_{HEC}$ of 0.012 ppm. The $BMCL_{HEC}$ was divided by a total uncertainty factor of 30 (10 for human variability and 3 for animal to human extrapolation after applying dosimetric adjustment).

Selection of the Critical Effect: The database of chronic-duration inhalation toxicity studies for acrolein was limited to a 1-year study in hamsters (Feron and Kruysse 1977) and a 2-year study in mice and rats (Matsumoto et al. 2021) (see Table A-2). In Matsumoto et al. (2021), nasal lesions were observed in both mice and rats; however, significant mortality occurred in both control and treated mice, precluding the use of these data for MRL derivation.

Table A-2. Select NOAEL and LOAEL Values in Animals Following Chronic-Duration Inhalation Exposure to Acrolein

		NOAEL/LOAEL (ppm)			
Species	Duration	NOAEL	LOAEL	Effect	Reference
Respiratory					
Mouse (B6D2F1/ Crlj)	2 years 5 days/week 6 hours/day (WB)	0.1 F 0.4M	0.4 F 1.6M	Nasal lesions (inflammation, hyperplasia, metaplasia, regeneration)	Matsumoto et al. 2021
Rat (F344/Du CrlCrlj)	2 years 5 days/week 6 hours/day (WB)	0.5	2	Nasal lesions (inflammation, metaplasia, eosinophilic changes, goblet cell hyperplasia)	Matsumoto et al. 2021[a]

Table A-2. Select NOAEL and LOAEL Values in Animals Following Chronic-Duration Inhalation Exposure to Acrolein

Species	Duration	NOAEL/LOAEL (ppm) NOAEL	LOAEL	Effect	Reference
Other effects					
Hamster (Golden Syrian)	52 weeks 5 days/week 7 hours/day		4	Decreased body weight; increased hemoglobin and packed cell volume	Feron and Kruysse 1977

[a]Selected study/endpoint for derivation of chronic-duration inhalation MRL.

F = female(s); LOAEL = lowest-observed-adverse-effect level; M = male(s); NOAEL = no-observed-adverse-effect level; (WB) = whole-body exposure

Selection of the Principal Study: Of the two chronic-duration inhalation studies for acrolein (Feron and Kruysse 1977; Matsumoto et al. 2021), Matsumoto et al. (2021) was a 2-year study in mice and rats that evaluated comprehensive toxicological endpoints. This study was selected as the principal study.

Summary of the Principal Study:

Matsumoto M, Yamano S, Senoh H, et al. 2021. Carcinogenicity and chronic toxicity of acrolein in rats and mice by two-year inhalation study. Regul Toxicol Pharmacol 121:104863. https://doi.org/10.1016/j.yrtph.2021.104863.

Groups of F344/DuCrlCrlj rats and B6D2F1/Crlj mice (50/sex/group) were exposed whole body to acrolein (purity 98.3%) vapor concentrations of 0, 0.1, 0.5, or 2 ppm or 0, 0.1, 0.4, or 1.6 ppm, respectively, for 6 hours/day, 5 days/week for 104 weeks (2 years). The animals were observed daily for clinical signs and mortality. Body weight and food consumption were measured once a week for the first 14 weeks and once every 4 weeks thereafter. Animals were sacrificed after the 2-year exposure period. At sacrifice, blood was collected under anesthesia after overnight fasting for hematology and blood biochemistry. All animals, including those found dead or moribund, underwent complete necropsy. All organs and tissues were weighed and excised for histology and the entire respiratory tract, including nasal cavity, pharynx, and larynx, was examined for histopathology for all animals.

At 0, 0.1, 0.5 and 2.0 ppm, the terminal survival rates were 82, 80, 74 and 84%, respectively, in male rats and 86, 84, 82 and 68%, respectively, in female rats. No differences in clinical signs were noted in any group. At 2 ppm in males, body weights were decreased by 12% and food consumption was decreased by 9%. In males at 2 ppm, hematology and serum biochemistry parameters were altered (increased mean corpuscular hemoglobin [MCH], decreased mean corpuscular volume [MCV], decreased cholesterol, triglycerides, phospholipids, and creatine, and increased AST, ALT, and ALP). Absolute and relative spleen weights were decreased by 22 and 24%, respectively, in males exposed to 2 ppm, but no associated histopathology was observed. No differences in serum biochemistry or organ weights were observed in female rats at any dose. Histopathological effects were identified in the nasal cavity of both males and females. Non-neoplastic histological changes observed in both sexes at 2 ppm included goblet cell hyperplasia, inflammation and squamous cell metaplasia of the respiratory epithelium, hyperplasia of the transitional epithelium, olfactory epithelium atrophy, edema of the lamina propria, and proliferation of the striated muscle. Increased eosinophilic change of the olfactory epithelium and respiratory metaplasia of the glands were observed in males only exposed to 2 ppm. The toxicological significance of the

eosinophilic change is uncertain, given the high incidence in controls (35/50) and the absence of an increase in similarly exposed females. The study authors reported increased incidences of "foreign body inflammation" at the highest concentration in both sexes, but did not provide further description of this finding, so its toxicological significance is also uncertain. Neoplastic changes include rhabdomyomas of the nasal cavity observed in four female rats exposed to 2 ppm (significant trend). There were no treatment-related neoplastic changes observed in other organs.

In mice, survival rates were significantly decreased in males and females; therefore, dosing was terminated early at week 93 and 99, respectively. The survival rates at 0, 0.1, 0.4 and 1.6 ppm were 22, 30, 28 and 30%, respectively, in males at the 93rd week and 22, 36, 28 and 38%, respectively, in females at the 99th week. Mortality was attributed to "renal lesion and/or deposition of amyloid" at necropsy. No clinical signs of toxicity were observed at any dose. Body weights were decreased by 17% in male mice at 1.6 ppm. There were no exposure-related differences in organ weights, hematology, or serum biochemistry in any of the groups. The most sensitive non-neoplastic lesions included inflammation and hyperplasia of the respiratory epithelium, which were increased in female mice at 0.4 and 1.6 ppm. Additional nasal lesions that were increased at 1.6 ppm only in male and female mice included exudate, metaplasia of the olfactory epithelium and glands, squamous cell metaplasia of the respiratory epithelium, atrophy of the olfactory epithelium, and regeneration and hyperplasia of the respiratory epithelium. Adenomas of the nasal cavity were observed in 16/50 female mice exposed to 1.6 ppm compared with 0/50 in the control, and were significant by Fisher's exact test and Peto's trend test.

Selection of the Point of Departure for the MRL: The data for nasal respiratory epithelial inflammation and respiratory gland metaplasia in male rats were selected for use in deriving the MRL. Significant mortality occurred in both control and treated mice, precluding the use of these data for MRL derivation. In female rats, the nasal histopathology data either did not exhibit a monotonic dose-response relationship or were not amenable to BMD modeling because there were no data to inform the shape of the curve at the region of interest (10% extra risk). In addition, a small number of female rats in the highest exposure group exhibited nasal neoplasms. Finally, the incidence of non-neoplastic histological changes was higher in males at 2 ppm compared to females. In male rats, the incidences of goblet cell hyperplasia and respiratory metaplasia of the olfactory epithelium were not amenable to BMD modeling because these endpoints also lacked data to inform the shape of the curve in the region of 10% extra risk (the incidences were 0 or 2% at 0.5 ppm and 72 or 98% at 2 ppm). Therefore, BMD modeling was performed using the data for respiratory epithelium inflammation and respiratory gland metaplasia in male rats, as shown in Table A-3.

Table A-3. Incidence of Selected Nasal Lesions in Male F344/DuCrlCrlj Rats Exposed to Acrolein for 6 Hours/Day, 5 Days/ Week for 2 Years

	Exposure concentration (ppm)			
	0	0.1	0.5	2.0
Respiratory epithelium inflammation	14/50	16/50	10/50	34/50
Respiratory gland metaplasia	15/50	12/50	17/50	38/50

Source: Matsumoto et al. 2021

Respiratory Epithelium Inflammation. BMD modeling was conducted using the data for respiratory epithelium inflammation in male F344/DuCrlCrlj rats administered acrolein via inhalation for 6 hours/day, 5 days/week for 2 years. The data were fit to all available dichotomous models in EPA's Benchmark Dose Software (BMDS, version 3.3) using a benchmark response (BMR) of 10% extra risk. Adequate model fit was judged by four criteria: goodness-of-fit statistics (p-value >0.1), visual inspection

of the dose-response curve, a 95% confidence limit on the BMC (BMCL) that is not 10 times lower than the lowest non-zero dose, and scaled residual within ±2 units at the data point (except the control) closest to the predefined BMR. Among all models providing adequate fit to the data, the lowest BMCL was selected as the POD when the difference between the BMCLs estimated from these models was >3-fold; otherwise, the BMCL from the model with the lowest Akaike information criterion (AIC) was chosen. BMDS recommended the Gamma model for the data, and after verifying the model fit by the four criteria listed above, this model was selected. The BMC/BMCL values are presented in Table A-4 and the fit of the selected model is presented in Figure A-1.

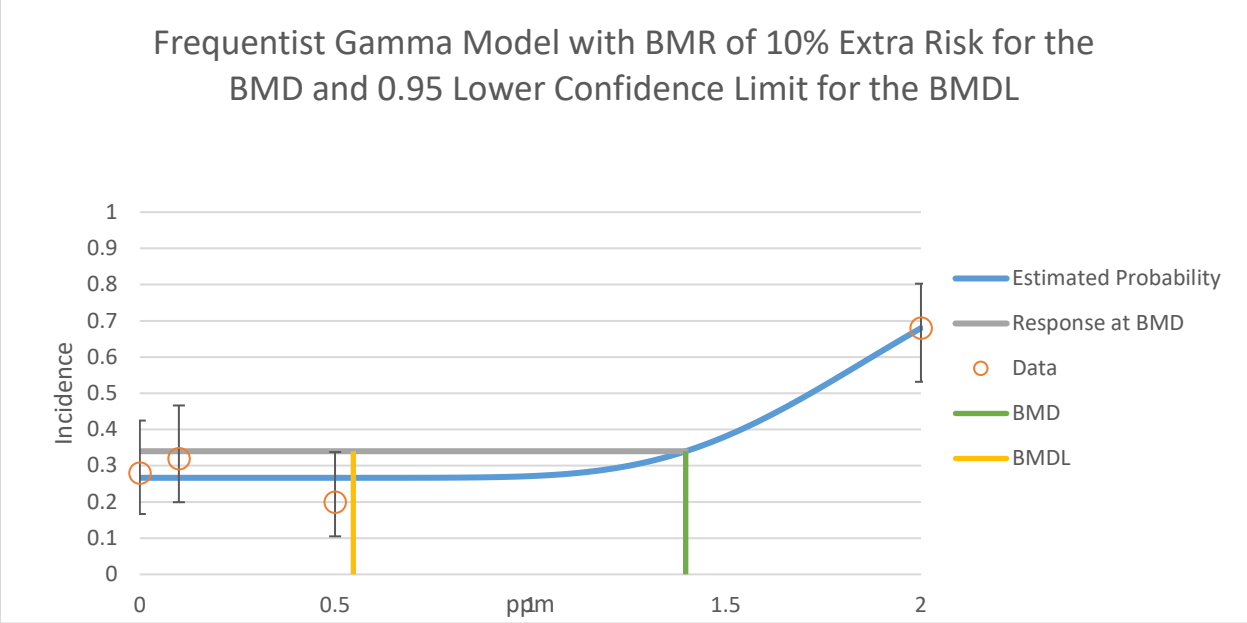
Table A-4. Model Predictions for Respiratory Epithelium Inflammation in Male F344/DuCrlCrlj Rats Exposed to Acrolein via Inhalation for 6 Hours/Day, 5 Days/Week for 104 Weeks (Matsumoto et al. 2021)

					Scaled residuals[c]	
Model	BMC_{10}[a] (ppm)	$BMCL_{10}$[a] (ppm)	p-Value[b]	AIC	Dose below BMC	Dose above BMC
Dichotomous Hill			NA	244.66	-0.91	-6.13×10^{-8}
Gamma[d,e]	**1.40**	**0.55**	**0.50**	**240.66**	**-0.91**	**8.77×10^{-6}**
Log-Logistic[f]	1.75	0.55	0.24	242.66	-0.91	1.19×10^{-8}
Multistage Degree 3[g]	1.01	0.48	0.44	241.00	-1.00	0.02
Multistage Degree 2[g]	0.73	0.39	0.32	242.09	-1.24	0.11
Multistage Degree 1[g]			0.09	246.79	0.71	-1.90
Weibull[d]	1.78	0.54	0.24	242.66	-0.91	4.45×10^{-8}
Logistic	0.43	0.34	0.16	244.49	0.87	-1.61
Log-Probit	1.79	0.55	0.24	242.66	-0.91	-2.17×10^{-8}
Probit	0.42	0.33	0.15	244.62	0.85	-1.64
Quantal Linear			0.09	246.79	0.71	-1.90

[a]BMC and BMCL values for models that do not provide adequate fit or yield BMCLs more than 10-fold lower than the lowest nonzero exposure concentration are not included in this table.
[b]Values <0.1 fail to meet conventional χ^2 goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the BMC.
[d]Power restricted to ≥1.
[e]All models provided an adequate fit to the data except for the Dichotomous Hill and Multistage 1-degree/Quantal linear models. Among the fit models, BMCLs were sufficiently close (differed by <3-fold). Therefore, the model with the lowest AIC was selected (Gamma).
[f]Slope restricted to ≥1.
[g]Betas restricted to ≥0.

AIC = Akaike Information Criterion; BMC = benchmark concentration (maximum likelihood estimate of the concentration associated with the selected benchmark response); $BMCL_{10}$ = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., 10 = dose associated with 10% extra risk); NA = saturated model, goodness-of-fit test could not be calculated

Figure A-1. Fit of the Gamma Model to Data for Acrolein, Respiratory Epithelium Inflammation in the Nose of Male F344/DuCrlCrlj Rats (Matsumoto et al. 2021)



Respiratory Gland Metaplasia. BMD modeling was conducted using the data for respiratory gland metaplasia in male F344/DuCrlCrlj rats administered acrolein via inhalation for 6 hours/day, 5 days/week for 2 years. The data were fit to all available dichotomous models in EPA's BMDS (version 3.3) using a BMR of 10% extra risk. Adequate model fit was judged by four criteria: goodness-of-fit statistics (p-value >0.1), visual inspection of the dose-response curve, a 95% confidence limit on the BMC (BMCL) that is not 10 times lower than the lowest non-zero dose, and scaled residual within ±2 units at the data point (except the control) closest to the predefined BMR. Among all models providing adequate fit to the data, the lowest BMCL was selected as the POD when the difference between the BMCLs estimated from these models was >3-fold; otherwise, the BMCL from the model with the lowest AIC was chosen. BMDS recommended the Logistic model for the data, and after verifying the model fit by the four criteria listed above, this model was selected. The BMC/BMCL values are presented in Table A-5 and the fit of the selected model is presented in Figure A-2.

Table A-5. Model Predictions for Respiratory Gland Metaplasia in Male F344/DuCrlCrlj Rats Exposed to Acrolein via Inhalation for 6 Hours/Day, 5 Days/Week for 104 Weeks (Matsumoto et al. 2021)

					Scaled residuals[c]	
Model	BMC_{10}[a] (ppm)	$BMCL_{10}$[a] (ppm)	p-Value[b]	AIC	Dose below BMC	Dose above BMC
Dichotomous Hill			NA	243.86	1.38×10^{-8}	1.95×10^{-9}
Gamma[d]	0.53	0.18	0.55	241.90	0.05	-0.004
Log-Logistic[e]	0.52	0.20	0.55	241.90	0.04	-0.004
Multistage Degree 3[f]	0.58	0.18	0.53	241.96	0.14	-0.01
Multistage Degree 2[f]	0.58	0.18	0.53	241.96	0.14	-0.01

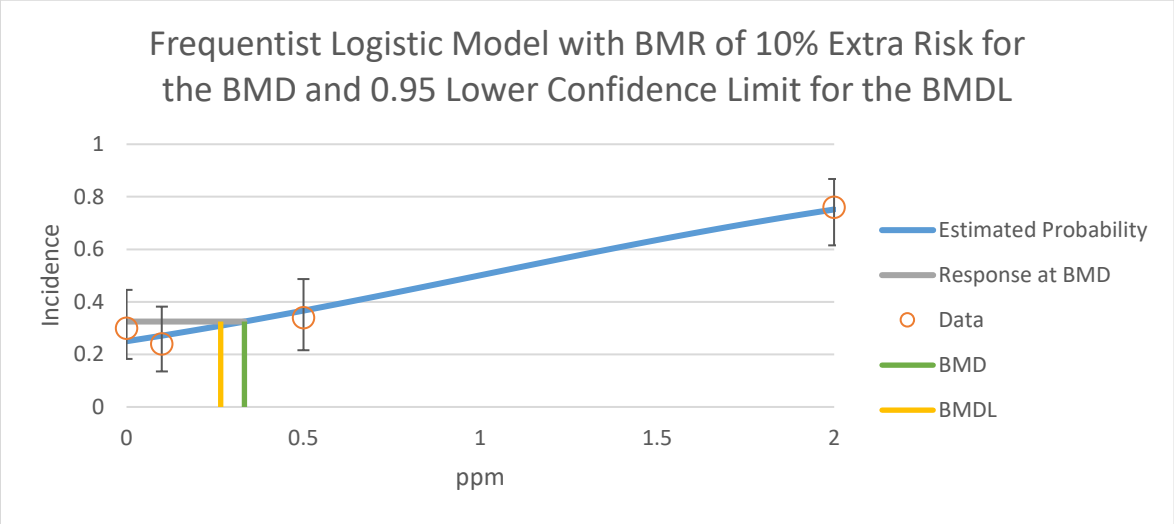
Table A-5. Model Predictions for Respiratory Gland Metaplasia in Male F344/DuCrlCrlj Rats Exposed to Acrolein via Inhalation for 6 Hours/Day, 5 Days/Week for 104 Weeks (Matsumoto et al. 2021)

Model	BMC_{10}[a] (ppm)	$BMCL_{10}$[a] (ppm)	p-Value[b]	AIC	Scaled residuals[c]	
					Dose below BMC	Dose above BMC
Multistage Degree 1[f]	0.21	0.15	0.43	242.07	-0.50	-0.77
Weibull[d]	0.54	0.18	0.54	241.93	0.06	-0.004
Logistic[g]	**0.33**	**0.27**	**0.68**	**240.47**	**-0.43**	**-0.31**
Log-Probit	0.51	0.22	0.56	241.87	0.008	-0.001
Probit	0.33	0.26	0.67	240.51	-0.43	-0.33
Quantal Linear	0.21	0.15	0.43	242.07	-0.50	-0.77

[a]BMC and BMCL values for models that do not provide adequate fit or yield BMCLs more than 10-fold lower than the lowest nonzero exposure concentration are not included in this table.
[b]Values <0.1 fail to meet conventional χ^2 goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the BMC.
[d]Power restricted to ≥1.
[e]Slope restricted to ≥1.
[f]Betas restricted to ≥0.
[g]All models provided an adequate fit to the data except for the Dichotomous Hill model. Among the fit models, BMCLs were sufficiently close (differed by <3-fold). Therefore, the model with the lowest AIC was selected (Logistic).

AIC = Akaike Information Criterion; BMC = benchmark concentration (maximum likelihood estimate of the concentration associated with the selected benchmark response); $BMCL_{10}$ = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., 10 = dose associated with 10% extra risk); NA = saturated model, goodness-of-fit test could not be calculated.

Figure A-2. Fit of the Logistic Model to Data for Acrolein, Respiratory Gland Metaplasia in the Nose of Male F344/DuCrlCrlj Rats (Matsumoto et al. 2021)



A summary of the potential POD values is shown in Table A-6. The lowest BMCL value for respiratory gland metaplasia was selected as the POD for derivation of the chronic-duration inhalation MRL.

Table A-6. Summary of Potential POD Values for Non-neoplastic Nasal Lesions in Male F344/DuCrlCrlj Rats (Matsumoto et al. 2021)

Endpoint	Selected model	BMC (ppm)	BMCL (ppm)
Respiratory epithelium inflammation	Gamma	1.4	0.55
Respiratory gland metaplasia	Logistic	0.33	0.27

BMC = benchmark concentration; BMCL = lower confidence limit on the BMC; POD = point of departure

Calculations

Adjustment for Intermittent Exposure: The animals in Matsumoto et al. (2021) were exposed for 6 hours/day, 5 days/week. Therefore, the BMCL was adjusted for intermittent exposure as follows:

$$BMCL_{ADJ} = BMCL \times \frac{6\ hours}{24\ hours} \times \frac{5\ days}{7\ days} = 0.27\ ppm \times \frac{6\ hours}{24\ hours} \times \frac{5\ days}{7\ days} = 0.048\ ppm$$

Human Equivalent Concentration: The critical effect of acrolein was nasal respiratory gland metaplasia in male rats; therefore, the $BMCL_{ADJ}$ was converted to an HEC by multiplying the $BMCL_{ADJ}$ by the rat-specific regional gas dose ratio that corresponds with the extrathoracic region ($RGDR_{ET}$). This $RGDR_{ET}$ is calculated using the following equation as defined by EPA (1994):

$$BMCL_{HEC} = BMCL_{ADJ} \times RGDR\ \frac{(Ve/SAet)_A}{(Ve/SAet)_H} = 0.048 * 0.25 = 0.012\ ppm$$

where:
$[V_e]_A$ = ventilation rate for male F344 rats = 0.254 L/minute (EPA 2012)
$[SA_{et}]_A$ = surface area of the extra-thoracic region in rats = 15 cm^2 (EPA 1994)
$[V_e]_H$ = ventilation rate for humans = 13.8 L/minute (EPA 1994)
$[SA_{et}]_H$ = surface area of the extra-thoracic region in humans = 200 cm^2 (EPA 1994)

PBPK modeling was considered for interspecies extrapolation. There is a computational fluid dynamics-PBPK model that predicts nasal tissue concentrations of naphthalene metabolites in rats and humans exposed by inhalation (Schroeter et al. 2008); however, there has been no direct evaluation of this model for predicting nasal tissue doses in humans. Model evaluation was limited to prediction of the overall dose-dependent and air flow-dependent nasal extraction fraction of acrolein in rats. Therefore, this model was not used for interspecies extrapolation.

Uncertainty Factor: The $BMCL_{HEC}$ of 0.012 ppm is divided by a total uncertainty factor (UF) of 30:

- 10 for human variability
- 3 for animal to human extrapolation after dosimetric adjustment

MRL = $BMCL_{HEC}$ ÷ UFs
MRL = 0.012 ppm ÷ (3x10) = 0.0004 ppm ($4x10^{-4}$ ppm)

Other Additional Studies or Pertinent Information that Lend Support to this MRL: The respiratory tract is a well-established target of acrolein exposure. Acute- and intermediate-duration inhalation exposures typically resulted in nasal irritation, reduced respiratory rate, and nasal lesions (inflammation and degenerative changes) reported across species. Mice and rats exposed to acrolein consistently exhibited adverse effects on the nasal olfactory and respiratory epithelium (Dorman et al. 2008; Feron et al. 1978; Leach et al. 1987; Liu et al. 2019; Lyon et al. 1970) with longer exposure durations, resulting in regenerative changes (hyperplasia and metaplasia) (Matsumoto et al. 2021). Available data in the same study selected for derivation of the MRL indicate that the respiratory effects (nasal lesions) observed were also observed in mice. The provisional MRL is equivalent to 0.4 ppb and is within the measured ambient air levels which range from 0.062 to 0.591 ppbv (0.14–1.36 µg/m^3) as determined from EPA's AQS (EPA 2023a) and discussed in Section 5.5

Agency Contacts (Chemical Managers): Sam Keith

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Acrolein
CAS Numbers: 107-02-8
Date: May 2024
Profile Status: Draft for Public Comment
Route: Oral
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration oral MRL.

Rationale for Not Deriving an MRL: No provisional acute-duration oral MRL was derived for acrolein. Only one study was available where measured effects were seen in the absence of increased mortality. In this study, increased plasma cholesterol, phospholipids, and triglycerides were observed at 5 mg/kg/day in mice given a single gavage dose (Conklin et al. 2010). The biological significance of these clinical chemistry changes is unclear because there is a lack of supporting data associating these changes to an adverse health effect (i.e., no significant effects were observed in liver and there are no other studies in the database that could provide insight as to the relevance of these findings). Histological staining for fat content in the liver was not altered with acrolein treatment. No reliable studies were located investigating gastrointestinal effects following acute-duration oral exposure.

Agency Contacts (Chemical Managers): Sam Keith

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Acrolein
CAS Numbers: 107-02-8
Date: May 2024
Profile Status: Draft for Public Comment
Route: Oral
Duration: Intermediate
Provisional MRL: 0.002 mg/kg/day
Critical Effect: Forestomach squamous epithelial hyperplasia
Reference: Auerbach et al. 2008; NTP 2006a
Point of Departure: $BMDL_{10}$ = 0.22 mg/kg/day
Uncertainty Factor: 100
LSE Graph Key: 11
Species: Mouse

MRL Summary: A provisional intermediate-duration oral MRL of 0.002 mg/kg/day was derived for acrolein based on forestomach squamous epithelial hyperplasia in female rats and male mice exposed to ≥1.25 mg/kg/day, 5 days/week for 14 weeks via gavage (Auerbach et al. 2008; NTP 2006a). The MRL is based on a lower confidence limit on the BMD (BMDL) of 0.22 mg/kg/day from BMD modeling of the data in male mice and divided by a total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Selection of the Critical Effect: Available intermediate-duration oral studies for acrolein report exposure-related gastrointestinal, cardiovascular, and body weight effects in rats and mice (see Table A-7). The cardiovascular effects observed in the Ismahil et al. (2011) study were not considered critical effects because the results were not supported by studies of longer duration and higher exposure (NTP 2006a; Parent et al. 1991a, 1992a, 1992b, 1992c). Gastrointestinal effects are considered the most sensitive effect, with forestomach squamous epithelial hyperplasia occurring at doses of ≥1.25 mg/kg/day in female rats and male mice. Although humans do not have a forestomach, the primary mechanism of toxicity of acrolein is epithelial tissue damage from direct contact and, therefore, epithelial hyperplasia is considered a suitable critical noncancer endpoint for deriving an oral MRL. Tissue damage would be expected to occur at the point of contact, even if it were another part of the gastrointestinal tract. Therefore, gastrointestinal effects were selected as the critical effect for derivation of the intermediate-duration oral MRL.

Table A-7. Select NOAEL and LOAEL Values in Animals Following Intermediate-Duration Oral Exposure to Acrolein

		NOAEL/LOAEL (mg/kg/day)			
Species	Duration	NOAEL	LOAEL	Effect	Reference
Gastrointestinal					
Rat (Fisher-344)	14 weeks 5 days/week (GW)	1.25 F	2.5 F	Forestomach squamous epithelial hyperplasia	Auerbach et al. 2008; NTP 2006a[a]
		2.5 M	5 M	Forestomach squamous epithelial hyperplasia	

Table A-7. Select NOAEL and LOAEL Values in Animals Following Intermediate-Duration Oral Exposure to Acrolein

Species	Duration	NOAEL/LOAEL (mg/kg/day) NOAEL	LOAEL	Effect	Reference
Mouse (B6C3F1)	14 weeks 5 days/week (GW)	1.25 M	2.5 M	Forestomach squamous epithelial hyperplasia	Auerbach et al. 2008; NTP 2006a
		2.5 F	5 F	Forestomach squamous epithelial hyperplasia	
Rat (Sprague-Dawley)	140 days 2 generations (GW)	3	6 (SLOAEL)	Stomach lesions (ulcers, erosion of the glandular mucosa, hyperplasia in the forestomach)	Parent et al. 1992c
Body weight					
Mouse (C57BL/6J)	48 days (GW)	1			Ismahil et al. 2011
Rat (SD)	8 weeks (GW)	2.5			Huang et al. 2013
Mouse (ICR)	4 weeks (GW)		2.5	Decreased body weight (15%)	Chen et al. 2019
Rat (Sprague-Dawley)	140 days 2 generations (GW)	6			Parent et al. 1992c
Mouse (B6C3F1)	14 weeks 5 days/week (GW)	10			Auerbach et al. 2008; NTP 2006a
Rat (Fisher-344)	14 weeks 5 days/week (GW)	5	10 F 10 M (SLOAEL)	Decreased body weight (10%) Decreased body weight (22%)	Auerbach et al. 2008; NTP 2006a
Cardiovascular					
Mouse (C57BL/6J)	48 days (GW)		1	Myocardial inflammation, myocyte hypertrophy and cell death, left ventricle remodeling and dysfunction	Ismahil et al. 2011

[a]Selected study/endpoint for derivation of intermediate-duration oral MRL.

F = female(s); GW = gavage in water; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; M = male(s); SLOAEL = serious lowest-observed-adverse-effect level; SD = Sprague-Dawley

Selection of the Principal Study: The oral study investigating forestomach squamous epithelial hyperplasia was selected as the principal study because it provided the lowest LOAEL with an accompanying NOAEL (Auerbach et al. 2008; NTP 2006a).

Summary of the Principal Study:

Auerbach SS, Mahler J, Travlos GS, et al. 2008. A comparative 90-day toxicity study of allyl acetate, allyl alcohol and acrolein. Toxicology 253:79-88. http://doi.org/10.1016/j.tox2008.08.014.

NTP. 2006a. NTP technical report on the comparative toxicity studies of allyl acetate, allyl alcohol, and acrolein. Research Triangle Park, NC: National Toxicology Program. https://ntp.niehs.nih.gov/sites/default/files/ntp/htdocs/st_rpts/tox048.pdf. June 21, 2023.

F344/N rats (10/sex/group) were administered 0, 0.75, 1.25, 2.5, 5.0, or 10.0 mg/kg/day of acrolein in 0.5% methyl cellulose 5 days/week for 14 weeks via gavage. B6C3F1 mice (10/sex/group) were administered 0, 1.25, 2.5, 5.0, 10 or 20 mg/kg/day of acrolein in 0.5% methyl cellulose 5 days/week for 14 weeks via gavage. Endpoints evaluated included lethality, clinical signs, body weight (weekly), hematology, clinical chemistry, urinalysis (after first dose and after 45th dose) for 3-HPMA, organ weights (spleen, liver, thymus, heart, lung, right testis, and kidney), and histopathology.

Rats. The study authors reported one male and one female accidental death (gavage errors) among animals exposed to 5 mg/kg/day, and no accidental deaths in other groups. Treatment-related mortalities were evident: 9/10 males and 8/10 females died prematurely or were sacrificed moribund, with the first deaths recorded during week 1 and the last during week 9. The cause of death was not reported, but animals in this dose group exhibited necrosis and hemorrhages in the stomach that were likely contributory. In addition to the high-dose mortalities, there were deaths at 2.5 and 5 mg/kg/day in males (2/10 and 1/10, respectively) and at 1.25 and 2.5 mg/kg/day (but not 5 mg/kg/day) in females (1/10 and 2/10, respectively). The incidences of mortalities (including accidental deaths) and timing of deaths are shown in Table A-8.

Table A-8. Survival and Incidences of Forestomach Hyperplasia in Rats Surviving Oral Exposure to Acrolein for 14 Weeks

	Dose (mg/kg/day)					
	0	0.75	1.25	2.5	5.0	10.0
Survival						
Males	10/10	10/10	10/10	8/10[a]	8/10[b]	1/10[c]
Females	10/10	10/10	9/10[d]	8/10[e]	9/10[f]	2/10[g]
Incidence (percent) of squamous epithelial hyperplasia in the forestomach among survivors						
Males	0/10	0/10	0/10	3/8	6/8[h]	1/1
Incidence (percent)	0%	0%	0%	38%	75%	100%
Females	0/10	0/10	3/9	5/8[h]	8/9[h]	2/2
Incidence (percent)	0%	0%	33%	63%	89%	100%

[a]Weeks of death: 6 and 7.
[b]Weeks of death: 6 and 7 (includes one accidental death).
[c]Weeks of death: 1, 2, 2, 2, 4, 6, 6, and 7. Although Auerbach et al. (2008) Table 1 and NTP (2006a) Table 6 reported that 2/10 male rats survived to termination, NTP (2006a) Table A5 and the NTP (2006b) data tables (indicated that only one male (animal number 814) survived to termination.
[d]Week of death: 5.
[e]Weeks of death: 3 and 6.
[f]Week of death: 7 (accidental death).
[g]Weeks of death: 1, 3, 4, 4, 4, 6, 7, and 9.
[h]Statistically significant at $p<0.05$ by Fisher's exact test performed for this review.

Sources: Auerbach et al. 2008; NTP 2006a, 2006b

Clinical signs observed in rats included abnormal breathing, eye and nasal discharge, ruffled fur, and thinness in the 10 mg/kg/day males and females. Terminal body weights were significantly decreased by 22% in males and 10% in females at 10 mg/kg/day compared to controls; however, only one male and two females survived to termination. In female rats, significant increases in absolute (8 and 13%) and

relative (11 and 26%) liver weights were seen at 5 and 10 mg/kg/day, respectively, compared to control. Red or white discoloration of the forestomach and glandular stomach was seen in male and female rats at 10 mg/kg/day. Dose-related increases in the incidences of forestomach squamous epithelial hyperplasia were observed in males at doses ≥2.5 mg/kg/day (statistically significant at ≥5 mg/kg/day) and in females at ≥1.25 mg/kg/day (statistically significant at ≥2.5 mg/kg/day); these data are shown in Table A-8. In addition to forestomach hyperplasia, high-dose (10 mg/kg/day) animals exhibited hemorrhage in the glandular stomach and forestomach. Hemorrhage in the glandular stomach was also reported in three males (one that died early and two that were sacrificed on schedule) in the 5 mg/kg/day group.

Mice. Among mice, four deaths were recorded as accidental: one control female mouse, one male in the 1.25 mg/kg/day group, and one male and one female in the 10 mg/kg/day group. Treatment-related deaths were also reported in mice; incidences are provided in Table A-9 along with accidental deaths. All mice in the 20 mg/kg/day groups died during the first week of the study; necropsy findings in the decedents included hemorrhages and necrosis in the glandular stomach and forestomach. Three other deaths that may have been treatment-related included one female mouse at 5 mg/kg/day and one male and one female in the 10 mg/kg/day groups. No clinical signs of toxicity were observed. No significant difference in terminal body weights or body weight gain were seen compared to control. Minimal, but significant increases in hemoglobin concentration and platelets was seen in males at 10 mg/kg/day and hematocrit values, hemoglobin concentration, and erythrocyte count in females at 2.5, 5, and 10 mg/kg/day compared to control. Significant increases in absolute liver weights (15%) and relative liver weights (19%) were seen in the 10 mg/kg/day males compared to control. The incidence of forestomach squamous epithelial hyperplasia was increased in males at all doses (statistically significant at ≥2.5 mg/kg/day) and in females at ≥2.5 mg/kg/day (statistically significant at ≥5 mg/kg/day); incidences are shown in Table A-9.

Table A-9. Survival and Incidences of Forestomach Hyperplasia in Mice Surviving Oral Exposure to Acrolein for 14 Weeks

	Dose (mg/kg/day)					
	0	1.25	2.5	5.0	10.0	20.0
Survival						
Males	10/10	9/10[a]	10/10	9/10[b]	9/10[c]	0/10[d]
Females	9/10[e]	10/10	10/10	9/10[f]	8/10[g]	0/10[d]
Incidence (percent) of squamous epithelial hyperplasia in the forestomach among survivors						
Males	0/10	2/9	6/10[h]	7/9[h]	9/9[h]	–
Incidence (percent)	0%	22%	60%	78%	100%	
Females	0/9	0/10	4/10	7/9[h]	6/8[h]	–
Incidence (percent)	0%	0%	40%	78%	75%	

[a]Week of death: 8 (accidental death).
[b]Week of death: 8 (accidental death).
[c]Week of death: 2.
[d]Week of death: 1.
[e]Week of death: 12 (accidental death).
[f]Week of death: 7 (missing).
[g]Weeks of death: 2 and 8 (includes one accidental death).
[h]Statistically significant at $p<0.05$ by Fisher's exact test performed for this review.

Sources: Auerbach et al. 2008; NTP 2006a, 2006b

Selection of the Point of Departure for the MRL: In order to identify the most sensitive POD, BMD modeling was performed on incidence data for forestomach squamous epithelial hyperplasia in female rats and male mice (Auerbach et al. 2008, NTP 2006a). Data for female rats and male mice were selected because they exhibited hyperplasia at lower doses than male rats and female mice.

Both Auerbach et al. (2008) and NTP (2006a) reported the incidences of histopathology findings in the number of animals initially assigned to each group (10/sex). However, animals that died prematurely may not have been exposed long enough to develop forestomach lesions, so these animals were censored from the dose-response analysis. Individual animal data were not reported by Auerbach et al. (2008) or NTP (2006a); however, NTP provided these data on their website (NTP 2006b). The incidences of forestomach squamous epithelial hyperplasia in animals that survived to termination were determined from the reports and data tables and are shown in Tables A-8 and A-9. Due to significant mortality in the high dose groups (10 mg/kg/day for rats and 20 mg/kg/day for mice), these dose groups were omitted from modeling. The incidences of forestomach squamous epithelial hyperplasia in female rats and male mice subjected to BMD modeling are shown in Table A-10.

Table A-10. Data on Forestomach Squamous Epithelial Hyperplasia Subjected to Benchmark Dose Modeling

	Dose (mg/kg/day)						
	0	0.75	1.25	2.5	5.0	10.0	20.0
Female rats	0/10	0/10	3/9	5/8	8/9	–[a]	NA
Male mice	0/10	NA	2/9	6/10	7/9	9/9	–[a]

[a]Dose group not included due to premature deaths.

NA = not applicable (dose not tested)

Sources: Auerbach et al. 2008; NTP 2006a, 2006b

BMD Modeling of Squamous Epithelial Hyperplasia of the Forestomach in Female F344 Rats. BMD modeling was conducted to identify a POD using the data for squamous epithelial hyperplasia in the forestomach of female F344/N rats administered acrolein via gavage for 5 days/week for 14 weeks. The highest dose group (10 mg/kg/day) was dropped from the analysis due to high mortality at this dose (only 2/10 females survived). The data for the remaining dose groups were fit to all available dichotomous models in EPA's BMDS (version 3.3) using a BMR of 10% extra risk. Adequate model fit was judged by four criteria: goodness-of-fit statistics (p-value >0.1), visual inspection of the dose-response curve, a 95% confidence limit on the BMD (BMDL) that is not 10 times lower than the lowest non-zero dose, and scaled residual within ±2 units at the data point (except the control) closest to the predefined BMR. Among all models providing adequate fit to the data, the lowest BMDL was selected as the POD when the difference between the BMDLs estimated from these models was >3-fold; otherwise, the BMDL from the model with the lowest AIC was chosen. BMDS recommended the frequentist Log-probit model for the data, and after verifying the model fit by the four criteria listed above, this model was selected to be considered as the basis for estimating this MRL. The model predictions for data in female rats are presented in Table A-11 and the fit of the selected model is presented in Figure A-3.

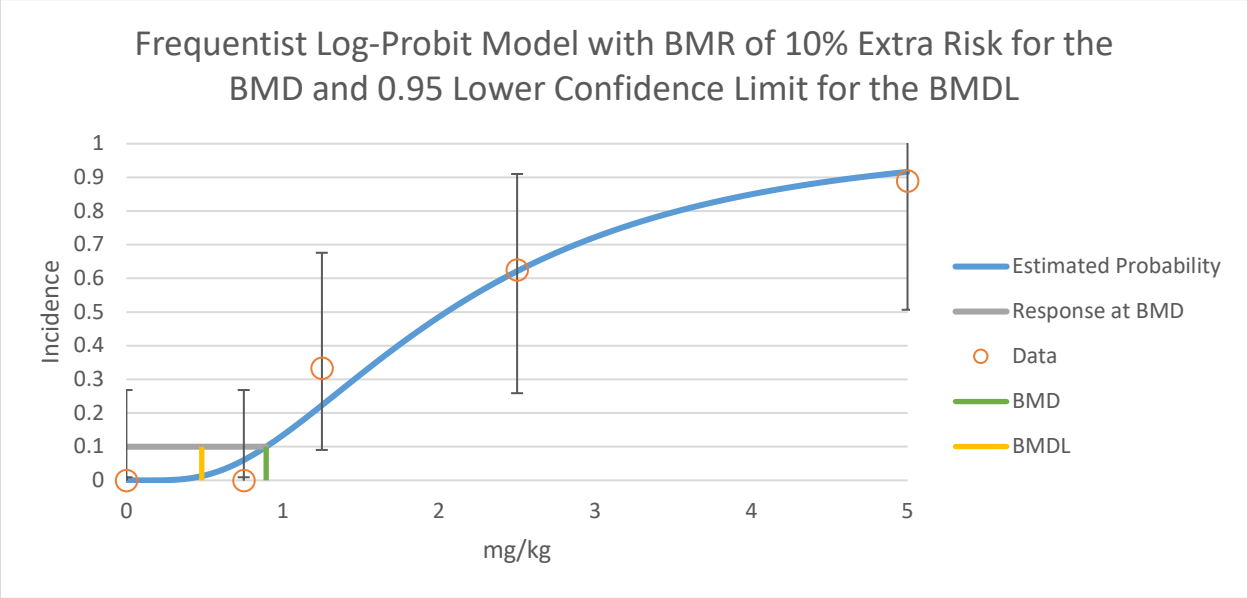
Table A-11. Model Predictions for Increased Incidence of Squamous Epithelial Hyperplasia in the Forestomach in Female F344/N Rats Exposed to Acrolein by Gavage for 14 Weeks (Auerbach et al. 2008; NTP 2006a)

Model	BMD_{10}[a] (mg/kg/day)	$BMDL_{10}$[a] (mg/kg/day)	p-Value[b]	AIC	Scaled residuals[c]	
					Dose below BMD	Dose above BMD
Dichotomous Hill	0.93	0.47	0.61	36.12	-0.71	0.65
Gamma[d]	0.83	0.33	0.70	34.91	-0.91	0.75
Log-Logistic[e]	0.87	0.44	0.75	34.43	-0.84	0.71
Multistage Degree 4[f]	0.73	0.27	0.62	35.68	-0.0004	-1.02
Multistage Degree 3[f]	0.73	0.27	0.62	35.68	-0.0004	-1.02
Multistage Degree 2[f]	0.73	0.27	0.62	35.68	-0.0004	-1.02
Multistage Degree 1[f]	0.33	0.22	0.68	35.83	-0.0004	-1.47
Weibull[d]	0.73	0.29	0.66	35.34	-0.0004	-1.02
Logistic	0.98	0.65	0.41	37.86	-1.06	1.01
Log-Probit[g]	**0.89**	**0.48**	**0.78**	**34.22**	**-0.78**	**0.70**
Probit	0.95	0.63	0.40	37.77	-1.04	1.03
Quantal Linear	0.33	0.22	0.68	35.83	-0.0004	-1.47

[a]BMD and BMDLs values for models that do not provide adequate fit are not included in this table.
[b]Values <0.1 fail to meet conventional χ^2 goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the BMD.
[d]Power restricted to ≥1.
[e]Slope restricted to ≥1.
[f]Betas (slope) restricted to ≥0.
[g]All models provided an adequate fit to the data. BMDLs were sufficiently close (differed by <3-fold). Therefore, the model with the lowest AIC was selected (Log-Probit).

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

Figure A-3. Fit of the Log-Probit Model to Incidence Data for Squamous Epithelial Hyperplasia in the Forestomach of Female F344/N Rats Following Oral Exposure to Acrolein for 14 Weeks (Auerbach et al. 2008; NTP 2006a)



BMD modeling of squamous epithelial hyperplasia of the forestomach in Male B6C3F1 mice. BMD modeling was conducted to identify a POD using the incidence data for squamous epithelial hyperplasia in the forestomach of male B6C3F1 mice administered acrolein via gavage for 5 days/week for 14 weeks. The highest dose group (20 mg/kg/day) was dropped from the analysis because all animals died during the first week of exposure. The data for the remaining dose groups were fit to all available dichotomous models in EPA's BMDS (version 3.3) using a BMR of 10% extra risk. Adequate model fit was judged by four criteria: goodness-of-fit statistics (p-value >0.1), visual inspection of the dose-response curve, a 95% confidence limit on the BMD (BMDL) that is not 10 times lower than the lowest non-zero dose, and scaled residual within ±2 units at the data point (except the control) closest to the predefined BMR. Among all models providing adequate fit to the data, the lowest BMDL was selected as the POD when the difference between the BMDLs estimated from these models was >3-fold; otherwise, the BMDL from the model with the lowest AIC was chosen. For the male B6C3F1 mice incidence data, BMDS recommended the Multistage 1-Degree and Quantal Linear models, which converged on the same form and yielded the same BMDL. After verifying the model fit by the four criteria listed above, the Quantal Linear model, which is more parsimonious than the Multistage Degree, was selected, and the BMDL associated with this model was selected to be considered as the basis for estimating this MRL. The model predictions for data in males are presented in Table A-12 and the fit of the selected model is presented in Figure A-4.

Table A-12. Model Predictions for Increased Incidence of Squamous Epithelial Hyperplasia of the Forestomach in Male B6C3F1 Mice Exposed to Acrolein by Gavage for 14 Weeks (Auerbach et al. 2008; NTP 2006a)

Model	BMD_{10}[a] (mg/kg/day)	$BMDL_{10}$[a] (mg/kg/day)	p-Value[b]	AIC	Scaled residuals[c]	
					Dose below BMD	Dose above BMD
Dichotomous Hill	0.81	0.24	0.99	37.62	-0.0004	-0.01
Gamma[d]	0.63	0.23	0.98	37.28	-0.0004	-0.16
Log-Logistic[e]	0.81	0.24	0.99	37.62	-0.0004	-0.01
Multistage Degree 4[f]	0.39	0.23	0.85	39.16	-0.0004	-0.38
Multistage Degree 3[f]	0.40	0.23	0.86	39.21	-0.0004	-0.36
Multistage Degree 2[f]	0.46	0.23	0.97	37.25	-0.0004	-0.28
Multistage Degree 1[f]	0.32	0.22	0.98	35.90	-0.0004	-0.59
Weibull[d]	0.57	0.23	0.98	37.26	-0.0004	-0.20
Logistic	0.98	0.63	0.68	39.94	-0.92	0.06
Log-Probit	0.83	0.26	0.99	37.42	-0.0004	-0.02
Probit	0.94	0.63	0.68	39.72	-0.86	0.09

Table A-12. Model Predictions for Increased Incidence of Squamous Epithelial Hyperplasia of the Forestomach in Male B6C3F1 Mice Exposed to Acrolein by Gavage for 14 Weeks (Auerbach et al. 2008; NTP 2006a)

Model	BMD_{10}[a] (mg/kg/day)	$BMDL_{10}$[a] (mg/kg/day)	p-Value[b]	AIC	Scaled residuals[c] Dose below BMD	Scaled residuals[c] Dose above BMD
Quantal Linear[g]	**0.32**	**0.22**	**0.98**	**35.90**	**-0.0004**	**-0.59**

[a]BMD and BMDLs values for models that do not provide adequate fit are not included in this table.
[b]Values <0.1 fail to meet conventional χ^2 goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the BMD.
[d]Power restricted to ≥1.
[e]Slope restricted to ≥1.
[f]Betas restricted to ≥0.
[g]All models provided an adequate fit to the data. BMDLs were sufficiently close (differed by <3-fold). Therefore, the model with the lowest AIC was selected. Two models (Multistage 1-degree and Quantal Linear) had the lowest AICs; the Quantal Linear model was selected because it is the more parsimonious model of the two.

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

Figure A-4. Fit of the Quantal Linear Model to Incidence Data for Squamous Epithelial Hyperplasia in the Forestomach of Male B6C3F1 Mice Following Oral Exposure to Acrolein for 14 Weeks (Auerbach et al. 2008; NTP 2006a)

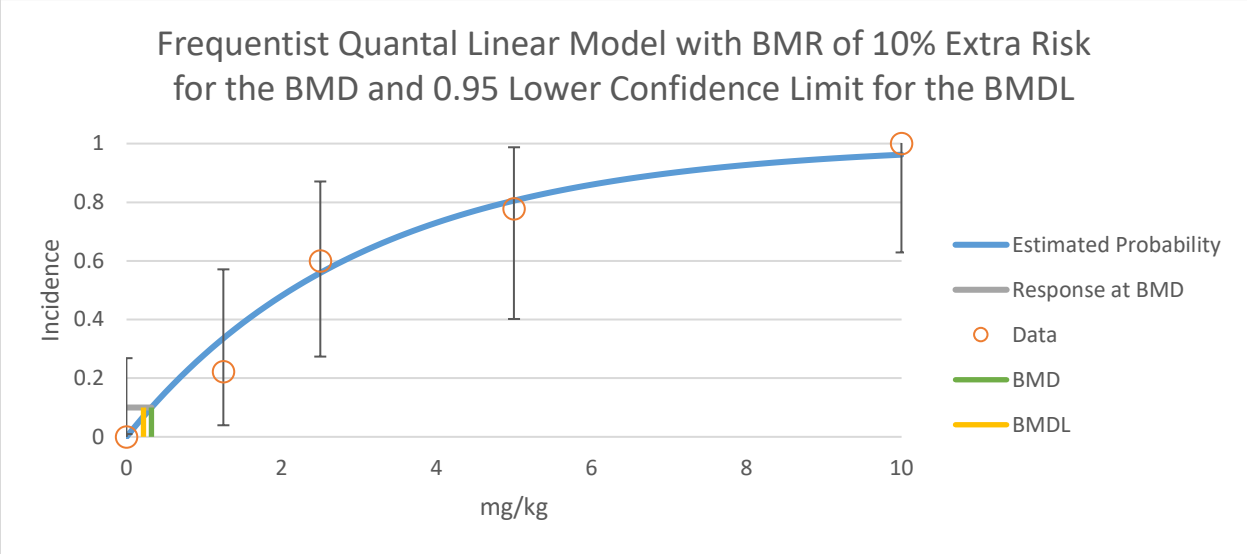


Table A-13 shows a summary of the candidate PODs obtained from BMD modeling of the data on forestomach squamous epithelial hyperplasia. The lowest POD was the BMDL of 0.22 mg/kg/day based on data in male B6C3F1 mice; this POD was selected for use in deriving the MRL.

Table A-13. Summary of Candidate POD Values Considered for Derivation of a Provisional Intermediate-Duration Oral MRL for Acrolein

Species	Duration	Effect	Candidate POD (mg/kg/day)	POD type	Reference
F344/N rat (female)	14 weeks	Forestomach squamous epithelial hyperplasia	0.48	$BMDL_{10}$	Auerbach et al. 2008; NTP 2006a
B6C3F1 mice (male)	14 weeks	Forestomach squamous epithelial hyperplasia	0.22	$BMDL_{10}$	Auerbach et al. 2008; NTP 2006a

BMD = maximum likelihood estimate of the dose associated with the selected benchmark response; $BMDL_{10}$ = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., 10 = dose associated with 10% extra risk); MRL = Minimal Risk Level; POD = point of departure

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

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

$$\begin{aligned} \text{MRL} &= BMDL_{10} \div \text{UFs} \\ &= 0.22 \text{ mg/kg/day} \div 100 = 0.0022 \text{ mg/kg/day} \\ &\approx 0.002 \text{ mg/kg/day after rounding} \end{aligned}$$

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Gastrointestinal effects have been reported in other rodent studies when acrolein was administered via gavage. Gastric ulceration was observed in rats given a single gavage dose of 25 mg/kg (Sakata et al. 1989) and in rabbits given 4 mg/kg/day for 12 days (Parent et al. 1993). Stomach lesions including ulcers, hemorrhage, hyperplasia of the forestomach, and erosion of the glandular mucosa were found in 2 generations of rats gavaged with 6 mg/kg/day (Parent et al. 1992c). Vomiting was also observed in a chronic-duration gavage study in which dogs were given 0.1 mg/kg/day (Parent et al. 1992b).

Agency Contacts (Chemical Managers): Sam Keith

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Acrolein
CAS Numbers: 107-02-8
Date: May 2024
Profile Status: Draft for Public Comment
Route: Oral
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration oral MRL.

Rationale for Not Deriving an MRL: No provisional chronic-duration oral MRL was derived for acrolein. A chronic-duration oral MRL cannot be derived because the lowest LOAEL value of 0.5 mg/kg/day (Parent et al. 1992a) is a SLOAEL value for decreased survival in rats, and vomiting in dogs is of questionable biological significance (Parent et al. 1992b). Although vomiting suggests gastrointestinal effects, no significant increase in gastrointestinal lesions were observed and vomiting frequency decreased over time, suggesting adaption to potential irritation.

Agency Contacts (Chemical Managers): Sam Keith

APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR ACROLEIN

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

B.1 LITERATURE SEARCH AND SCREEN

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

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

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

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

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

B.1.1 Literature Search

The current literature search was intended to update the 2007 Toxicological Profile for Acrolein; thus, the literature search was restricted to studies published between January 2005 and July 2022. The following main databases were searched in July 2022:

- PubMed
- National Technical Reports Library (NTRL)
- Scientific and Technical Information Network's TOXCENTER

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

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

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

Table B-2. Database Query Strings

Database search date	Query string
PubMed	
7/2022	((("Acrolein"[mh] NOT "Acrolein/analogs and derivatives"[mh]) OR ("Acrolein/analogs and derivatives"[mh] AND ("Acraldehyde"[tiab] OR "Acrolein"[tiab] OR "Acrylaldehyde"[tiab] OR "Acrylic aldehyde"[tiab] OR "Allyl aldehyde"[tiab] OR "Aqualine"[tiab] OR "Magnacide"[tiab] OR "Papite"[tiab] OR "Propenal"[tiab] OR "Slimicide"[tiab] OR "2-Propenal"[tiab] OR "Acquinite"[tiab] OR "Aqualin"[tiab] OR "Crolean"[tiab] OR "Ethylene aldehyde"[tiab] OR "Propylene aldehyde"[tiab])) OR (("Acraldehyde"[tiab] OR "Acrolein"[tiab] OR "Acrylaldehyde"[tiab] OR "Acrylic aldehyde"[tiab] OR "Allyl aldehyde"[tiab] OR "Aqualine"[tiab] OR "Magnacide"[tiab] OR "Papite"[tiab] OR "Propenal"[tiab] OR "Slimicide"[tiab] OR "2-Propenal"[tiab] OR "Acquinite"[tiab] OR "Aqualin"[tiab] OR "Crolean"[tiab] OR "Ethylene aldehyde"[tiab] OR "Propylene aldehyde"[tiab]) AND (to[sh] OR po[sh] OR ae[sh] OR pk[sh] OR ai[sh] OR ci[sh] OR bl[sh] OR cf[sh] OR ur[sh] OR "pharmacology"[sh:noexp] OR "environmental exposure"[mh] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR "Computational biology"[mh] OR "Medical Informatics"[mh] OR Genomics[mh] OR Genome[mh] OR Proteomics[mh] OR Proteome[mh] OR Metabolomics[mh] OR Metabolome[mh] OR Genes[mh] OR "Gene expression"[mh] OR Phenotype[mh] OR genetics[mh] OR genotype[mh] OR Transcriptome[mh] OR ("Systems Biology"[mh] AND ("Environmental Exposure"[mh] OR "Epidemiological Monitoring"[mh] OR analysis[sh])) OR "Transcription, Genetic "[mh] OR "Reverse transcription"[mh] OR "Transcriptional activation"[mh] OR "Transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, Messenger"[mh] OR "RNA, Transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "Reverse Transcriptase Polymerase Chain Reaction"[mh] OR "Base Sequence"[mh] OR "Trans-activators"[mh] OR "Gene Expression Profiling"[mh] OR (me[sh] AND ("humans"[mh] OR "animals"[mh])) OR toxicokinetics[mh:noexp])))) AND (2005:3000[mhda] OR 2005:3000[edat] OR 2005:3000[crdat] OR 2005:3000[dp])) OR ((("Acraldehyde"[tw] OR "Acrolein"[tw] OR "Acrylaldehyde"[tw] OR "Acrylic aldehyde"[tw] OR "Allyl aldehyde"[tw] OR "Aqualine"[tw] OR "Magnacide"[tw] OR "Papite"[tw] OR "Propenal"[tw] OR "Slimicide"[tw] OR "2-Propenal"[tw] OR "Acquinite"[tw] OR "Aqualin"[tw] OR "Crolean"[tw] OR "Ethylene aldehyde"[tw] OR "Propylene aldehyde"[tw]) AND (2005:3000[edat] OR 2005:3000[crdat] OR 2005:3000[dp])) NOT medline[sb]) "Acroleine"[tiab] AND (2005:3000[edat] OR 2005:3000[crdat] OR 2005:3000[dp])

Table B-2. Database Query Strings

Database search date	Query string
NTRL	
7/2022	"2-Propenal" OR "Acraldehyde" OR "Acrolein" OR "Acrylaldehyde" OR "Acrylic aldehyde" OR "Allyl aldehyde" OR "Aqualine" OR "Magnacide" OR "Papite" OR "Propenal" OR "Slimicide" OR "Acquinite" OR "acrilaldehido" OR "Aqualin" OR "Crolean" OR "Ethylene aldehyde" OR "Propylene aldehyde" "Acroleine"
Toxcenter	
7/2022	L1 10495 SEA FILE=TOXCENTER 107-02-8 L2 10434 SEA FILE=TOXCENTER L1 NOT TSCATS/FS L3 9383 SEA FILE=TOXCENTER L2 NOT PATENT/DT L4 5251 SEA FILE=TOXCENTER L3 AND PY>=2005 ACTIVATE TOXQUERY/Q --------- L5 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) L6 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT) L7 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50) L8 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT L9 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?) L10 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?) L11 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?) L12 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE)) L13 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?) L14 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?) L15 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?) L16 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?) L17 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?) L18 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?) L19 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?) L20 QUE (ENDOCRIN? AND DISRUPT?) L21 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?) L22 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?) L23 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)

Table B-2. Database Query Strings

Database search date	Query string
	L24 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?)
	L25 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)
	L26 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?)
	L27 QUE (NEPHROTOX? OR HEPATOTOX?)
	L28 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?)
	L29 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?)
	L30 QUE L5 OR L6 OR L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR L28 OR L29
	L31 QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE OR PORCINE OR MONKEY? OR MACAQUE?)
	L32 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE)
	L33 QUE L30 OR L31 OR L32
	L34 QUE (NONHUMAN MAMMALS)/ORGN
	L35 QUE L33 OR L34
	L36 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?)
	L37 QUE L35 OR L36

	L38 3697 SEA FILE=TOXCENTER L4 AND L37
	L39 3257 SEA FILE=TOXCENTER L4 AND L30
	L40 979 SEA FILE=TOXCENTER L39 AND MEDLINE/FS
	L41 706 SEA FILE=TOXCENTER L39 AND BIOSIS/FS
	L42 1567 SEA FILE=TOXCENTER L39 AND CAPLUS/FS
	L43 5 SEA FILE=TOXCENTER L39 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS)
	L44 2504 DUP REM L40 L41 L43 L42 (753 DUPLICATES REMOVED)
	L*** DEL 979 S L39 AND MEDLINE/FS
	L*** DEL 979 S L39 AND MEDLINE/FS
	L45 978 SEA FILE=TOXCENTER L44
	L*** DEL 706 S L39 AND BIOSIS/FS
	L*** DEL 706 S L39 AND BIOSIS/FS
	L46 442 SEA FILE=TOXCENTER L44
	L*** DEL 1567 S L39 AND CAPLUS/FS
	L*** DEL 1567 S L39 AND CAPLUS/FS
	L47 1081 SEA FILE=TOXCENTER L44
	L*** DEL 5 S L39 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS)
	L*** DEL 5 S L39 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS)
	L48 3 SEA FILE=TOXCENTER L44
	L49 1526 SEA FILE=TOXCENTER (L45 OR L46 OR L47 OR L48) NOT MEDLINE/FS

Table B-2. Database Query Strings

Database search date	Query string
	D SCAN L49

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS via ChemView	
7/2022	Compounds searched: 107-02-8
NTP	
7/2022	"Acrolein" "Propenal" "2-Propenal" "Slimicide" "Allyl aldehyde" "Aqualine" "Acraldehyde" "Acrylaldehyde" "Acrylic aldehyde" "Magnacide" "Papite" "Acquinite" "Acrilaldehido" "Aqualin" "Crolean" "Ethylene aldehyde" "Propylene aldehyde" "Acroleine"
Regulations.gov	
7/2022	Limited to 2005-2022; Notices "Acrolein" "Slimicide" "Magnacide" "2-Propenal" "Allyl aldehyde" "Aqualine" "Acraldehyde" "Acrylaldehyde" "Acrylic aldehyde" "Papite" "Acquinite" "Acroleine" "Aqualin" "Crolean" "Ethylene aldehyde" "Propylene aldehyde"
NPIRS	
7/2022	Compounds searched: 107-02-8
NIH RePORTER	
4/2023	Search Criteria - Fiscal Year: Active Projects; Text Search: "2-Propenal" OR "Acquinite" OR "Acraldehyde" OR "Acrolein" OR "Acroleine" OR "Acrylaldehyde" OR "Acrylic aldehyde" OR "Allyl aldehyde" OR "Aqualin" OR "Aqualine" OR "Crolean" OR "Ethylene aldehyde" OR "Magnacide" OR "Papite" OR "Propenal" OR "Propylene aldehyde" OR "Slimicide" (advanced) Limit to: Project Title, Project Terms, Project Abstracts
Other	Identified throughout the assessment process

The 2022 results were:

- Number of records identified from PubMed, NTRL, and TOXCENTER (after duplicate removal): 3,229
- Number of records identified from other strategies: 93
- Total number of records to undergo literature screening: 3,322

B.1.2 Literature Screening

A two-step process was used to screen the literature search to identify relevant studies on acrolein:

- Title and abstract screen
- Full text screen

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

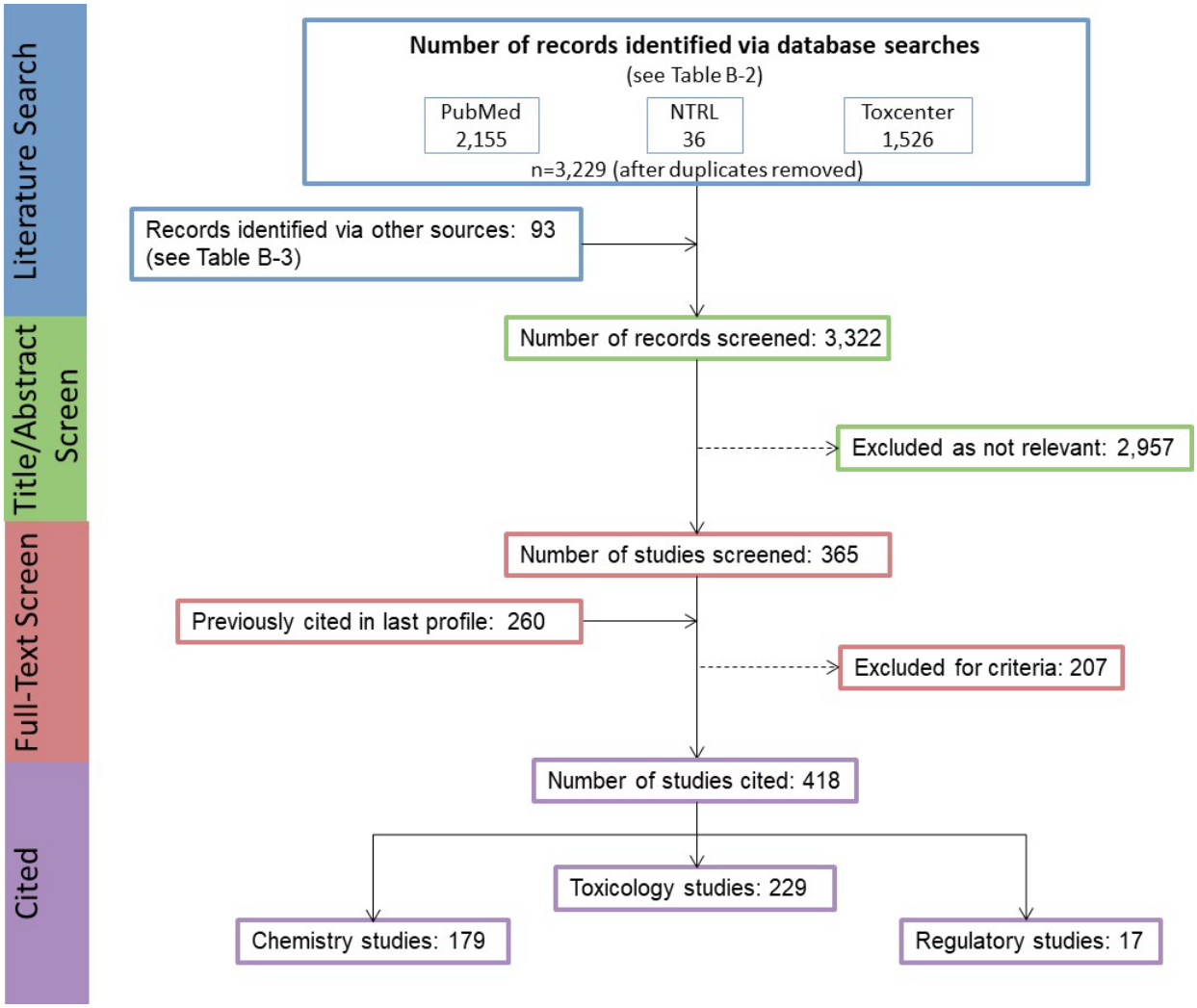
- Number of titles and abstracts screened: 3,322
- Number of studies considered relevant and moved to the next step: 365

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

- Number of studies undergoing full text review: 365
- Number of studies cited in the previous toxicological profile: 260
- Total number of studies cited in the profile: 418

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

Figure B-1. July 2022 Literature Search Results and Screen for Acrolein



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

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

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

C.1 PROBLEM FORMULATION

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

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

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

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

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

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

C.2 LITERATURE SEARCH AND SCREEN FOR HEALTH EFFECTS STUDIES

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

C.2.1 Literature Search

As noted in Appendix B, the current literature search was intended to update the 2007 Toxicological Profile for Acrolein; thus, the literature search was restricted to studies published between January 2005 and July 2022. See Appendix B for the databases searched and the search strategy.

A total of 3,322 records relevant to all sections of the toxicological profile were identified (after duplicate removal).

C.2.2 Literature Screening

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

Title and Abstract Screen. In the Title and Abstract Screen step, 3,322 records were reviewed; 44 documents were considered to meet the health effects inclusion criteria in Table C-1 and were moved to the next step in the process.

Full Text Screen. In the second step in the literature screening process for the systematic review, a full text review of 87 health effect documents (documents identified in the update literature search and documents cited in older versions of the profile) was performed. From those 87 documents (128 studies), 50 documents (67 studies) were included in the qualitative review.

C.3 EXTRACT DATA FROM HEALTH EFFECTS STUDIES

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

Table C-2. Data Extracted From Individual Studies

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

A summary of the extracted data for each study is presented in the Supplemental Document for Acrolein and overviews of the results of the inhalation, oral and dermal exposure studies are presented in Sections 2.2–2.19 of the profile and in the Levels Significant Exposures tables in Section 2.1 of the profile (Tables 2-1, 2-2 and 2-3, respectively).

C.4 IDENTIFY POTENTIAL HEALTH EFFECT OUTCOMES OF CONCERN

Overviews of the potential health effect outcomes for acrolein identified in human and animal studies are presented in Tables C-3 and C-4, respectively. The available human studies are primarily limited to controlled exposure studies and a few epidemiology studies of the general population assessing ocular, nose and throat irritation and respiratory function following inhalation exposure to acrolein. Exposure was assumed to be chronic for cross-sectional epidemiological studies evaluating potential respiratory effects. Most animal studies evaluated inhalation exposure, although a few oral and dermal studies were available. The most sensitive effects in laboratory animals and humans following exposure to acrolein include respiratory effects (inhalation), immune effects (inhalation) and gastrointestinal effects (oral).

There were 67 studies (published in 50 documents) examining these potential outcomes carried through to Steps 4–8 of the systematic review.

APPENDIX C

Table C-3. Overview of the Health Outcomes for Acrolein Evaluated In Human Studies

	Body weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological	Neurological	Reproductive	Developmental	Other Noncancer	Caner
Inhalation studies																	
Cohort																	
Case control		5 4											1 0				
Population		4 3	4 4				1 1									1 1	
Case series		2 2							1 1	1 1			1 1				
Oral studies																	
Cohort																	
Case control																	
Population																	
Case series																	
Dermal studies																	
Cohort																	
Case control									1 1	5 5							
Population																	
Case series									2 2								

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

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

	Body weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological[a]	Neurological[a]	Reproductive[a]	Developmental	Other Noncancer	Caner
Inhalation studies																	
Acute-duration		37	9		5	2	8	1			3	9	2			3	
		33	8		3	0	4	1			1	5	1			3	
Intermediate-duration	18	19	15		13	1	15	15			3	10	10	5	1	1	
	9	18	0		2	0	3	0			0	1	0	0	0	0	
Chronic-duration	3	3	1		3		3	3	2		2	3	3	3			3
	3	3	0		1		0	0	0		0	0	0	0			2
Oral studies																	
Acute-duration	3	2		1	1		2	2				1	1	1	2		
	2	1		1	0		2	0				0	1	0	1		
Intermediate-duration	7	4	5	4	2	4	4	4	3	2	4	4	6	4	2	1	
	3	3	1	4	1	1	0	0	0	0	0	2	2	0	1	1	
Chronic-duration	3	3	3	3	3	3	3	3	3	3	3	3	3	3			4
	0	0	0	1	1	0	0	0	0	0	0	0	0	0			1
Dermal studies																	
Acute-duration										5							
										5							
Intermediate-duration										8							
										4							
Chronic-duration																	

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

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

C.5 ASSESS THE RISK OF BIAS FOR INDIVIDUAL STUDIES

C.5.1 Risk of Bias Assessment

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

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

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

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

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

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

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

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

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

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

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

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

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

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

The results of the risk of bias assessment for the different types of acrolein health effects studies (observational epidemiology, human-controlled exposure and animal experimental studies) are presented in Tables C-8, C-9, and C-10, respectively.

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

Reference	Risk of bias criteria and ratings						Risk of bias tier
	Selection bias	Confounding bias	Attrition / exclusion bias	Detection bias		Selective reporting bias	
	Were the comparison groups appropriate?	Did the study design or analysis account for important confounding and modifying variables?*	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?*	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	
Outcome: Respiratory effects							
Case-control							
Kuang et al. 2021	+	–	+	–	+	+	Second
Cross-sectional studies							
Annesi-Maesano et al. 2012	+	+	+	+	+	+	First
deCastro 2014	+	+	+	+	–	+	Second
Sakellaris et al. 2021	+	+	+	+	–	+	Second
Wang et al. 2022	+	+	+	–	+	+	Second

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias

*Key question used to assign risk of bias tier

Table C-9. Summary of Risk of Bias Assessment for Acrolein – Human-Controlled Exposure Studies

Reference	Risk of bias criteria and ratings							Risk of bias tier
	Selection bias		Performance bias	Attrition/ exclusion bias	Detection bias		Selective reporting bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were the research personnel and human subjects blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	
Outcome: Respiratory effects								
Inhalation acute exposure								
Dwivedi et al. 2015	–	+	+	++	++	+	+	First
Weber-Tschopp et al. 1977 (40 minutes)	–	+	–	–	–	+	+	Second
Weber-Tschopp et al. 1977 (1 hour)	–	+	–	–	–	+	+	Second
Weber-Tschopp et al. 1977 (1.5 minutes)	–	+	–	–	–	+	+	Second
Outcome: Immunological effects								
Inhalation acute exposure								
Dwivedi et al. 2015	–	+	+	++	++	+	+	First

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias

*Key question used to assign risk of bias tier.

Table C-10. Summary of Risk of Bias Assessment for Acrolein—Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias: Was administered dose or exposure level adequately randomized?	Selection bias: Was the allocation to study groups adequately concealed?	Performance bias: Were experimental conditions identical across study groups?	Performance bias: Were the research personnel blinded to the study group during the study?	Attrition/ exclusion bias: Were outcome data complete without attrition or exclusion from analysis?	Detection bias: Is there confidence in the exposure characterization?	Detection bias: Is there confidence in the outcome assessment?*	Selective reporting bias: Were all measured outcomes reported?	Risk of bias tier
Outcome: Respiratory effects									
Inhalation acute exposure									
Arumugam et al. 1999a	–	+	++	+	+	++	++	+	First
Babiuk et al. 1985	–	+	+	+	–	+	–	+	Second
Ballantyne et al. 1989 (4 hours)	–	+	–	+	–	–	– –	–	Third
Buckley et al. 1984	–	+	+	+	+	+	+	+	First
Cassee et al. 1996a (6 hours)	+	+	+	+	+	+	+	+	First
Cassee et al. 1996a (3 days)	+	+	+	+	+	–	+	++	First
Cassee et al. 1996b	–	+	+	+	+	+	+	++	First
Hazari et al. 2008	–	+	+	+	–	–	+	+	First
Kane and Alarie 1977	–	+	–	+	+	+	+	+	First
Kurhanewicz et al. 2018	–	+	+	+	–	–	+	++	First
Morris 1996	–	+	+	+	–	+	+	++	First
Morris et al. 2003 (0.3, 1.6, 3.9, RD_{50} study)	–	+	+	+	–	–	+	++	First
Morris et al. 2003 (0, 1.3 ppm)	–	+	+	+	–	–	+	++	First
Murphy et al. 1963	–	+	–	+	–	–	+	–	Second
Nielsen et al. 1984	–	+	–	+	++	+	+	–	First
Perez et al. 2013 (WKY rat)	+	+	+	+	+	–	+	+	First

Table C-10. Summary of Risk of Bias Assessment for Acrolein—Experimental Animal Studies

Reference	Risk of bias criteria and ratings								Risk of bias tier
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	
Perez et al. 2013 (SH rat)	+	+	+	+	+	–	+	–	First
Perez et al. 2015 (SH rat)	+	+	+	+	+	–	+	+	First
Steinhagen and Barrow 1984 (B6C3F1 mouse)	–	+	+	+	+	–	+	+	First
Steinhagen and Barrow 1984 (Swiss-Webster mouse)	–	+	+	+	+	–	+	+	First
Snow et al. 2017 (Wistar rat)	–	+	+	+	++	–	+	++	First
Snow et al. 2017 (GK rat)	–	+	+	+	++	–	+	++	First
Inhalation intermediate exposure									
Bouley et al. 1975 (15–180 days)	–	+	–	+	–	–	+	–	Second
Conklin et al. 2017b	–	+	–	+	–	–	+	+	Second
Costa et al. 1986; Kutzman et al. 1985; NTP 1981	+	+	+	+	–	–	+	++	First
Dorman et al. 2008	–	+	+	+	+	++	+	++	First
Feron et al. 1978 (rat)	–	+	+	+	–	–	+	+	First
Feron et al. 1978 (rabbit)	–	+	+	+	–	–	+	+	First
Feron et al. 1978 (hamster)	–	+	+	+	–	–	+	+	First
Kutzman et al. 1984 (hypertension-resistant)	+	+	+	+	–	–	+	+	First

Table C-10. Summary of Risk of Bias Assessment for Acrolein—Experimental Animal Studies

Reference	Risk of bias criteria and ratings								Risk of bias tier
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	
Kutzman et al. 1984 (hypertension-sensitive)	+	+	+	+	–	–	+	+	First
Leach et al. 1987	–	+	–	+	–	–	+	+	Second
Liu et al. 2019	–	+	+	+	–	–	++	+	First
Lyon et al. 1970 (monkey, repeated)	–	+	–	+	–	–	+	+	Second
Lyon et al. 1970 (monkey, continuous)	–	+	–	+	–	–	+	+	Second
Lyon et al. 1970 (dog, repeated	–	+	–	+	–	–	+	+	Second
Lyon et al. 1970 (dog, continuous)	–	+	–	+	–	–	+	+	Second
Lyon et al. 1970 (rat, repeated)	–	+	–	+	–	–	+	+	Second
Lyon et al. 1970 (rat, continuous)	–	+	–	+	–	–	+	+	Second
Lyon et al. 1970 (guinea pig, repeated)	–	+	–	+	–	–	+	+	Second
Lyon et al. 1970 (guinea pig, continuous)	–	+	–	+	–	–	+	+	Second
Inhalation chronic exposure									
Feron and Kruysse 1977	–	+	–	+	–	–	–	–	Third
Matsumoto et al. 2021 (rat)	++	+	+	+	+	+	+	+	First

Table C-10. Summary of Risk of Bias Assessment for Acrolein—Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias: Was administered dose or exposure level adequately randomized?	Selection bias: Was the allocation to study groups adequately concealed?	Performance bias: Were experimental conditions identical across study groups?	Performance bias: Were the research personnel blinded to the study group during the study?	Attrition/ exclusion bias: Were outcome data complete without attrition or exclusion from analysis?	Detection bias: Is there confidence in the exposure characterization?	Detection bias: Is there confidence in the outcome assessment?*	Selective reporting bias: Were all measured outcomes reported?	Risk of bias tier
Matsumoto et al. 2021 (mouse)	++	+	+	+	–	+	+	+	First
Oral acute exposure									
EPA 1983	++	+	++	–	–	+	+	+	First
Sakata et al. 1989	–	+	+	+	–	–	+	+	First
Oral intermediate exposure									
Auerbach et al. 2008; NTP 2006a (rat)	+	+	+	+	–	+	+	–	First
Auerbach et al. 2008; NTP 2006a (mouse)	+	+	+	+	–	+	+	–	First
Parent et al. 1992c (2-generation)	++	+	–	–	–	++	+	+	First
Oral chronic exposure									
Parent et al. 1992a (rat)	+	+	–	–	–	++	+	+	First
Parent et al. 1992b (dog)	+	+	–	+	–	++	+	+	Second
Outcome: Immune effects									
Inhalation acute exposure									
Aranyi et al. 1986 (1 day)	–	+	–	+	+	–	+	+	First
Aranyi et al. 1986 (5 days)	–	+	–	+	+	–	+	+	First
Astry and Jakab 1983	–	+	–	+	–	–	+	+	Second
Danyal et al. 2016	–	+	–	+	–	–	+	+	Second

Table C-10. Summary of Risk of Bias Assessment for Acrolein—Experimental Animal Studies

Reference	Risk of bias criteria and ratings								Risk of bias tier
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	
Kasahara et al. 2008	–	+	–	+	–	–	+	+	Second
Kim et al. 2019	–	+	–	+	–	–	+	+	Second
O'Brien et al. 2016	+	+	–	+	+	–	+	–	First
Skog 1950	–	+	–	+	–	–	+	+	Second
Inhalation intermediate exposure									
Bouley et al. 1975 (15–180 days)	–	+	–	+	–	–	+	–	Second
Conklin et al. 2017b	–	+	–	+	–	–	+	+	Second
Costa et al. 1986; Kutzman et al. 1985; NTP 1981	+	+	+	+	–	–	+	++	First
Feron et al. 1978 (rat)	–	+	+	+	–	–	+	+	First
Feron et al. 1978 (rabbit)	–	+	+	+	–	–	+	+	First
Feron et al. 1978 (hamster)	–	+	+	+	–	–	+	+	First
Kutzman et al. 1984 (hypertension-resistant)	+	+	+	+	–	–	+	+	First
Kutzman et al. 1984 (hypertension-sensitive)	+	+	+	+	–	–	+	+	First
Leach et al. 1987	–	+	–	+	–	–	+	+	Second
Sherwood et al. 1986	–	+	+	+	+	–	+	+	First

Table C-10. Summary of Risk of Bias Assessment for Acrolein—Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias: Was administered dose or exposure level adequately randomized?	Selection bias: Was the allocation to study groups adequately concealed?	Performance bias: Were experimental conditions identical across study groups?	Performance bias: Were the research personnel blinded to the study group during the study?	Attrition/ exclusion bias: Were outcome data complete without attrition or exclusion from analysis?	Detection bias: Is there confidence in the exposure characterization?	Detection bias: Is there confidence in the outcome assessment?*	Selective reporting bias: Were all measured outcomes reported?	Risk of bias tier
Inhalation chronic exposure									
Feron and Kruysse 1977	–	+	–	+	–	–	–	–	Third
Matsumoto et al. 2021 (rat)	++	+	+	+	+	+	+	+	First
Matsumoto et al. 2021 (mouse)	++	+	+	+	–	+	+	+	First
Oral acute exposure									
Sakata et al. 1989	++	+	+	+	–	–	+	+	First
Oral intermediate exposure									
Auerbach et al. 2008; NTP 2006a (rat)	+	+	+	+	–	+	+	+	First
Auerbach et al. 2008; NTP 2006a (mouse)	+	+	+	+	–	+	+	–	First
Parent et al. 1992c (2-generation)	++	+	–	+	–	++	+	+	First
Oral chronic exposure									
Parent et al. 1991a (mouse)	+	+	–	+	–	++	+	+	First
Parent et al. 1992a (rat)	+	+	–	+	–	++	+	+	First
Parent et al. 1992b (dog)	+	+	–	+	–	++	+	+	First
Outcome: Gastrointestinal effects									
Oral acute exposure									
Sakata et al. 1989	++	+	+	+	+	–	+	+	First

Table C-10. Summary of Risk of Bias Assessment for Acrolein—Experimental Animal Studies

Reference	Risk of bias criteria and ratings								Risk of bias tier
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	
Oral intermediate exposure									
Auerbach et al. 2008; NTP 2006a (rat)	+	+	+	+	–	+	+	++	First
Auerbach et al. 2008; NTP 2006a (mouse)	+	+	+	+	–	+	+	++	First
Parent et al. 1992c (2-generation)	++	+	+	+	+	++	+	+	First
Oral chronic exposure									
Parent et al. 1991a (mouse)	+	+	–	+	–	++	+	–	First
Parent et al. 1992a (rat)	+	+	–	+	–	++	+	+	First
Parent et al. 1992b (dog)	+	+	–	+	–	++	+	+	First

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias

*Key question used to assign risk of bias tier.

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

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

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

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

C.6.1 Initial Confidence Rating

In ATSDR's modification to the OHAT approach, the body of evidence for an association (or no association) between exposure to acrolein and a particular outcome was given an initial confidence rating based on the key features of the individual studies examining that outcome. The presence of these key features of study design was determined for individual studies using four "yes or no" questions, which were customized for epidemiology, human controlled exposure, or experimental animal study designs. Separate questionnaires were completed for each outcome assessed in a study. The key features for observational epidemiology (cohort, population, and case-control) studies, human controlled exposure, and experimental animal studies are presented in Tables C-11, C-12, and C-13, respectively. The initial confidence in the study was determined based on the number of key features present in the study design:

- **High Initial Confidence:** Studies in which the responses to the four questions were "yes".

- **Moderate Initial Confidence:** Studies in which the responses to only three of the questions were "yes".

- **Low Initial Confidence:** Studies in which the responses to only two of the questions were "yes".

- **Very Low Initial Confidence:** Studies in which the response to one or none of the questions was "yes".

Table C-11. Key Features of Study Design for Observational Epidemiology Studies

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

Table C-12. Key Features of Study Design for Human-Controlled Exposure Studies

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

Table C-13. Key Features of Study Design for Experimental Animal Studies

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

The presence or absence of the key features and the initial confidence levels for studies examining respiratory, immunological and gastrointestinal effects observed in the observational epidemiology, human controlled exposure studies and animal experimental studies are presented in Tables C-14, C-15, and C-16, respectively.

Table C-14. Presence of Key Features of Study Design for Acrolein—Observational Epidemiology Studies

Reference	Key features: Controlled exposure	Exposure prior to outcome	Outcomes assessed on an individual level	Comparison group	Initial study confidence
Outcome: Respiratory effects					
Case-control					
Kuang et al. 2021	No	Yes	Yes	Yes	Moderate
Cross-sectional studies					
Annesi-Maesano et al. 2012	No	Yes	Yes	Yes	Moderate
deCastro 2014	No	Yes	Yes	Yes	Moderate
Sakellaris et al. 2021	No	Yes	Yes	Yes	Moderate
Wang et al. 2022	No	Yes	Yes	No	Low

Table C-15. Presence of Key Features of Study Design for Acrolein—Human-Controlled Exposure

Reference	Key features: Comparison group or served as own controls	Sufficient number of subjects tested	Appropriate outcome assessment	Adequate data for statistical analysis	Initial study confidence
Outcome: Respiratory effects					
Inhalation acute					
Dwivedi et al. 2015	Yes	Yes	Yes	Yes	High
Weber-Tschopp et al. 1977 (40 minutes)	Yes	Yes	Yes	No	Moderate
Weber-Tschopp et al. 1977 (1 hour)	Yes	Yes	Yes	No	Moderate
Weber-Tschopp et al. 1977 (1.5 minutes)	Yes	Yes	Yes	No	Moderate
Outcome: Immunological effects					
Inhalation acute					
Dwivedi et al. 2015	Yes	Yes	No	Yes	Moderate

Table C-16. Presence of Key Features of Study Design for Acrolein—Experimental Animal Studies

Reference	Key features				Initial study confidence
	Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	
Outcome: Respiratory effects					
Inhalation acute exposure					
Arumugam et al. 1999a	Yes	Yes	Yes	Yes	High
Babiuk et al. 1985	Yes	No	No	Yes	Low
Ballantyne et al. 1989 (4 hours)	No	Yes	Yes	No	Low
Buckley et al. 1984	Yes	Yes	Yes	No	Moderate
Cassee et al. 1996a (6 hours)	Yes	Yes	Yes	No	Moderate
Cassee et al. 1996a (3 days)	Yes	Yes	Yes	No	Moderate
Cassee et al. 1996b	No	No	Yes	Yes	Low
Hazari et al. 2008	Yes	Yes	Yes	Yes	High
Kane and Alarie 1977	No	No	Yes	Yes	Low
Kurhanewicz et al. 2018	Yes	Yes	Yes	Yes	High
Morris 1996	Yes	Yes	No	Yes	Moderate
Morris et al. 2003 (0.3, 1.6, 3.9, RD_{50} study)	Yes	No	Yes	Yes	Moderate
Morris et al. 2003	Yes	Yes	Yes	Yes	High
Murphy et al. 1963	Yes	Yes	Yes	No	Moderate
Nielsen et al. 1984	Yes	Yes	Yes	Yes	High
Perez et al. 2013 (WKY rat)	Yes	Yes	Yes	No	Moderate
Perez et al. 2013 (SH rat)	Yes	Yes	Yes	No	Moderate
Perez et al. 2015 (SH rat)	Yes	Yes	Yes	Yes	High
Steinhagen and Barrow 1984 (B6C3F1 mouse)	No	No	Yes	Yes	Low
Steinhagen and Barrow 1984 (Swiss-Webster)	No	No	Yes	Yes	Low
Snow et al. 2017 (Wistar)	Yes	Yes	Yes	Yes	High
Snow et al. 2017 (GK)	Yes	Yes	Yes	Yes	High
Inhalation intermediate exposure					
Bouley et al. 1975 (15–180 days)	Yes	Yes	No	No	Low
Conklin et al. 2017b	Yes	Yes	Yes	Yes	High
Dorman et al. 2008	Yes	Yes	Yes	Yes	High
Feron et al. 1978 (rat)	Yes	Yes	Yes	No	Moderate
Feron et al. 1978 (rabbit)	Yes	No	Yes	No	Low

Table C-16. Presence of Key Features of Study Design for Acrolein—Experimental Animal Studies

Reference	Key features				Initial study confidence
	Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	
Feron et al. 1978 (hamster)	Yes	Yes	Yes	No	Moderate
Costa et al. 1986; Kutzman et al. 1985; NTP 1981	Yes	Yes	Yes	Yes	High
Kutzman et al. 1984 (hypertension-resistant)	Yes	Yes	Yes	No	Moderate
Kutzman et al. 1984 (hypertension-sensitive)	Yes	Yes	Yes	No	Moderate
Leach et al. 1987	Yes	Yes	Yes	No	Moderate
Liu et al. 2019	Yes	Yes	Yes	Yes	High
Lyon et al. 1970 (monkey, repeated)	Yes	Yes	Yes	Yes	High
Lyon et al. 1970 (monkey, continuous)	Yes	Yes	Yes	Yes	High
Lyon et al. 1970 (dog, repeated)	Yes	No	Yes	Yes	Moderate
Lyon et al. 1970 (dog, continuous)	Yes	No	Yes	Yes	Moderate
Lyon et al. 1970 (rat, repeated)	Yes	Yes	Yes	Yes	High
Lyon et al. 1970 (rat, continuous)	Yes	Yes	Yes	Yes	High
Lyon et al. 1970 (guinea pig, repeated)	Yes	Yes	Yes	Yes	High
Lyon et al. 1970 (guinea pig, continuous)	Yes	Yes	Yes	Yes	High
Inhalation chronic exposure					
Feron and Kruysse 1977	Yes	No	Yes	Yes	Moderate
Matsumoto et al. 2021 (rat)	Yes	Yes	Yes	Yes	High
Matsumoto et al. 2021 (mouse)	Yes	Yes	Yes	Yes	High
Oral acute exposure					
EPA 1983	Yes	Yes	No	No	Low
Sakata et al. 1989	No	Yes	Yes	No	Low
Oral intermediate exposure					
Auerbach et al. 2008; NTP 2006a (rat)	Yes	Yes	Yes	No	Moderate
Auerbach et al. 2008; NTP 2006a (mouse)	Yes	Yes	Yes	No	Moderate
Parent et al. 1992c (2-generation)	Yes	Yes	Yes	No	Moderate
Oral chronic exposure					
Parent et al. 1992a (rat)	Yes	Yes	Yes	No	Moderate
Parent et al. 1992b (dog)	Yes	Yes	Yes	No	Moderate

Table C-16. Presence of Key Features of Study Design for Acrolein—Experimental Animal Studies

Reference	Key features				Initial study confidence
	Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	
Outcome: Immune effects					
Inhalation acute exposure					
Aranyi et al. 1986 (1 day)	Yes	Yes	Yes	Yes	High
Aranyi et al. 1986 (5 days)	Yes	Yes	Yes	Yes	High
Astry and Jakab 1983	Yes	Yes	Yes	Yes	High
Danyal et al. 2016	Yes	Yes	Yes	Yes	High
Kasahara et al. 2008	Yes	No	Yes	Yes	Moderate
Kim et al. 2019	Yes	Yes	Yes	Yes	High
O'Brien et al. 2016	Yes	Yes	Yes	No	Moderate
Skog 1950	No	Yes	Yes	No	Low
Spiess et al. 2013	Yes	No	Yes	Yes	Moderate
Inhalation intermediate exposure					
Bouley et al. 1975 (15–180 days)	Yes	Yes	No	No	Low
Conklin et al. 2017b	Yes	Yes	Yes	Yes	High
Costa et al. 1986; Kutzman et al. 1985; NTP 1981	Yes	Yes	Yes	Yes	High
Feron et al. 1978 (rat)	Yes	Yes	Yes	No	Moderate
Feron et al. 1978 (rabbit)	Yes	No	Yes	No	Low
Feron et al. 1978 (hamster)	Yes	Yes	Yes	No	Moderate
Kutzman et al. 1984 (hypertension-resistant)	Yes	Yes	Yes	No	Moderate
Kutzman et al. 1984 (hypertension-sensitive)	Yes	Yes	Yes	No	Moderate
Leach et al. 1987	Yes	Yes	Yes	No	Moderate
Sherwood et al. 1986	Yes	Yes	Yes	Yes	High
Inhalation chronic exposure					
Feron and Kruysse 1977	Yes	No	Yes	Yes	Moderate
Matsumoto et al. 2021 (rat)	Yes	Yes	Yes	Yes	High
Matsumoto et al. 2021 (mouse)	Yes	Yes	Yes	Yes	High
Sakata et al. 1989	No	Yes	Yes	No	Low

Table C-16. Presence of Key Features of Study Design for Acrolein—Experimental Animal Studies

Reference	Key features				Initial study confidence
	Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	
Oral intermediate exposure					
Auerbach et al. 2008; NTP 2006a (rat)	Yes	Yes	Yes	No	Moderate
Auerbach et al. 2008; NTP 2006a (mouse)	Yes	Yes	Yes	No	Moderate
Parent et al. 1992c (2-generation)	Yes	Yes	Yes	No	Moderate
Oral chronic exposure					
Parent et al. 1991a (mouse)	Yes	Yes	Yes	Yes	High
Parent et al. 1992a (rat)	Yes	Yes	Yes	No	Moderate
Parent et al. 1992b (dog)	Yes	Yes	Yes	No	Moderate
Outcome: Gastrointestinal effects					
Oral acute exposure					
Sakata et al. 1989	No	Yes	Yes	No	Low
Oral Intermediate exposure					
Auerbach et al. 2008; NTP 2006a (rat)	Yes	Yes	Yes	Yes	High
Auerbach et al. 2008; NTP 2006a (mouse)	Yes	Yes	Yes	Yes	High
Parent et al. 1992c (2-generation)	Yes	Yes	Yes	Yes	High
Oral chronic exposure					
Parent et al. 1991a (mouse)	Yes	Yes	Yes	No	Moderate
Parent et al. 1992a (rat)	Yes	Yes	Yes	No	Moderate
Parent et al. 1992b (dog)	Yes	Yes	Yes	No	Moderate

A summary of the initial confidence ratings for each outcome is presented in Table C-17. If individual studies for a particular outcome and study type had different study quality ratings, then the highest confidence rating for the group of studies was used to determine the initial confidence rating for the body of evidence; any exceptions were noted in Table C-17.

Table C-17. Initial Confidence Rating for Acrolein Health Effects Studies

	Initial study confidence	Initial confidence rating
Outcome: Respiratory effects		
Inhalation acute exposure		
Human studies		
Dwivedi et al. 2015	High	High
Weber-Tschopp et al. 1977 (40 minutes)	Moderate	
Weber-Tschopp et al. 1977 (1 hour)	Moderate	
Weber-Tschopp et al. 1977 (1.5 minutes)	Moderate	
Animal studies		
Arumugam et al. 1999a	High	High
Babiuk et al. 1985	Low	
Ballantyne et al. 1989 4 hours	Low	
Buckley et al. 1984	Moderate	
Cassee et al. 1996a (6 hours)	Moderate	
Cassee et al. 1996a (3 days)	Moderate	
Cassee et al. 1996b	Low	
Hazari et al. 2008	High	
Kane and Alarie 1977	Low	
Kurhanewicz et al. 2018	High	
Morris 1996	Moderate	
Morris et al. 2003 (0.3, 1.6, 3.9, RD_{50} study)	Moderate	
Morris et al. 2003	High	
Murphy et al. 1963	Moderate	
Nielsen et al. 1984	High	
Perez et al. 2013 (WKY rat)	Moderate	
Perez et al. 2013 (SH rat)	Moderate	
Perez et al. 2015 (SH rat)	High	
Steinhagen and Barrow 1984 (B6C3F1 mouse)	Low	
Steinhagen and Barrow 1984 (Swiss-Webster mouse)	Low	
Snow et al. 2017 (Wistar rat)	High	
Snow et al. 2017 (GK rat)	High	
Inhalation intermediate exposure		
Animal studies		
Bouley et al. 1975 (15–180 days)	Low	High
Conklin et al. 2017b	High	
Costa et al. 1986; Kutzman et al. 1985; NTP 1981	High	
Dorman et al. 2008	High	
Feron et al. 1978 (rat)	Moderate	
Feron et al. 1978 (rabbit)	Low	
Feron et al. 1978 (hamster)	Moderate	

Table C-17. Initial Confidence Rating for Acrolein Health Effects Studies

	Initial study confidence	Initial confidence rating
Kutzman et al. 1984 (hypertension-resistant)	Moderate	
Kutzman et al. 1984 (hypertension-sensitive)	Moderate	
Leach et al. 1987	Moderate	
Liu et al. 2019	High	
Lyon et al. 1970 (monkey, repeated)	High	
Lyon et al. 1970 (monkey, continuous)	High	
Lyon et al. 1970 (dog, repeated)	Moderate	
Lyon et al. 1970 (dog, continuous)	Moderate	
Lyon et al. 1970 (rat, repeated)	High	
Lyon et al. 1970 (rat, continuous)	High	
Lyon et al. 1970 (guinea pig, repeated)	High	
Lyon et al. 1970 (guinea pig, continuous)	High	
Inhalation chronic exposure		
Human studies		
Annesi-Maesano et al. 2012	Moderate	
deCastro 2014	Moderate	
Kuang et al. 2021	Moderate	Moderate
Sakellaris et al. 2021	Moderate	
Wang et al. 2022	Low	
Animal studies		
Feron and Kruysse 1977	Moderate	
Matsumoto et al. 2021 (rat)	High	High
Matsumoto et al. 2021 (mouse)aw	High	
Oral acute studies		
Animal studies		
EPA 1983	Low	Low
Sakata et al. 1989	Low	
Oral intermediate studies		
Animal studies		
Auerbach et al. 2008; NTP 2006a (rat)	Moderate	
Auerbach et al. 2008; NTP 2006a (mouse)	Moderate	Moderate
Parent et al. 1992c (2-generation)	Moderate	
Oral chronic studies		
Animal studies		
Parent et al. 1992a (rat)	Moderate	Moderate
Parent et al. 1992b (dog)	Moderate	
Outcome: Immune effects		
Inhalation acute studies		
Human studies		
Dwivedi et al. 2015	Moderate	Moderate

Table C-17. Initial Confidence Rating for Acrolein Health Effects Studies

	Initial study confidence	Initial confidence rating
Animal studies		
Aranyi et al. 1986 (1 day)	High	High
Aranyi et al. 1986 (5 days)	High	
Astry and Jakab 1983	High	
Danyal et al. 2016	High	
Kasahara et al. 2008	Moderate	
Kim et al. 2019	High	
O'Brien et al. 2016	Moderate	
Skog 1950	Low	
Spiess et al. 2013	Moderate	
Inhalation intermediate studies		
Animal studies		
Bouley et al. 1975 (15–180 days)	Low	High
Conklin et al. 2017b	High	
Costa et al. 1986; Kutzman et al. 1985; NTP 1981	High	
Feron et al. 1978 (rat)	Moderate	
Feron et al. 1978 (rabbit)	Low	
Feron et al. 1978 (hamster)	Moderate	
Kutzman et al. 1984 (hypertension-resistant)	Moderate	
Kutzman et al. 1984 (hypertension-sensitive)	Moderate	
Leach et al. 1987	Moderate	
Sherwood et al. 1986	High	
Inhalation chronic studies		
Animal studies		
Feron and Kruysse 1977	Moderate	High
Matsumoto et al. 2021 (rat)	High	
Matsumoto et al. 2021 (mouse)	High	
Oral acute studies		
Animal studies		
Sakata et al. 1989	Low	Low
Oral intermediate studies		
Animal studies		
Auerbach et al. 2008; NTP 2006a (rat)	Moderate	Moderate
Auerbach et al. 2008; NTP 2006a (mouse)	Moderate	
Parent et al. 1992c (2-generation)	Moderate	
Oral chronic studies		
Animal studies		
Parent et al. 1991a (mouse)	High	High
Parent et al. 1992a (rat)	Moderate	
Parent et al. 1992b (dog)	Moderate	

Table C-17. Initial Confidence Rating for Acrolein Health Effects Studies

	Initial study confidence	Initial confidence rating
Outcome: Gastrointestinal effects		
Oral acute studies		
Animal studies		
Sakata et al. 1989	Low	Low
Oral intermediate studies		
Animal studies		
Auerbach et al. 2008; NTP 2006a (rat)	High	High
Auerbach et al. 2008; NTP 2006a (mouse)	High	
Parent et al. 1992c (2-generation)	High	
Oral chronic studies		
Animal studies		
Parent et al. 1991a (mouse)	Moderate	Moderate
Parent et al. 1992a (rat)	Moderate	
Parent et al. 1992b (dog)	Moderate	

C.6.2 Adjustment of the Confidence Rating

The initial confidence rating was then downgraded or upgraded depending on whether there were substantial issues that would decrease or increase confidence in the body of evidence. The nine properties of the body of evidence that were considered are listed below. The summaries of the assessment of the confidence in the body of evidence for respiratory, immunological, and gastrointestinal effects are presented in Table C-18. If the confidence ratings for a particular outcome were based on more than one type of human study, then the highest confidence rating was used for subsequent analyses. An overview of the confidence in the body of evidence for all health effects associated with acrolein exposure is presented in Table C-19.

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

- **Risk of bias.** Evaluation of whether there is substantial risk of bias across most of the studies examining the outcome. This evaluation used the risk of bias tier groupings for individual studies examining a particular outcome (Tables C-8, C-9, and C-10). Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for risk of bias:
  - No downgrade if most studies are in the risk of bias first tier
  - Downgrade one confidence level if most studies are in the risk of bias second tier
  - Downgrade two confidence levels if most studies are in the risk of bias third tier

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

- Downgrade one confidence level if there is variability across studies in the magnitude or direction of the effect
- Downgrade two confidence levels if there is substantial variability across studies in the magnitude or direct of the effect

- **Indirectness.** Evaluation of four factors that can affect the applicability, generalizability, and relevance of the studies:
  - Relevance of the animal model to human health—unless otherwise indicated, studies in rats, mice, and other mammalian species are considered relevant to humans
  - Directness of the endpoints to the primary health outcome—examples of secondary outcomes or nonspecific outcomes include organ weight in the absence of histopathology or clinical chemistry findings in the absence of target tissue effects
  - Nature of the exposure in human studies and route of administration in animal studies—inhalation, oral, and dermal exposure routes are considered relevant unless there are compelling data to the contrary
  - Duration of treatment in animal studies and length of time between exposure and outcome assessment in animal and prospective human studies—this should be considered on an outcome-specific basis

  Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for indirectness:
  - No downgrade if none of the factors are considered indirect
  - Downgrade one confidence level if one of the factors is considered indirect
  - Downgrade two confidence levels if two or more of the factors are considered indirect

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

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

Table C-18. Adjustments to the Initial Confidence in the Body of Evidence

	Initial confidence	Adjustments to the initial confidence rating	Final confidence
Outcome: Respiratory effects			
Human studies	High	-1 for risk of bias	Moderate
Animal studies	High	+ 1 for consistency	High
Outcome: Immune effects			
Human	Moderate	-1 for indirectness	Low
Animal studies	High	-1 for inconsistency	Moderate
Outcome: Gastrointestinal effects			
Animal studies	High	+ 1 for consistency	High

Table C-19. Confidence in the Body of Evidence for Acrolein

	Confidence in body of evidence	
Outcome	Human studies	Animal studies
Respiratory	Moderate	High
Immune	Low	Moderate
Gastrointestinal	No data	High

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

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

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

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

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

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

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

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

A summary of the level of evidence of health effects for acrolein is presented in Table C-20.

Table C-20. Level of Evidence of Health Effects for Acrolein

Outcome	Confidence in body of evidence	Direction of health effect	Level of evidence for health effect
Human studies			
Respiratory	Moderate	Health effect	Moderate
Immunological	Low	No health effect	Inadequate
Animal studies			
Respiratory	High	Health effect	High
Immunological	Moderate	Health effect	Moderate
Gastrointestinal	High	Health effect	Moderate

C.8 INTEGRATE EVIDENCE TO DEVELOP HAZARD IDENTIFICATION CONCLUSIONS

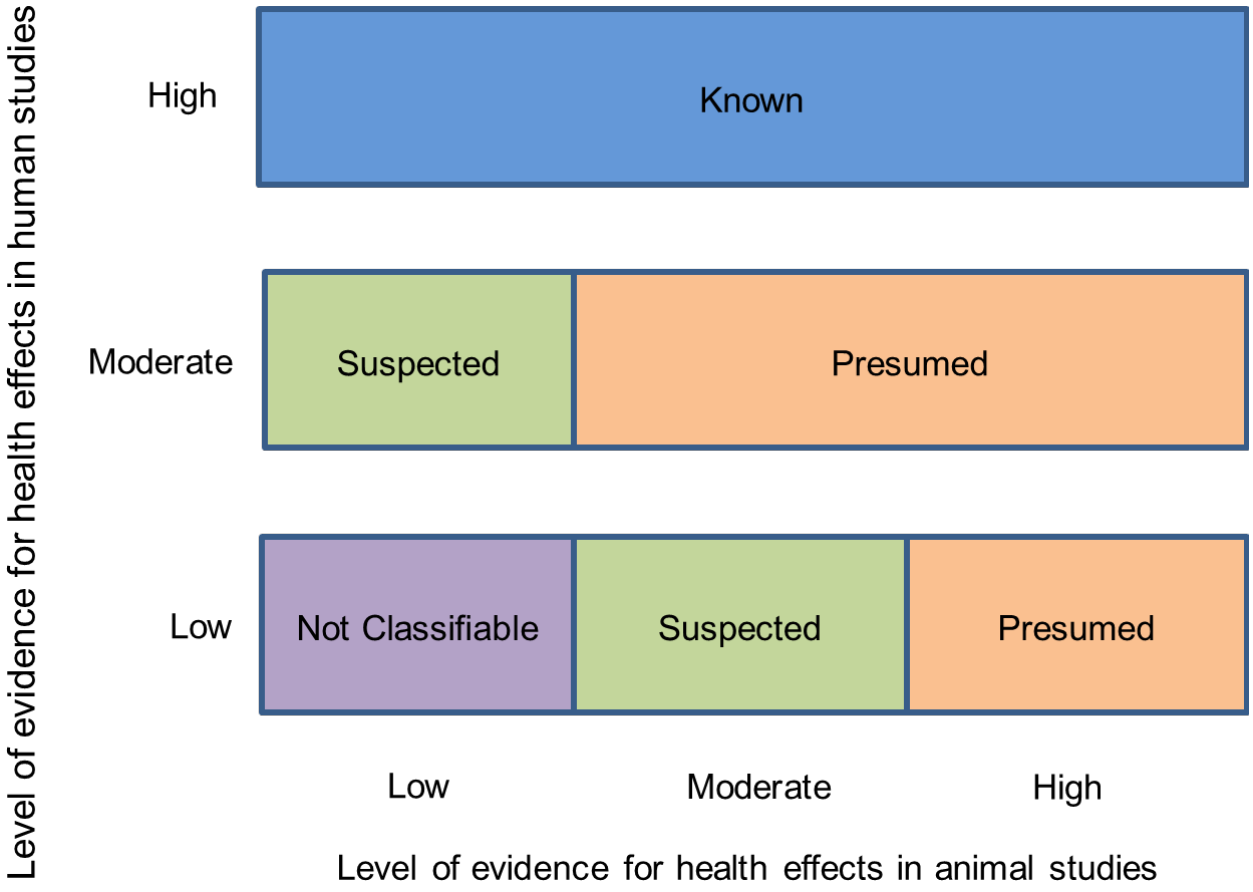
The final step involved the integration of the evidence streams for the human studies and animal studies to allow for a determination of hazard identification conclusions. For health effects, there were four hazard identification conclusion categories:

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

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

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

Figure C-1. Hazard Identification Scheme



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

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

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

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

The hazard identification conclusions for acrolein are listed below and summarized in Table C-21.

Presumed Health Effects

- Respiratory
  - Moderate level of evidence of respiratory effects in humans based on respiratory effects (nose and throat irritation, decreased respiratory rate, and/or dyspnea) reported in a human controlled exposure study (Weber-Tschopp et al. 1977) and case reports of occupational workers (CDC 2013; Champeix et al. 1966). Epidemiology studies have also reported associations between acrolein exposure and respiratory irritation symptoms (Sakellaris et al. 2021), prevalence of asthma (Annesi-Maesano et al. 2012; deCastro et al. 2014; Kuang et al. 2021), and decrements in pulmonary function (Wang et al. 2022).
  - High level of evidence of respiratory effects in animals based on nasal and pulmonary lesions, altered pulmonary function, and increased lung weights following acute-, intermediate-, and chronic-duration inhalation in rodents (see Tables 2-4, 2-5, and 2-6 in Section 2.4). The respiratory tract is a clear target of toxicity in animals.

Suspected Health Effects

- Immunological
  - Inadequate evidence of immunological effects in humans from a single controlled exposure to acrolein. No changes in inflammatory markers were seen in the serum or sputum of volunteers that inhaled acrolein (Dwivedi et al. 2015).
  - Moderate level of evidence of immunological effects in animals based on altered immune function in several studies including decreased bactericidal activity, decreased alveolar macrophages, or increased mortality from pulmonary bacterial infection (Aranyi et al. 1986; Astry and Jakab 1983; Bouley et al. 1975; Sherwood et al. 1986) and a suppression of the pulmonary immune responses to ovalbumin challenge in rodents (Kim et al. 2019; O'Brien et al. 2016; Spiess et al. 2013).
- Gastrointestinal
  - No studies were located regarding gastrointestinal effects in humans.
  - Moderate level of evidence of gastrointestinal effect in animals based on stomach lesions including ulcers, hemorrhage, hyperplasia of the forestomach, and/or erosion of the glandular mucosa were seen after intermediate-duration exposure (Auerbach et al. 2008; NTP 2006a; Parent et al. 1992c). No histological changes were seen in rodents after chronic-duration oral exposure, suggesting that possible adaptation to irritating effects may have occurred (Parent et al. 1991a, 1992a, 1992b).

Table C-21. Hazard Identification Conclusions for Acrolein

Outcome	Hazard identification
Respiratory	Presumed
Immune	Suspected
Gastrointestinal	Suspected

APPENDIX D. USER'S GUIDE

Chapter 1. Relevance to Public Health

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

1. What effects are known to occur in humans?

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

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

Minimal Risk Levels (MRLs)

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

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

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

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

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

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

Chapter 2. Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

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

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

TABLE LEGEND

See Sample LSE Table (page D-5)

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

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

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

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

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

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

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

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

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

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

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

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

FIGURE LEGEND

See Sample LSE Figure (page D-6)

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

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

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

(14) Levels of exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(15) LOAEL. In this example, the half-shaded circle that is designated 51R identifies a LOAEL critical endpoint in the rat upon which a chronic oral exposure MRL is based. The key number 51 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 6.1 mg/kg/day (see entry 51 in the sample LSE table) to the MRL of 0.008 mg/kg/day (see footnote "c" in the sample LSE table).

(16) CEL. Key number 59R is one of studies for which CELs were derived. The diamond symbol refers to a CEL for the test species (rat). The number 59 corresponds to the entry in the LSE table.

(17) Key to LSE figure. The key provides the abbreviations and symbols used in the figure.

Table 2-X. Levels of Significant Exposure to [Chemical X] – Oral (1)

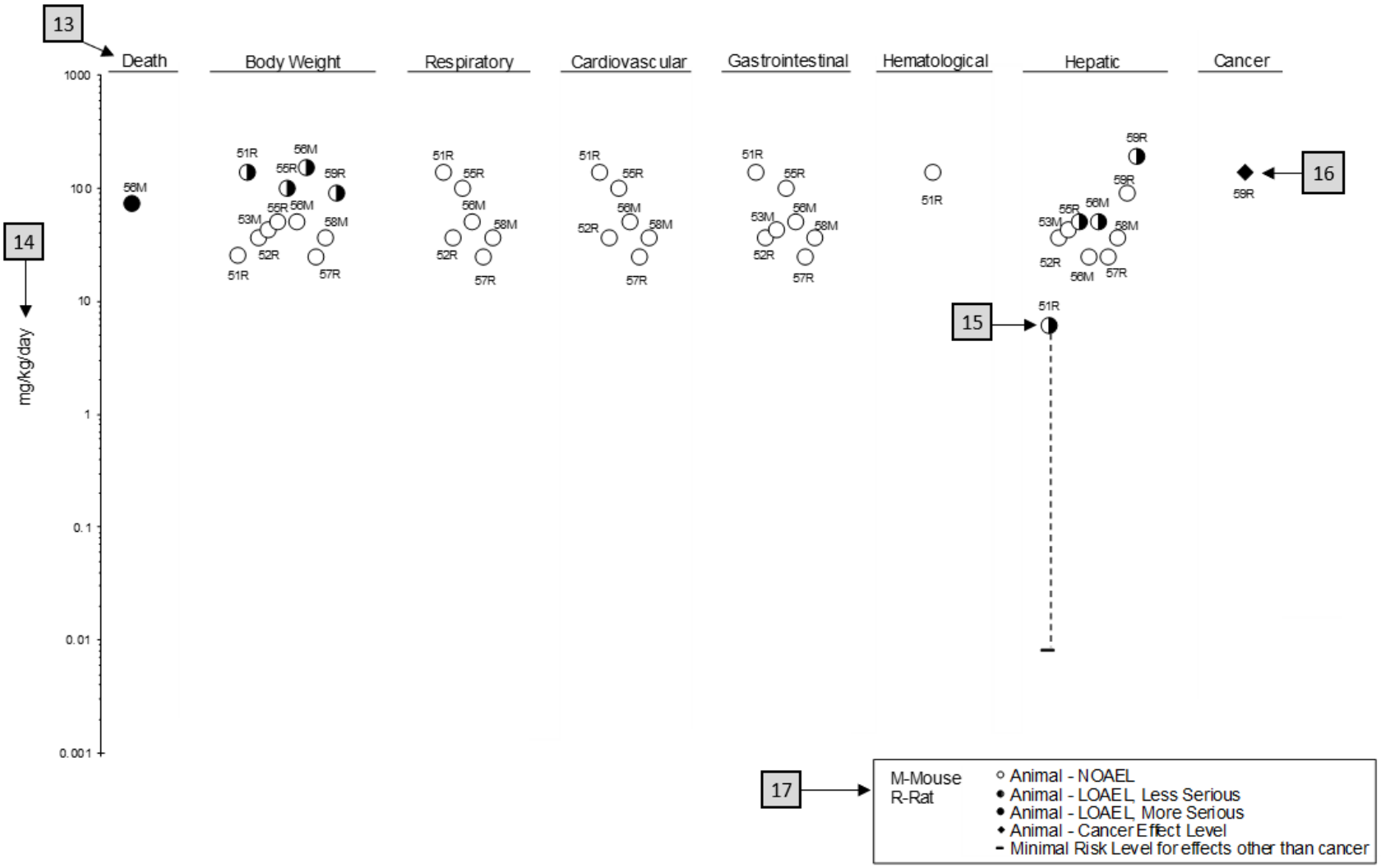
Figure key[a] (4)	Species (strain) No./group (4)	Exposure parameters (5)	Doses (mg/kg/day) (5)	Parameters monitored (6)	Endpoint (7)	NOAEL (mg/kg/day) (8)	Less serious LOAEL (mg/kg/day) (9)	Serious LOAEL (mg/kg/day) (9)	Effect
CHRONIC EXPOSURE (2)									
51 (3)	Rat (Wistar) 40 M, 40 F	2 years (F)	M: 0, 6.1, 25.5, 138.0 F: 0, 8.0, 31.7, 168.4	CS, WI, BW, OW, HE, BC, HP	Bd wt	25.5	138.0		Decreased body weight gain in males (23–25%) and females (31–39%)
					Hemato	138.0			
					Hepatic		6.1[c]		Increases in absolute and relative weights at ≥6.1/8.0 mg/kg/day after 12 months of exposure; fatty generation at ≥6.1 mg/kg/day in males and at ≥31.7 mg/kg/day in females, and granulomas in females at 31.7 and 168.4 mg/kg/day after 12, 18, or 24 months of exposure and in males at ≥6.1 mg/kg/day only after 24 months of exposure
Aida et al. 1992 (10)									
52	Rat (F344) 78 M	104 weeks (W)	0, 3.9, 20.6, 36.3	CS, BW, FI, BC, OW, HP	Hepatic	36.3			
					Renal	20.6	36.3		Increased incidence of renal tubular cell hyperplasia
					Endocr	36.3			
George et al. 2002									
59	Rat (Wistar) 58M, 58F	Lifetime (W)	M: 0, 90 F: 0, 190	BW, HP	Cancer		190 F		Increased incidence of hepatic neoplastic nodules in females only; no additional description of the tumors was provided
Tumasonis et al. 1985									

[a]The number corresponds to entries in Figure 2-x.

(11) [b]Used to derive an acute-duration oral minimal risk level (MRL) of 0.1 mg/kg/day based on the $BMDL_{05}$ of 10 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

[c]Used to derive a chronic-duration oral MRL of 0.008 mg/kg/day based on the $BMDL_{10}$ of 0.78 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Figure 2-X. Levels of Significant Exposure to [Chemical X] - Oral



APPENDIX E. QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances may find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Relevance to Public Health: The Relevance to Public Health Section provides an overview of exposure and health effects and evaluates, interprets, and assesses the significance of toxicity data to human health. A table listing minimal risk levels (MRLs) is also included in this chapter.

Chapter 2: Health Effects: Specific health effects identified in both human and animal studies are reported by type of health effect (e.g., death, hepatic, renal, immune, reproductive), route of exposure (e.g., inhalation, oral, dermal), and length of exposure (e.g., acute, intermediate, and chronic).
NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting.

Pediatrics:
Section 3.2 Children and Other Populations that are Unusually Susceptible
Section 3.3 Biomarkers of Exposure and Effect

ATSDR Information Center

Phone: 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY)
Internet: http://www.atsdr.cdc.gov

ATSDR develops educational and informational materials for health care providers categorized by hazardous substance, clinical condition, and/or by susceptible population. The following additional materials are available online:

Clinician Briefs and Overviews discuss health effects and approaches to patient management in a brief/factsheet style. They are narrated PowerPoint presentations with Continuing Education credit available (see https://www.atsdr.cdc.gov/emes/health_professionals/clinician-briefs-overviews.html).

Managing Hazardous Materials Incidents is a set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident (see https://www.atsdr.cdc.gov/MHMI/index.html).

Fact Sheets (ToxFAQs™) provide answers to frequently asked questions about toxic substances (see https://www.atsdr.cdc.gov/toxfaqs/Index.asp).

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. Contact: NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015 • Web Page: https://www.cdc.gov/nceh/.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 395 E Street, S.W., Suite 9200, Patriots Plaza Building, Washington, DC 20201 • Phone: 202-245-0625 or 1-800-CDC-INFO (800-232-4636) • Web Page: https://www.cdc.gov/niosh/.

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. Contact: NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212 • Web Page: https://www.niehs.nih.gov/.

Clinical Resources (Publicly Available Information)

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: http://www.aoec.org/.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266 • Web Page: http://www.acoem.org/.

The American College of Medical Toxicology (ACMT) is a nonprofit association of physicians with recognized expertise in medical toxicology. Contact: ACMT, 10645 North Tatum Boulevard, Suite 200-111, Phoenix AZ 85028 • Phone: 844-226-8333 • FAX: 844-226-8333 • Web Page: http://www.acmt.net.

The Pediatric Environmental Health Specialty Units (PEHSUs) is an interconnected system of specialists who respond to questions from public health professionals, clinicians, policy makers, and the public about the impact of environmental factors on the health of children and reproductive-aged adults. Contact information for regional centers can be found at http://pehsu.net/findhelp.html.

The American Association of Poison Control Centers (AAPCC) provide support on the prevention and treatment of poison exposures. Contact: AAPCC, 515 King Street, Suite 510, Alexandria VA 22314 • Phone: 701-894-1858 • Poison Help Line: 1-800-222-1222 • Web Page: http://www.aapcc.org/.

APPENDIX F. GLOSSARY

Absorption—The process by which a substance crosses biological membranes and enters systemic circulation. Absorption can also refer to the taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure—Exposure to a chemical for a duration of ≤14 days, as specified in the Toxicological Profiles.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)—The amount of a chemical adsorbed by sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Benchmark Dose (BMD) or Benchmark Concentration (BMC)—is the dose/concentration corresponding to a specific response level estimate using a statistical dose-response model applied to either experimental toxicology or epidemiology data. For example, a BMD_{10} would be the dose corresponding to a 10% benchmark response (BMR). The BMD is determined by modeling the dose-response curve in the region of the dose-response relationship where biologically observable data are feasible. The BMDL or BMCL is the 95% lower confidence limit on the BMD or BMC.

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers—Indicators signaling events in biologic systems or samples, typically classified as markers of exposure, effect, and susceptibility.

Cancer Effect Level (CEL)—The lowest dose of a chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or malignant tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-control study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without the outcome.

Case Report—A report that describes a single individual with a particular disease or exposure. These reports may suggest some potential topics for scientific research, but are not actual research studies.

Case Series—Reports that describe the experience of a small number of individuals with the same disease or exposure. These reports may suggest potential topics for scientific research, but are not actual research studies.

Ceiling Value—A concentration that must not be exceeded.

Chronic Exposure—Exposure to a chemical for ≥365 days, as specified in the Toxicological Profiles.

Clastogen—A substance that causes breaks in chromosomes resulting in addition, deletion, or rearrangement of parts of the chromosome.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome, and who are disease-free at start of follow-up. Often, at least one exposed group is compared to one unexposed group, while in other cohorts, exposure is a continuous variable and analyses are directed towards analyzing an exposure-response coefficient.

Cross-sectional Study—A type of epidemiological study of a group or groups of people that examines the relationship between exposure and outcome to a chemical or to chemicals at a specific point in time.

Data Needs—Substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment.

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the response or amount of the response.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the effect occurs. Effects include malformations and variations, altered growth, and *in utero* death.

Epidemiology—The investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Excretion—The process by which metabolic waste products are removed from the body.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic, or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one-half of a quantity of a chemical from the body or environmental media.

Health Advisory—An estimate of acceptable drinking water levels for a chemical substance derived by EPA and based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Immediately Dangerous to Life or Health (IDLH)—A condition that poses a threat of life or health, or conditions that pose an immediate threat of severe exposure to contaminants that are likely to have adverse cumulative or delayed effects on health.

Immunotoxicity—Adverse effect on the functioning of the immune system that may result from exposure to chemical substances.

Incidence—The ratio of new cases of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure—Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

***In Vitro*—**Isolated from the living organism and artificially maintained, as in a test tube.

***In Vivo*—**Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO})—The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50})—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{Lo})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50})—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50})—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

Metabolism—Process in which chemical substances are bio transformed in the body that could result in less toxic and/or readily excreted compounds or produce a biologically active intermediate.

Minimal LOAEL—Indicates a minimal adverse effect or a reduced capacity of an organ or system to absorb additional toxic stress that does not necessarily lead to the inability of the organ or system to function normally.

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a Minimal Risk Level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity—The state of being diseased; the morbidity rate is the incidence or prevalence of a disease in a specific population.

Mortality—Death; the mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations, which are changes in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a hazardous substance.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Although effects may be produced at this dose, they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An odds ratio that is greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) regulatory limit on the amount or concentration of a substance not to be exceeded in workplace air averaged over any 8-hour work shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests (insects or other organisms harmful to cultivated plants or animals).

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments, which, in general, do not represent real, identifiable anatomic regions of the body, whereas the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic endpoints. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—A type of physiologically based dose-response model that is comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information, including tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as blood:air partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which a group is followed over time and the pertinent observations are made on events occurring after the start of the study.

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation RfC is expressed in units of mg/m^3 or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily oral exposure of the human population to a potential hazard that is likely to be without risk of deleterious noncancer health effects during a lifetime. The oral RfD is expressed in units of mg/kg/day.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). RQs are (1) ≥1 pound or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a hazardous substance. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a hazardous substance.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, existing health condition, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio/Relative Risk—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio that is greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed group.

Serious LOAEL—A dose that evokes failure in a biological system and can lead to morbidity or mortality.

Short-Term Exposure Limit (STEL)—A STEL is a 15-minute TWA exposure that should not be exceeded at any time during a workday.

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which it is believed that nearly all workers may be repeatedly exposed, day after day, for a working lifetime without adverse effect. The TLV may be expressed as a Time-Weighted Average (TLV-TWA), as a Short-Term Exposure Limit (TLV-STEL), or as a ceiling limit (TLV-C).

Time-Weighted Average (TWA)—An average exposure within a given time period.

Toxicokinetic—The absorption, distribution, metabolism, and elimination of toxic compounds in the living organism.

Toxics Release Inventory (TRI)—The TRI is an EPA program that tracks toxic chemical releases and pollution prevention activities reported by industrial and federal facilities.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL), Reference Dose (RfD), or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis (3 being the approximate logarithmic average of 10 and 1).

Xenobiotic—Any substance that is foreign to the biological system.

APPENDIX G. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

AAPCC	American Association of Poison Control Centers
ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ACMT	American College of Medical Toxicology
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AEGL	Acute Exposure Guideline Level
AIC	Akaike's information criterion
AIHA	American Industrial Hygiene Association
ALT	alanine aminotransferase
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BCF	bioconcentration factor
BMD/C	benchmark dose or benchmark concentration
BMD_X	dose that produces a X% change in response rate of an adverse effect
$BMDL_X$	95% lower confidence limit on the BMD_X
BMDS	Benchmark Dose Software
BMR	benchmark response
BUN	blood urea nitrogen
C	centigrade
CAA	Clean Air Act
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
cm	centimeter
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DWEL	drinking water exposure level
EAFUS	Everything Added to Food in the United States
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
ERPG	emergency response planning guidelines
F	Fahrenheit
F1	first-filial generation
FDA	Food and Drug Administration
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FR	Federal Register

FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GGT	γ-glutamyl transferase
GRAS	generally recognized as safe
HEC	human equivalent concentration
HED	human equivalent dose
HHS	Department of Health and Human Services
HPLC	high-performance liquid chromatography
HSDB	Hazardous Substances Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
IFN-γ	interferon-γ
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	kilokilogram; 1 kilokilogram is equivalent to 1,000 kilograms and 1 metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactate dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Level of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
MRL	Minimal Risk Level
MS	mass spectrometry
MSHA	Mine Safety and Health Administration
Mt	metric ton
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NCEH	National Center for Environmental Health
ND	not detected
ng	nanogram
NHANES	National Health and Nutrition Examination Survey

NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NTP	National Toxicology Program
OR	odds ratio
OSHA	Occupational Safety and Health Administration
PAC	Protective Action Criteria
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PEHSU	Pediatric Environmental Health Specialty Unit
PEL	permissible exposure limit
PEL-C	permissible exposure limit-ceiling value
pg	picogram
PND	postnatal day
POD	point of departure
ppb	parts per billion
ppbv	parts per billion by volume
ppm	parts per million
ppt	parts per trillion
RD50	exposure concentration producing a 50% respiratory rate decrease
REL	recommended exposure limit
REL-C	recommended exposure limit-ceiling value
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SD	standard deviation
SE	standard error
SGOT	serum glutamic oxaloacetic transaminase (same as aspartate aminotransferase or AST)
SGPT	serum glutamic pyruvic transaminase (same as alanine aminotransferase or ALT)
SIC	standard industrial classification
SLOAEL	serious lowest-observed-adverse-effect level
SMR	standardized mortality ratio
sRBC	sheep red blood cell
STEL	short term exposure limit
TLV	threshold limit value
TLV-C	threshold limit value-ceiling value
TNFα	tumor necrosis factor-alpha
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor

U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
USNRC	U.S. Nuclear Regulatory Commission
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result