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.

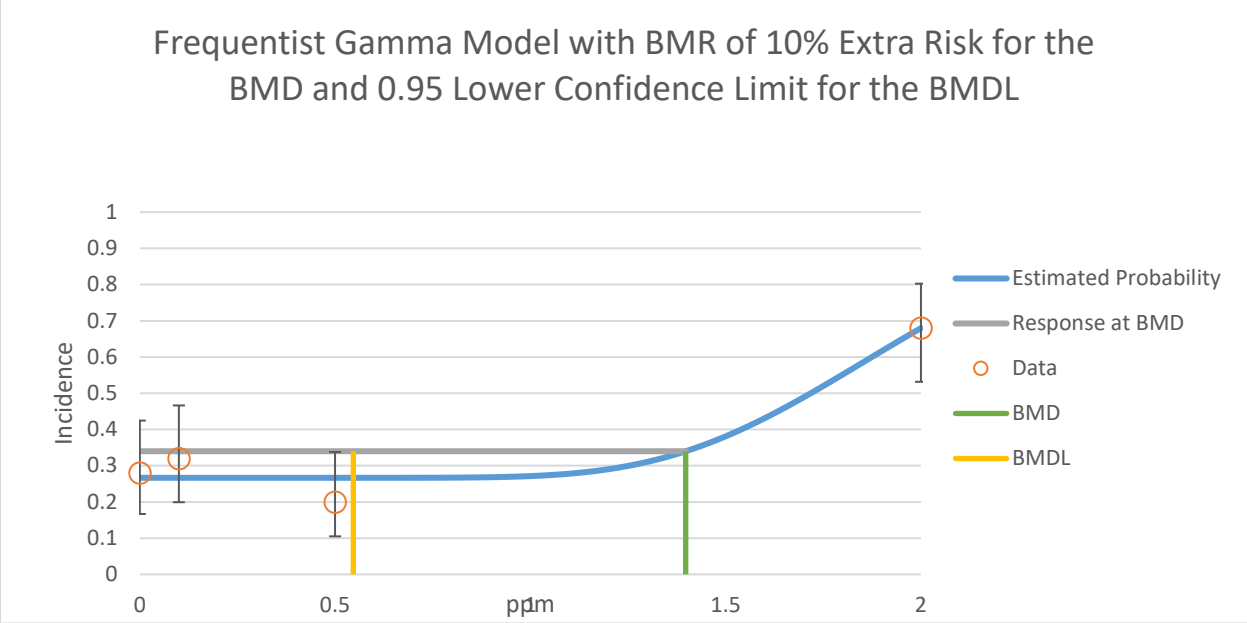
Table A-4. Model Predictions for Respiratory Epithelium Inflammation in Male F344/DuCrlCrlj Rats Exposed to Acrolein via Inhalation for 6 Hours/Day, 5 Days/Week for 104 Weeks (Matsumoto et al. 2021)

					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

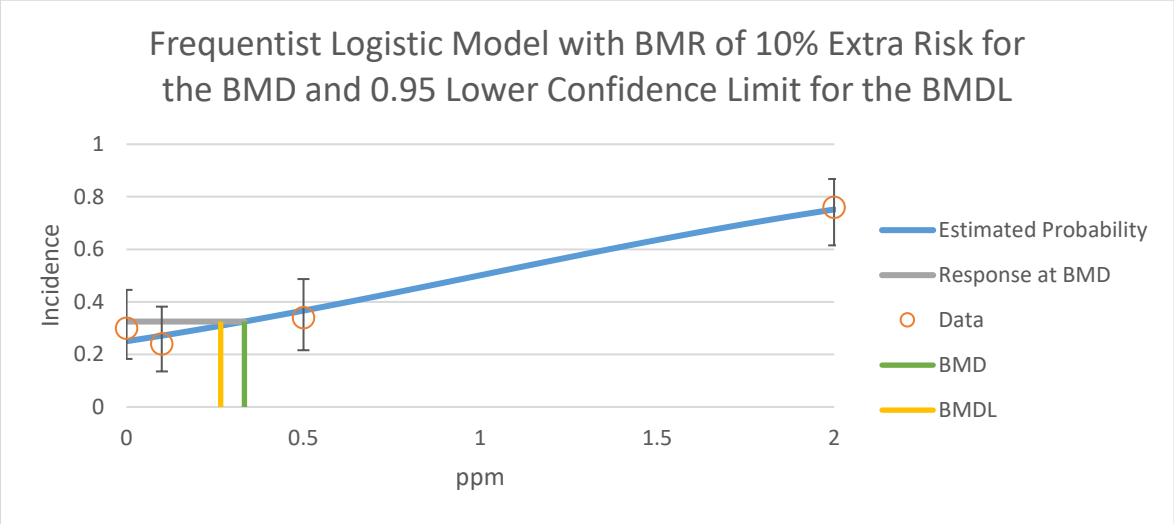
Table A-5. Model Predictions for Respiratory Gland Metaplasia in Male F344/DuCrlCrlj Rats Exposed to Acrolein via Inhalation for 6 Hours/Day, 5 Days/Week for 104 Weeks (Matsumoto et al. 2021)

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.

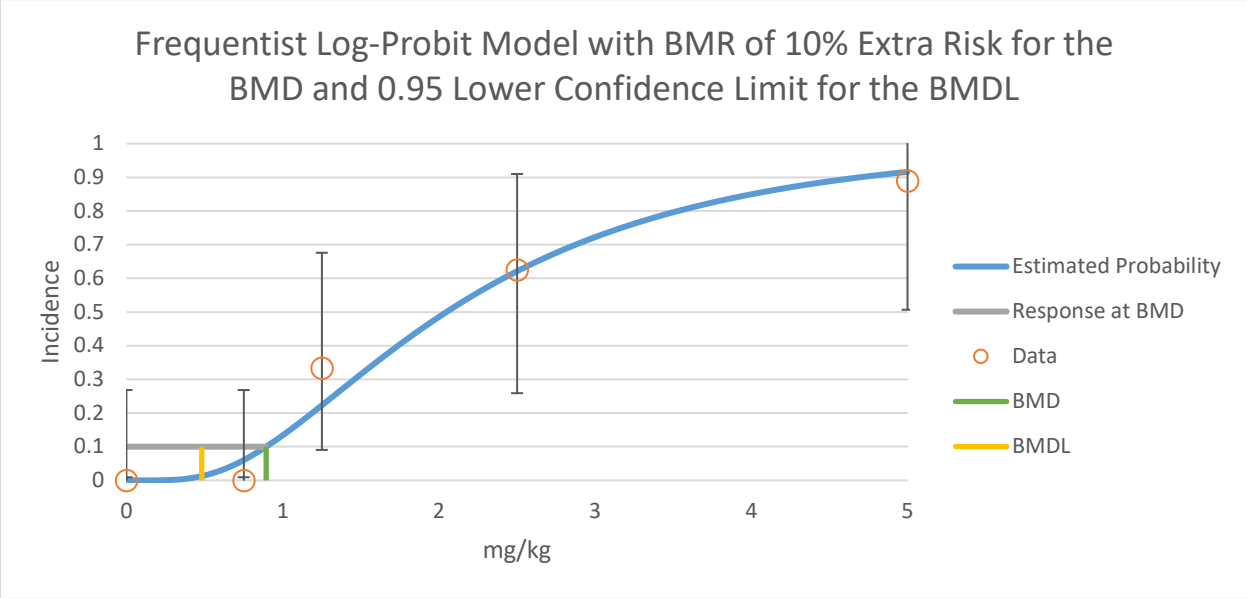
Table A-11. Model Predictions for Increased Incidence of Squamous Epithelial Hyperplasia in the Forestomach in Female F344/N Rats Exposed to Acrolein by Gavage for 14 Weeks (Auerbach et al. 2008; NTP 2006a)

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)

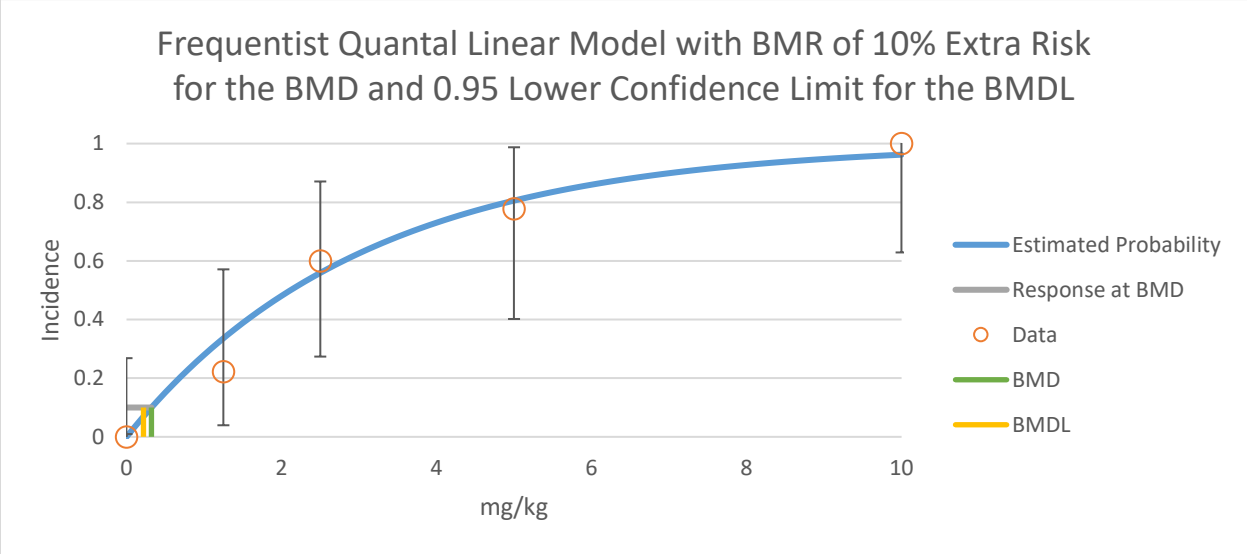


Table A-13 shows a summary of the candidate PODs obtained from BMD modeling of the data on forestomach squamous epithelial hyperplasia. The lowest POD was the BMDL of 0.22 mg/kg/day based on data in male B6C3F1 mice; this POD was selected for use in deriving the MRL.

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.

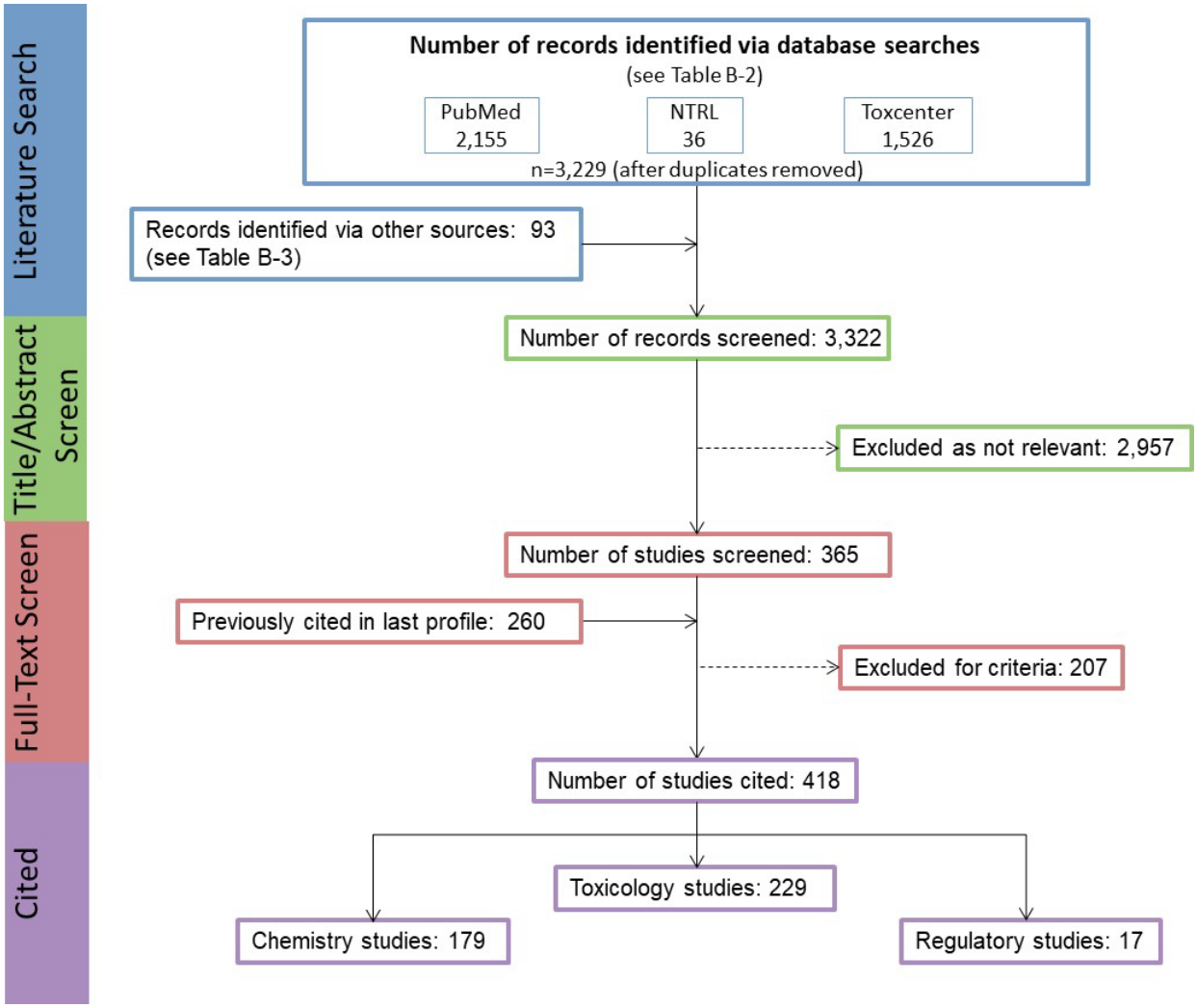
- Number of titles and abstracts screened: 3,322
- Number of studies considered relevant and moved to the next step: 365

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

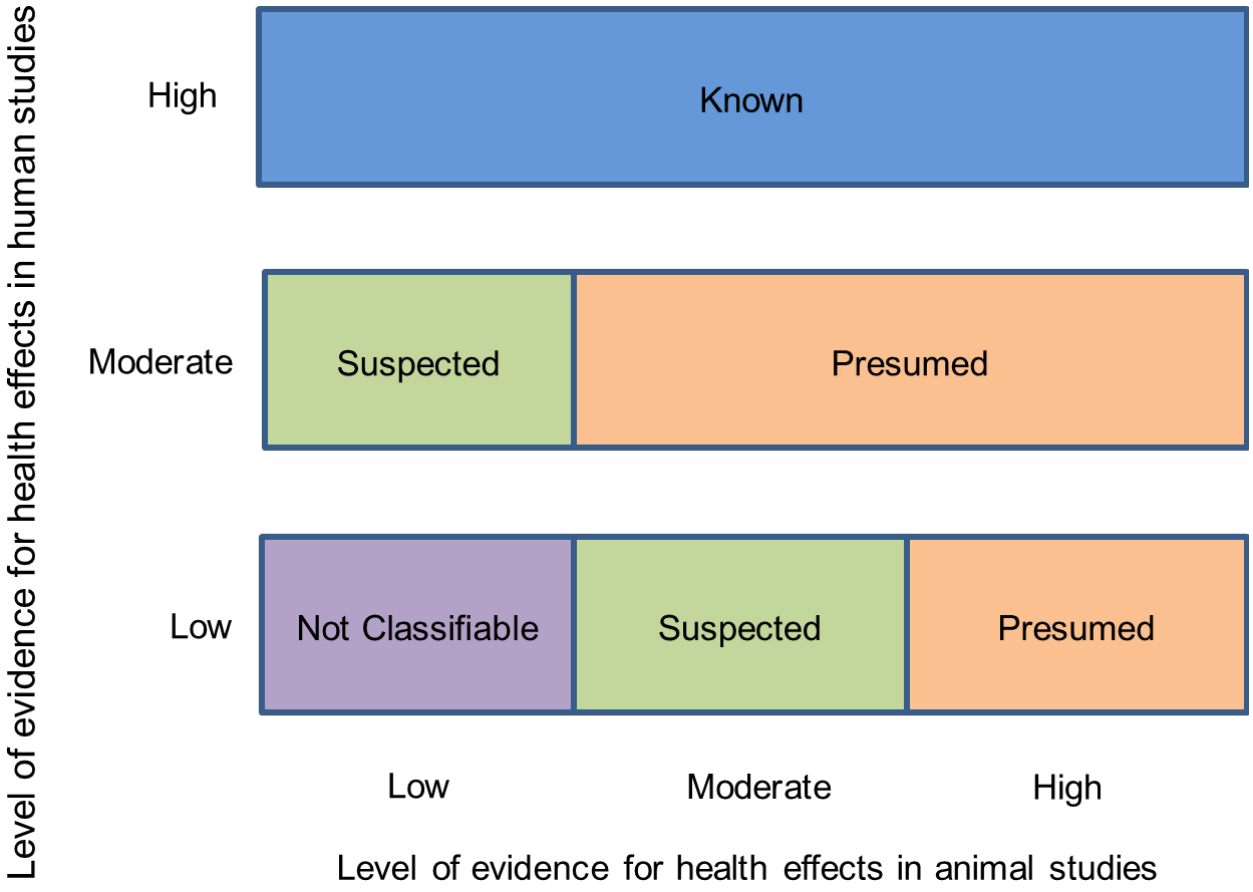
The final step involved the integration of the evidence streams for the human studies and animal studies to allow for a determination of hazard identification conclusions. For health effects, there were four hazard identification conclusion categories:

- **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)

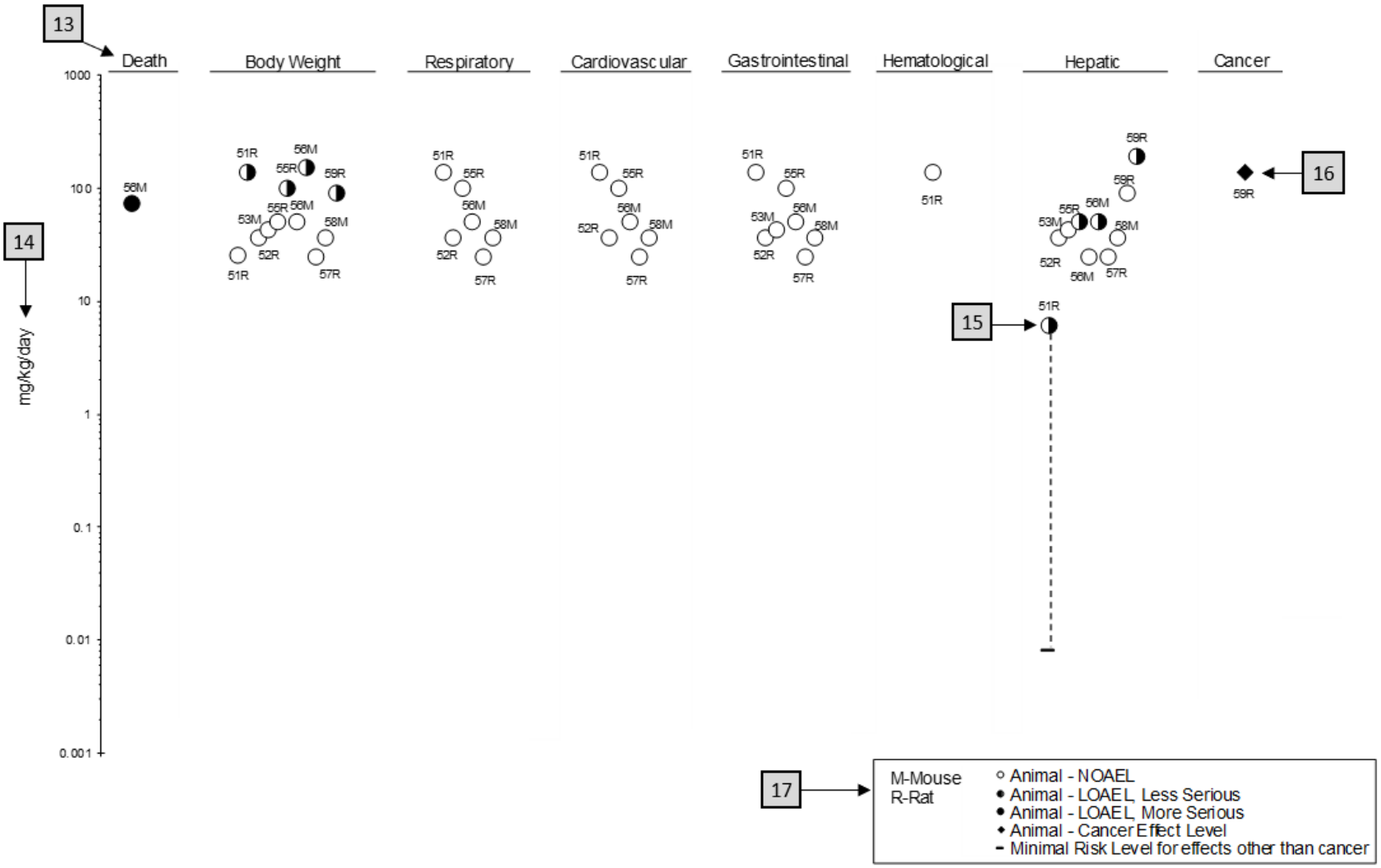
Figure key[a] (4)	Species (strain) No./group (4)	Exposure parameters (5)	Doses (mg/kg/day) (5)	Parameters monitored (6)	Endpoint (7)	NOAEL (mg/kg/day) (8)	Less serious LOAEL (mg/kg/day) (9)	Serious LOAEL (mg/kg/day) (9)	Effect
CHRONIC EXPOSURE (2)									
51 (3)	Rat (Wistar) 40 M, 40 F	2 years (F)	M: 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