APPENDIX A. ATSDR MINIMAL RISK LEVEL WORKSHEETS

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

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

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

APPENDIX A

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

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

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

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

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

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

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

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

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

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

Agency Contacts (Chemical Managers): Mohammad Shoeb

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

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

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

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

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

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

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

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

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

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

Summary of the Principal Study:

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

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

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

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

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

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

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

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

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

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

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

Source: Nemec et al. (2008)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

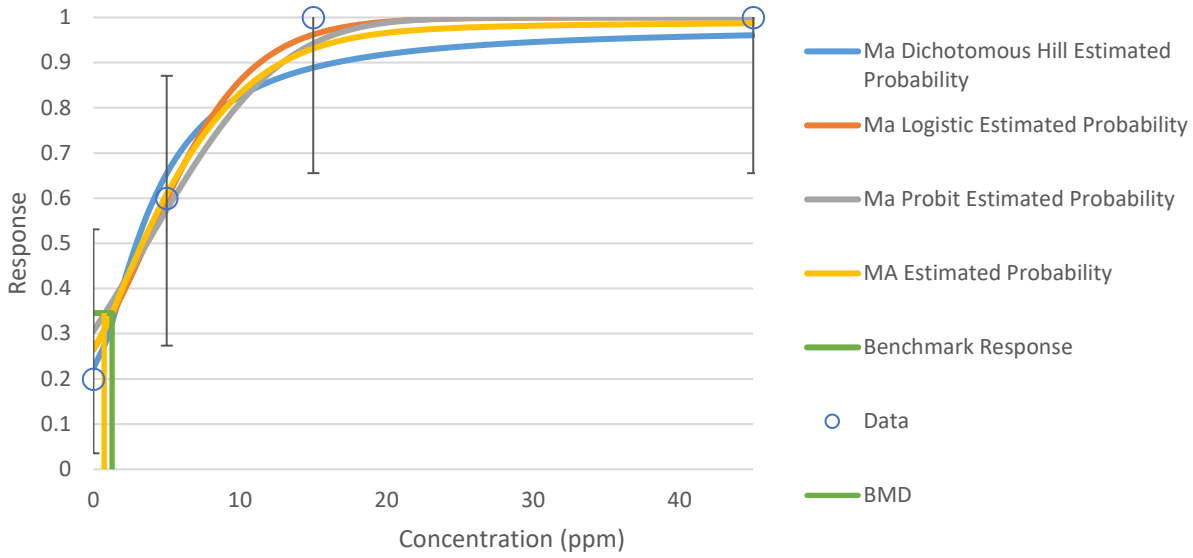
Table A-7. Potential Points of Departure for Intermediate-Duration Inhalation MRL for Acrylonitrile

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

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

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

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



Calculations

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

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

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

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

Where:

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

Minute volume (V_E)

Human: 13.8 L/minute (EPA 1994a)

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

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

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

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

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

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

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

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

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

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

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

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

Agency Contacts (Chemical Managers): Mohammad Shoeb

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

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

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

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

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

Agency Contacts (Chemical Managers): Mohammad Shoeb

MINIMAL RISK LEVEL (MRL) WORKSHEET

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

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

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

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

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

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

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

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

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

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

Summary of the Principal Study:

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

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

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

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

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

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

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

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

Source: Murray et al. 1978

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

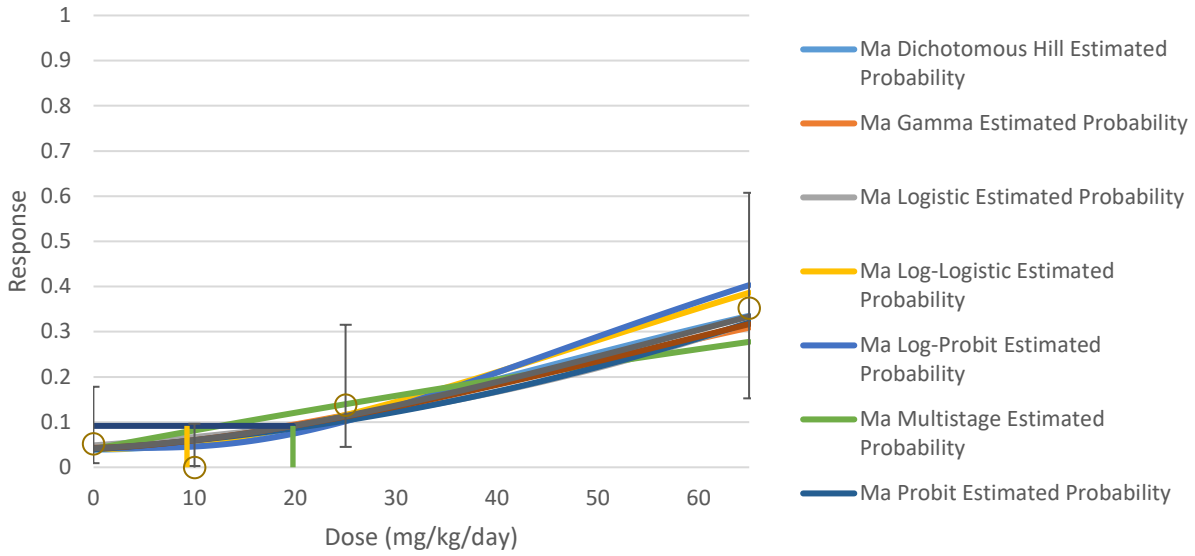
Table A-15. Potential Points of Departure for the Acute-duration Oral MRL for Acrylonitrile

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

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

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

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



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

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

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

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

Agency Contacts (Chemical Managers): Mohammad Shoeb

MINIMAL RISK LEVEL (MRL) WORKSHEET

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

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

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

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

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

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

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

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

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

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

Summary of the Principal Study:

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

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

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

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

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

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

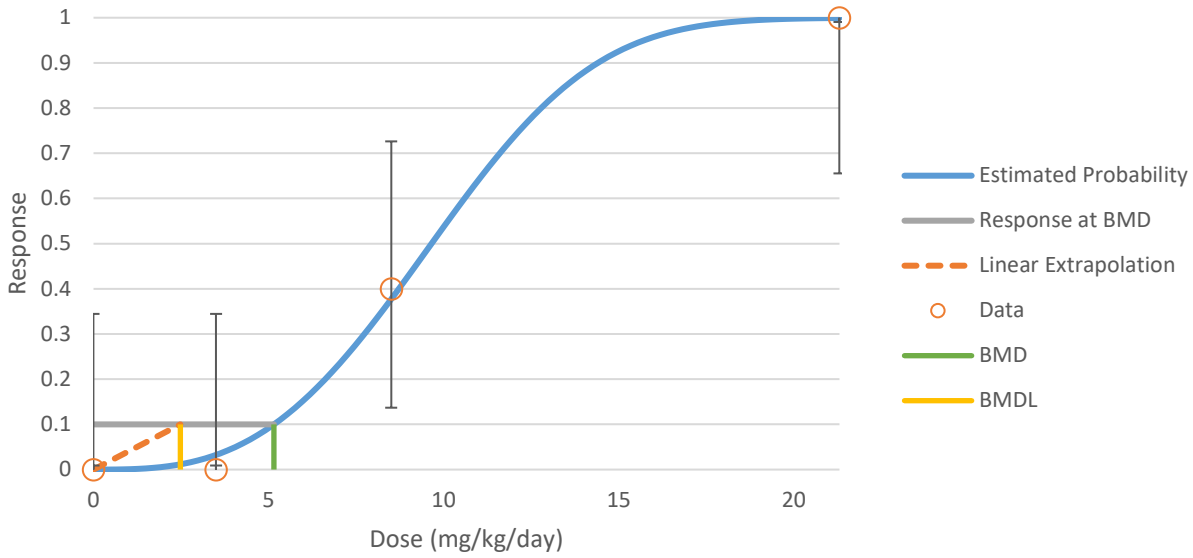
Table A-17. Results from BMD Analysis of Incidence of Squamous Cell Hyperplasia in Male Rats Exposed to Acrylonitrile in Drinking Water for 1 Year (Quast 2002)

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

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

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

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



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

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

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

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

Agency Contacts (Chemical Managers): Mohammad Shoeb

MINIMAL RISK LEVEL (MRL) WORKSHEET

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

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

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

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

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

[a]Decreased survival reported at this dose.

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

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

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

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

[a]Decreased survival reported at this dose.

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

Summary of the Principal Study:

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

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

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

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

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

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

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

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

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

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

Agency Contacts (Chemical Managers): Mohammad Shoeb

APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR ACRYLONITRILE

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

B.1 LITERATURE SEARCH AND SCREEN

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

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

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

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

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

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

B.1.1 Literature Search

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

APPENDIX B

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

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

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

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

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

Table B-2. Database Query Strings

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

Table B-2. Database Query Strings

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

Table B-2. Database Query Strings

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

Table B-2. Database Query Strings

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

Table B-2. Database Query Strings

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

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

Table B-2. Database Query Strings

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

Table B-2. Database Query Strings

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

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

Table B-2. Database Query Strings

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

Table B-3. Strategies to Augment the Literature Search

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

Table B-3. Strategies to Augment the Literature Search

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

The 2021 pre-public comment search results were:

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

The 2023 post-public comment search results were:

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

B.1.2 Literature Screening

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

- Title and abstract screen
- Full text screen

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

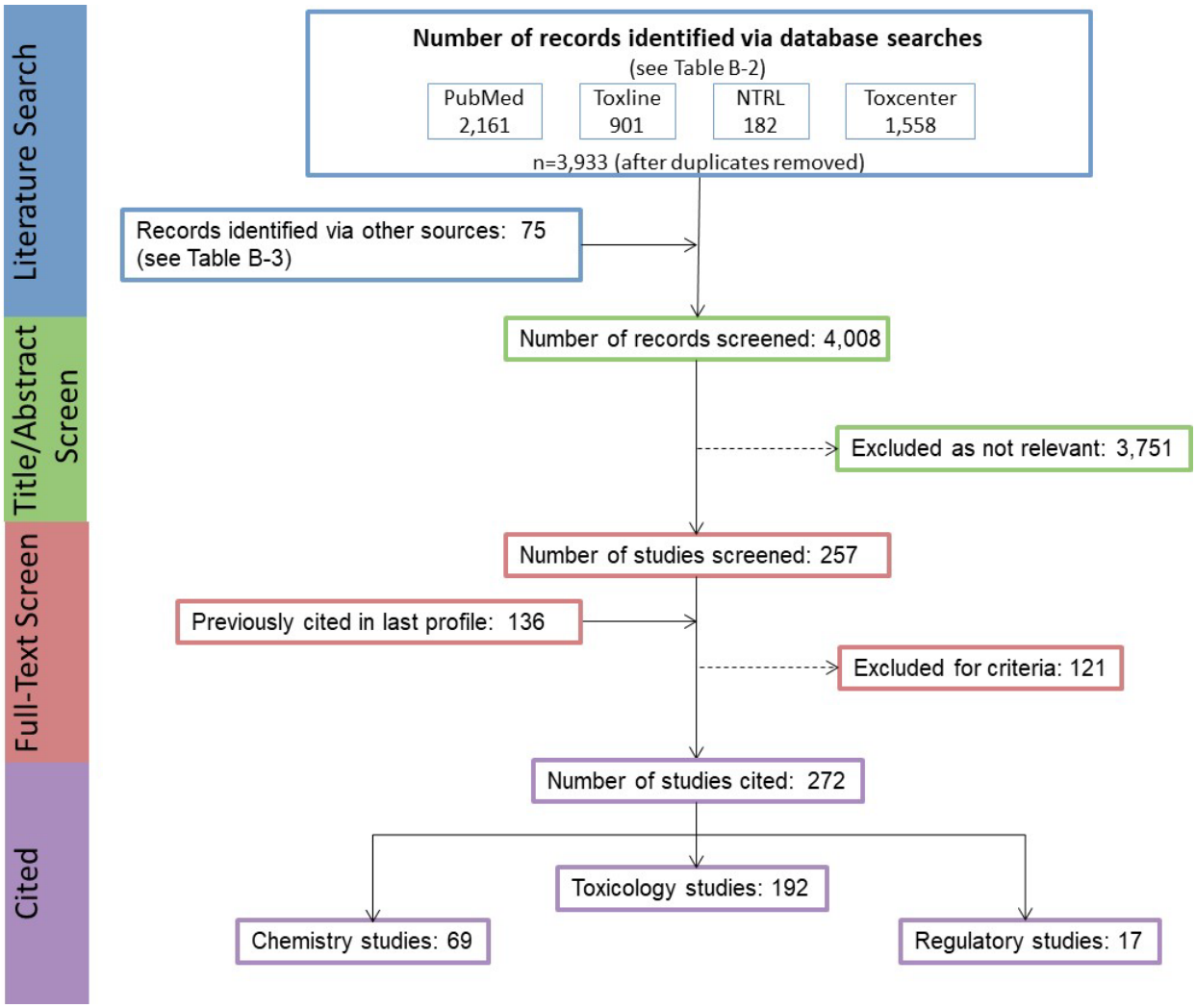
- Number of titles and abstracts screened: 4,008
- Number of studies considered relevant and moved to the next step: 257

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

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

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

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



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

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

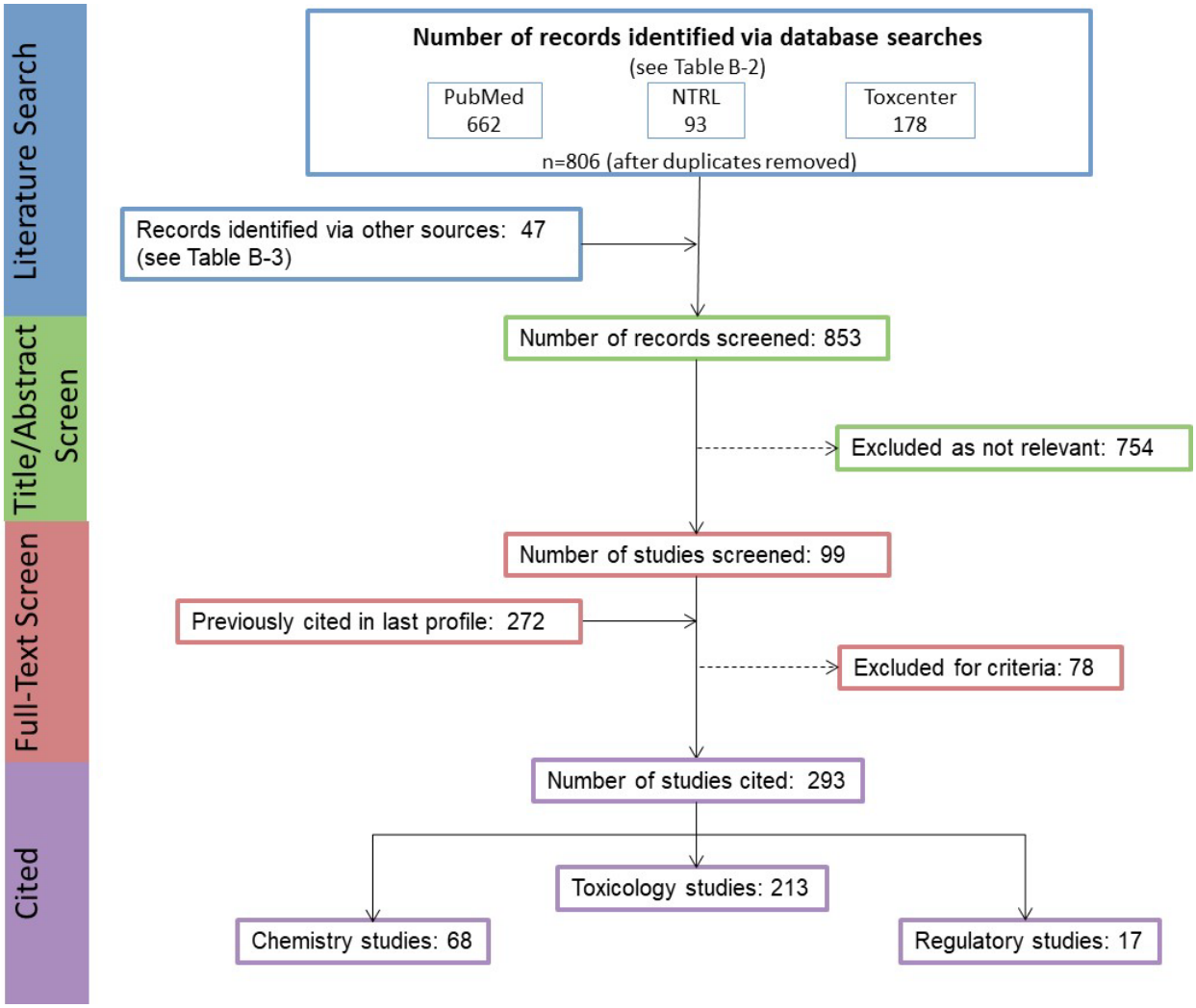
- Number of titles and abstracts screened: 853
- Number of studies considered relevant and moved to the next step: 99

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

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

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

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



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

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

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

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

C.1 PROBLEM FORMULATION

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

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

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

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

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

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

C.2 LITERATURE SEARCH AND SCREEN FOR HEALTH EFFECTS STUDIES

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

C.2.1 Literature Search

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

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

C.2.2 Literature Screening

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

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

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

C.3 EXTRACT DATA FROM HEALTH EFFECTS STUDIES

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

Table C-2. Data Extracted from Individual Studies

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

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

C.4 IDENTIFY POTENTIAL HEALTH EFFECT OUTCOMES OF CONCERN

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

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

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

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

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

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

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

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

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

C.5 ASSESS THE RISK OF BIAS FOR INDIVIDUAL STUDIES

C.5.1 Risk of Bias Assessment

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

*Key question used to assign risk of bias tier.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

C.6.1 Initial Confidence Rating

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

C.6.2 Adjustment of the Confidence Rating

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

C.8 INTEGRATE EVIDENCE TO DEVELOP HAZARD IDENTIFICATION CONCLUSIONS

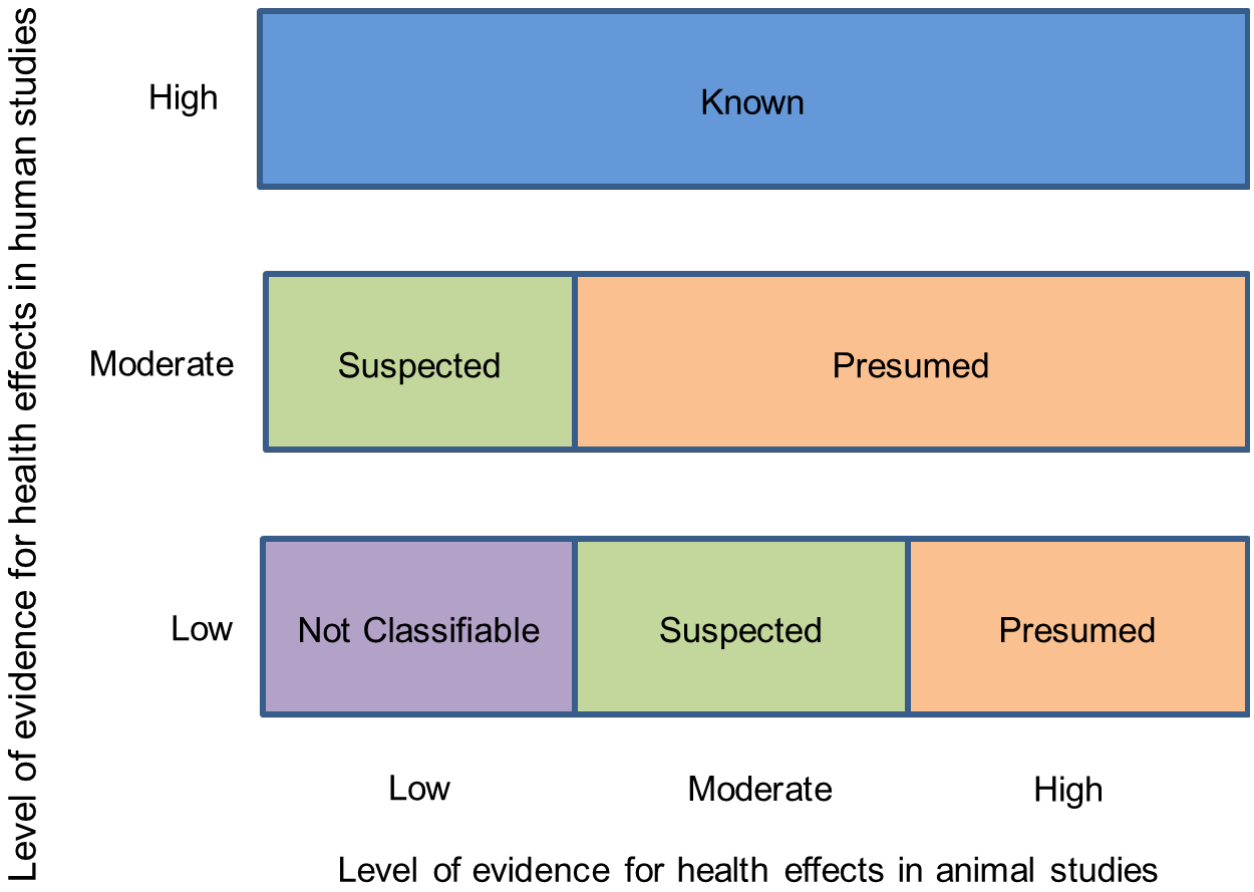
The final step involved the integration of the evidence streams for the human studies and animal studies to allow for a determination of hazard identification conclusions. For health effects, there were four hazard identification conclusion categories:

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

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

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

Figure C-1. Hazard Identification Scheme



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

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

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

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

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

Presumed Health Effects

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

Table C-19. Hazard Identification Conclusions for Acrylonitrile

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

APPENDIX D. USER'S GUIDE

Chapter 1. Relevance to Public Health

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

1. What effects are known to occur in humans?

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

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

Minimal Risk Levels (MRLs)

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

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

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

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

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

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

Chapter 2. Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

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

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

TABLE LEGEND

See Sample LSE Table (page D-5)

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

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

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

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

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

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

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

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

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

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

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

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

FIGURE LEGEND

See Sample LSE Figure (page D-6)

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

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

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

(14) Levels of exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(15) LOAEL. In this example, the half-shaded circle that is designated 51R identifies a LOAEL critical endpoint in the rat upon which a chronic oral exposure MRL is based. The key number 51 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 6.1 mg/kg/day (see entry 51 in the sample LSE table) to the MRL of 0.008 mg/kg/day (see footnote "c" in the sample LSE table).

(16) CEL. Key number 59R is one of studies for which CELs were derived. The diamond symbol refers to a CEL for the test species (rat). The number 59 corresponds to the entry in the LSE table.

(17) Key to LSE figure. The key provides the abbreviations and symbols used in the figure.

Table 2-X. Levels of Significant Exposure to [Chemical X] – Oral (1)

Figure key[a] (3)	Species (strain) No./group (4)	Exposure parameters (5)	Doses (mg/kg/day) (5)	Parameters monitored (6)	Endpoint (7)	NOAEL (mg/kg/day) (8)	Less serious LOAEL (mg/kg/day) (9)	Serious LOAEL (mg/kg/day) (9)	Effect
CHRONIC EXPOSURE (2)									
51	Rat (Wistar) 40 M, 40 F	2 years (F)	M: 0, 6.1, 25.5, 138.0 F: 0, 8.0, 31.7, 168.4	CS, WI, BW, OW, HE, BC, HP	Bd wt	25.5	138.0		Decreased body weight gain in males (23–25%) and females (31–39%)
					Hemato	138.0			
					Hepatic		6.1[c]		Increases in absolute and relative weights at ≥6.1/8.0 mg/kg/day after 12 months of exposure; fatty generation at ≥6.1 mg/kg/day in males and at ≥31.7 mg/kg/day in females, and granulomas in females at 31.7 and 168.4 mg/kg/day after 12, 18, or 24 months of exposure and in males at ≥6.1 mg/kg/day only after 24 months of exposure
Aida et al. 1992 (10)									
52	Rat (F344) 78 M	104 weeks (W)	0, 3.9, 20.6, 36.3	CS, BW, FI, BC, OW, HP	Hepatic	36.3			
					Renal	20.6	36.3		Increased incidence of renal tubular cell hyperplasia
					Endocr	36.3			
George et al. 2002									
59	Rat (Wistar) 58M, 58F	Lifetime (W)	M: 0, 90 F: 0, 190	BW, HP	Cancer		190 F		Increased incidence of hepatic neoplastic nodules in females only; no additional description of the tumors was provided
Tumasonis et al. 1985									

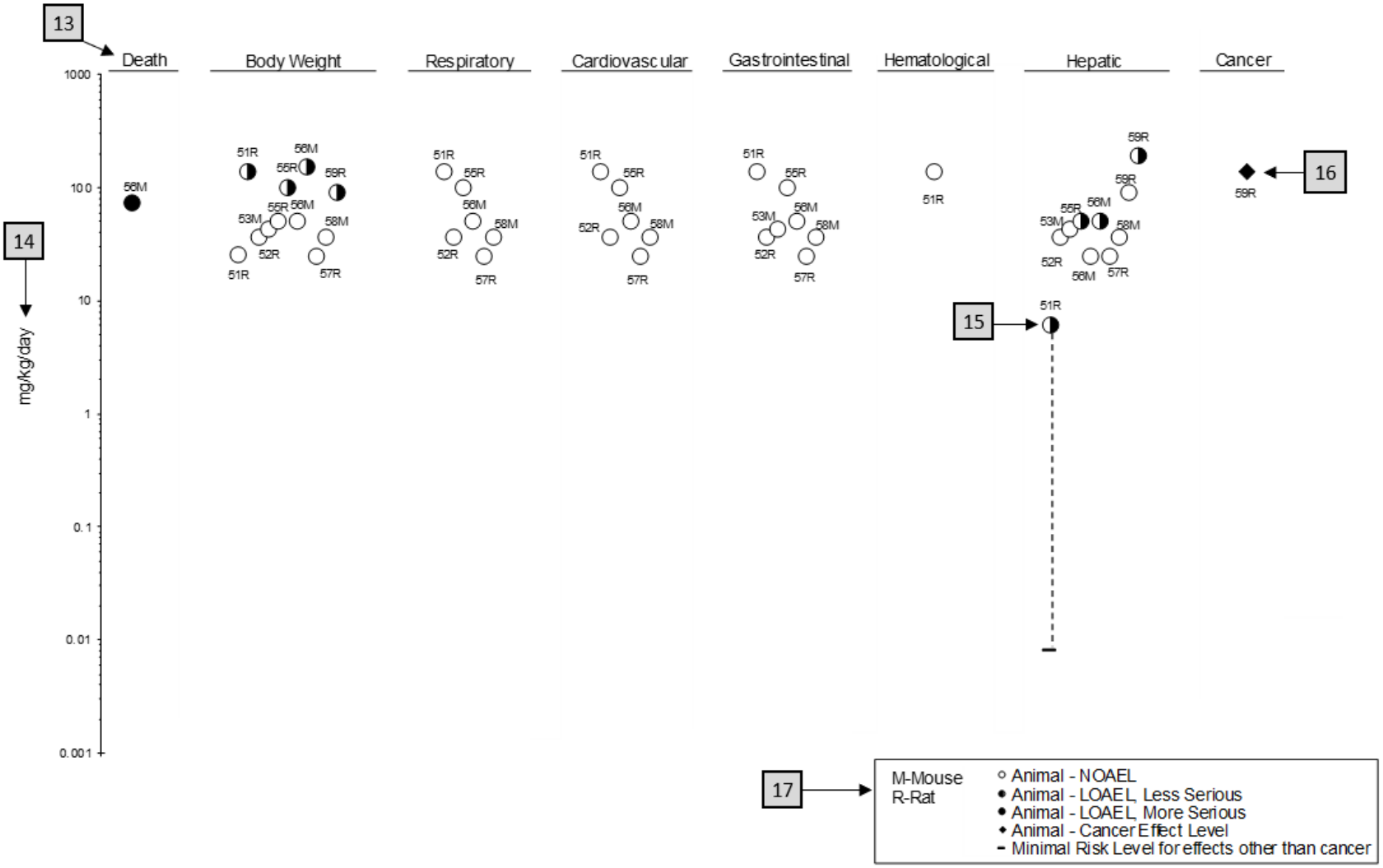
[a]The number corresponds to entries in Figure 2-x.

(11) [b]Used to derive an acute-duration oral minimal risk level (MRL) of 0.1 mg/kg/day based on the $BMDL_{05}$ of 10 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

[c]Used to derive a chronic-duration oral MRL of 0.008 mg/kg/day based on the $BMDL_{10}$ of 0.78 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

APPENDIX D

Figure 2-X. Levels of Significant Exposure to [Chemical X] - Oral



APPENDIX E. QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances may find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Relevance to Public Health: The Relevance to Public Health Section provides an overview of exposure and health effects and evaluates, interprets, and assesses the significance of toxicity data to human health. A table listing minimal risk levels (MRLs) is also included in this chapter.

Chapter 2: Health Effects: Specific health effects identified in both human and animal studies are reported by type of health effect (e.g., death, hepatic, renal, immune, reproductive), route of exposure (e.g., inhalation, oral, dermal), and length of exposure (e.g., acute, intermediate, and chronic).
NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting.

Pediatrics:

Section 3.2 Children and Other Populations that are Unusually Susceptible
Section 3.3 Biomarkers of Exposure and Effect

ATSDR Information Center

Phone: 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY)
Internet: http://www.atsdr.cdc.gov

ATSDR develops educational and informational materials for health care providers categorized by hazardous substance, clinical condition, and/or by susceptible population. The following additional materials are available online:

Clinician Briefs and Overviews discuss health effects and approaches to patient management in a brief/factsheet style. They are narrated PowerPoint presentations with Continuing Education credit available (see https://www.atsdr.cdc.gov/environmental-medicine/hcp/emhsis/index.html).

Managing Hazardous Materials Incidents is a set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident (see https://www.atsdr.cdc.gov/MHMI/index.html).

Fact Sheets (ToxFAQs™) provide answers to frequently asked questions about toxic substances (see https://wwwn.cdc.gov/TSP/ToxFAQs/ToxFAQsLanding.aspx).

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. Contact: NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015 • Web Page: https://www.cdc.gov/nceh/.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 400 7th Street, S.W., Suite 5W, Washington, DC 20024 • Phone: 202-245-0625 or 1-800-CDC-INFO (800-232-4636) • Web Page: https://www.cdc.gov/niosh/.

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. Contact: NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212 • Web Page: https://www.niehs.nih.gov/.

Clinical Resources (Publicly Available Information)

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: http://www.aoec.org/.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266 • Web Page: http://www.acoem.org/.

The American College of Medical Toxicology (ACMT) is a nonprofit association of physicians with recognized expertise in medical toxicology. Contact: ACMT, 10645 North Tatum Boulevard, Suite 200-111, Phoenix AZ 85028 • Phone: 844-226-8333 • FAX: 844-226-8333 • Web Page: http://www.acmt.net.

The Pediatric Environmental Health Specialty Units (PEHSUs) is an interconnected system of specialists who respond to questions from public health professionals, clinicians, policy makers, and the public about the impact of environmental factors on the health of children and reproductive-aged adults. Contact information for regional centers can be found at https://www.pehsu.net/.

The American Association of Poison Control Centers (AAPCC) provide support on the prevention and treatment of poison exposures. Contact: AAPCC, 515 King Street, Suite 510, Alexandria VA 22314 • Phone: 701-894-1858 • Poison Help Line: 1-800-222-1222 • Web Page: http://www.aapcc.org/.

APPENDIX F. GLOSSARY

Absorption—The process by which a substance crosses biological membranes and enters systemic circulation. Absorption can also refer to the taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure—Exposure to a chemical for a duration of ≤14 days, as specified in the Toxicological Profiles.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)—The amount of a chemical adsorbed by sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Benchmark Dose (BMD) or Benchmark Concentration (BMC)—is the dose/concentration corresponding to a specific response level estimate using a statistical dose-response model applied to either experimental toxicology or epidemiology data. For example, a BMD_{10} would be the dose corresponding to a 10% benchmark response (BMR). The BMD is determined by modeling the dose-response curve in the region of the dose-response relationship where biologically observable data are feasible. The BMDL or BMCL is the 95% lower confidence limit on the BMD or BMC.

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers—Indicators signaling events in biologic systems or samples, typically classified as markers of exposure, effect, and susceptibility.

Cancer Effect Level (CEL)—The lowest dose of a chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or malignant tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-control study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without the outcome.

Case Report—A report that describes a single individual with a particular disease or exposure. These reports may suggest some potential topics for scientific research, but are not actual research studies.

Case Series—Reports that describe the experience of a small number of individuals with the same disease or exposure. These reports may suggest potential topics for scientific research, but are not actual research studies.

Ceiling Value—A concentration that must not be exceeded.

Chronic Exposure—Exposure to a chemical for ≥365 days, as specified in the Toxicological Profiles.

Clastogen—A substance that causes breaks in chromosomes resulting in addition, deletion, or rearrangement of parts of the chromosome.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome, and who are disease-free at start of follow-up. Often, at least one exposed group is compared to one unexposed group, while in other cohorts, exposure is a continuous variable and analyses are directed towards analyzing an exposure-response coefficient.

Cross-sectional Study—A type of epidemiological study of a group or groups of people that examines the relationship between exposure and outcome to a chemical or to chemicals at a specific point in time.

Data Needs—Substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment.

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the response or amount of the response.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the effect occurs. Effects include malformations and variations, altered growth, and *in utero* death.

Epidemiology—The investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Excretion—The process by which metabolic waste products are removed from the body.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic, or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one-half of a quantity of a chemical from the body or environmental media.

Health Advisory—An estimate of acceptable drinking water levels for a chemical substance derived by EPA and based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Immediately Dangerous to Life or Health (IDLH)—A condition that poses a threat of life or health, or conditions that pose an immediate threat of severe exposure to contaminants that are likely to have adverse cumulative or delayed effects on health.

Immunotoxicity—Adverse effect on the functioning of the immune system that may result from exposure to chemical substances.

Incidence—The ratio of new cases of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure—Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

***In Vitro*—**Isolated from the living organism and artificially maintained, as in a test tube.

***In Vivo*—**Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO})—The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50})—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{Lo})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50})—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50})—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

Metabolism—Process in which chemical substances are biotransformed in the body that could result in less toxic and/or readily excreted compounds or produce a biologically active intermediate.

Minimal LOAEL—Indicates a minimal adverse effect or a reduced capacity of an organ or system to absorb additional toxic stress that does not necessarily lead to the inability of the organ or system to function normally.

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a Minimal Risk Level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity—The state of being diseased; the morbidity rate is the incidence or prevalence of a disease in a specific population.

Mortality—Death; the mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations, which are changes in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a hazardous substance.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Although effects may be produced at this dose, they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An odds ratio that is greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) regulatory limit on the amount or concentration of a substance not to be exceeded in workplace air averaged over any 8-hour work shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests (insects or other organisms harmful to cultivated plants or animals).

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments, which, in general, do not represent real, identifiable anatomic regions of the body, whereas the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic endpoints. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—A type of physiologically based dose-response model that is comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information, including tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as blood:air partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which a group is followed over time and the pertinent observations are made on events occurring after the start of the study.

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation RfC is expressed in units of mg/m^3 or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily oral exposure of the human population to a potential hazard that is likely to be without risk of deleterious noncancer health effects during a lifetime. The oral RfD is expressed in units of mg/kg/day.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). RQs are (1) ≥1 pound or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a hazardous substance. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a hazardous substance.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, existing health condition, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio/Relative Risk—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio that is greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed group.

Serious LOAEL—A dose that evokes failure in a biological system and can lead to morbidity or mortality.

Short-Term Exposure Limit (STEL)—A STEL is a 15-minute TWA exposure that should not be exceeded at any time during a workday.

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which it is believed that nearly all workers may be repeatedly exposed, day after day, for a working lifetime without adverse effect. The TLV may be expressed as a Time-Weighted Average (TLV-TWA), as a Short-Term Exposure Limit (TLV-STEL), or as a ceiling limit (TLV-C).

Time-Weighted Average (TWA)—An average exposure within a given time period.

Toxicokinetic—The absorption, distribution, metabolism, and elimination of toxic compounds in the living organism.

Toxics Release Inventory (TRI)—The TRI is an EPA program that tracks toxic chemical releases and pollution prevention activities reported by industrial and federal facilities.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL), Reference Dose (RfD), or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis (3 being the approximate logarithmic average of 10 and 1).

Xenobiotic—Any substance that is foreign to the biological system.

APPENDIX G. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

AAPCC	American Association of Poison Control Centers
ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ACMT	American College of Medical Toxicology
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AEGL	Acute Exposure Guideline Level
AIC	Akaike's information criterion
AIHA	American Industrial Hygiene Association
ALT	alanine aminotransferase
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BCF	bioconcentration factor
BMD/C	benchmark dose or benchmark concentration
BMD_X	dose that produces a X% change in response rate of an adverse effect
$BMDL_X$	95% lower confidence limit on the BMD_X
BMDS	Benchmark Dose Software
BMR	benchmark response
BUN	blood urea nitrogen
C	centigrade
CAA	Clean Air Act
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
cm	centimeter
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DWEL	drinking water exposure level
EAFUS	Everything Added to Food in the United States
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
ERPG	emergency response planning guidelines
F	Fahrenheit
F1	first-filial generation
FDA	Food and Drug Administration
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FR	Federal Register

FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GGT	γ-glutamyl transferase
GRAS	generally recognized as safe
HEC	human equivalent concentration
HED	human equivalent dose
HHS	Department of Health and Human Services
HPLC	high-performance liquid chromatography
HSDB	Hazardous Substances Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	kilokilogram; 1 kilokilogram is equivalent to 1,000 kilograms and 1 metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactate dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Level of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
MRL	Minimal Risk Level
MS	mass spectrometry
MSHA	Mine Safety and Health Administration
Mt	metric ton
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NCEH	National Center for Environmental Health
ND	not detected
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences

NIOSH	National Institute for Occupational Safety and Health
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NTP	National Toxicology Program
OR	odds ratio
OSHA	Occupational Safety and Health Administration
PAC	Protective Action Criteria
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PEHSU	Pediatric Environmental Health Specialty Unit
PEL	permissible exposure limit
PEL-C	permissible exposure limit-ceiling value
pg	picogram
PND	postnatal day
POD	point of departure
ppb	parts per billion
ppbv	parts per billion by volume
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure limit
REL-C	recommended exposure limit-ceiling value
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SD	standard deviation
SE	standard error
SGOT	serum glutamic oxaloacetic transaminase (same as aspartate aminotransferase or AST)
SGPT	serum glutamic pyruvic transaminase (same as alanine aminotransferase or ALT)
SIC	standard industrial classification
SLOAEL	serious lowest-observed-adverse-effect level
SMR	standardized mortality ratio
sRBC	sheep red blood cell
STEL	short term exposure limit
TLV	threshold limit value
TLV-C	threshold limit value-ceiling value
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey

USNRC	U.S. Nuclear Regulatory Commission
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result