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*:** Vinyl chloride
CAS Numbers: 75-01-4
Date: January 2024
Profile Status: Final
Route: Inhalation
Duration: Acute
MRL: 0.5 ppm; 1.3 mg/m^3
Critical Effect: Delayed ossification
References: John et al. 1977, 1981
Point of Departure: NOAEL of 50 ppm; $NOAEL_{HEC}$ = 15 ppm
Uncertainty Factor: 30
LSE Graph Key: 14
Species: Mouse

MRL Summary: An acute-duration inhalation MRL of 0.5 ppm (1.3 mg/m^3) was derived for vinyl chloride based on a developmental endpoint of delayed ossification NOAEL of 50 ppm and a LOAEL of 500 ppm for mice administered vinyl chloride for 7 hours/day on GDs 6–15 (John et al. 1977, 1981). The inhalation concentration of 50 ppm was duration adjusted ($NOAEL_{ADJ}$) to a continuous exposure of 15 ppm. The partition coefficient in mice is greater than that in humans; therefore, a default value of 1 is used for the ratio resulting in a $NOAEL_{HEC}$ of 15 ppm. The $NOAEL_{HEC}$ of 15 ppm was divided by a total uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustment and 10 for human variability).

Selection of the Critical Effect: Available data indicate that developmental effects are the most sensitive target for toxic effects following acute-duration inhalation exposure to vinyl chloride (Table A-1). Delayed ossification was observed in both mice and rabbits at 500 ppm, which is the lowest LOAEL identified for developmental effects (John et al. 1977, 1981). The mouse study included a lower concentration (50 ppm), which was a NOAEL. Exposure of pregnant rats to 2,500 ppm 7 hours/day over GDs 6–15 resulted in ureter dilatation in the offspring (John et al. 1977, 1981).

Relative kidney weight was increased by 20% in pregnant rats exposed to ≥100 ppm vinyl chloride 6 hours/day on GDs 6–19 (Thornton et al. 2002). This endpoint was not chosen as the basis of the acute-duration inhalation MRL because absolute kidney weights were similar to controls and no other parameters were available to evaluate the potential for renal toxicity (i.e., no clinical chemistry, urinalysis, or histopathology data). A number of studies in animals identified acute-duration LOAELs for frank narcosis and severe lung, liver, and kidney damage following exposures of 10,000–400,000 ppm of vinyl chloride (Table 2-1).

Table A-1. Summary of Candidate Critical Effects for Acute-Duration Inhalation MRL for Vinyl Chloride

Species	Duration	NOAEL (ppm)	LOAEL (ppm)	Effect	Reference
Developmental effects[a]					
Rat (Sprague-Dawley)	GDs 6–15 10 days 7 hours/day	500	2,500	Ureter dilatation (developmental)	John et al. 1977, 1981

Table A-1. Summary of Candidate Critical Effects for Acute-Duration Inhalation MRL for Vinyl Chloride

Species	Duration	NOAEL (ppm)	LOAEL (ppm)	Effect	Reference
Mouse (CF-1)	GDs 6–15 10 days 7 hours/day	50	500	Delayed ossification	John et al. 1977, 1981
Rabbit (New Zealand)	GDs 6–18 13 days 7 hours/day	ND	500	Delayed ossification	John et al. 1977, 1981
Hepatic effects					
Rat (Sprague-Dawley)	GDs 6–15 10 days 7 hours/day	500	2,500	9 and 10% increase in absolute and relative liver weight, respectively	John et al. 1977, 1981
Renal effects					
Rat (Sprague-Dawley)	GDs 6–19 4–6 hours/day	10	100	20% increase in relative kidney weight	Thornton et al. 2002

[a]Selected critical effect.

GD = gestational day; LOAEL = lowest-observed-adverse-effect level; MRL = Minimal Risk Level; ND = not determined; NOAEL = no -observed-adverse-effect level

Selection of the Principal Study: The study by John et al. (1977, 1981) was selected as the principal study for the derivation of an acute-duration inhalation MRL based on the NOAEL of 50 ppm for delayed ossification. This study identified the lowest LOAEL for developmental endpoints (500 ppm).

Summary of the Principal Study:

John JA, Smith FA, Leong BKJ, et al. 1977. The effects of maternally inhaled vinyl chloride on embryonal and fetal development in mice, rats, and rabbits. Toxicol Appl Pharmacol 39:497-513.

John JA, Smith FA, Schwetz BA. 1981. Vinyl chloride: Inhalation teratology study in mice, rats, and rabbits. Environ Health Perspect 41:171-177.

CF-1 mice (19–26 per group) were exposed to vinyl chloride at concentrations of 0, 50, or 500 ppm for 7 hours/day on GDs 6–15 (John et al. 1977, 1981). Concurrent control groups (47 animals total) were used, one for each dose level. Control groups were sham-exposed to filtered room air. Whole body exposure was conducted in chambers of 3.7 m^3 volume under dynamic conditions. Animals were observed daily for clinical signs, and maternal body weights were measured several times during gestation. Animals were euthanized on GD 18 by carbon dioxide inhalation. Maternal liver weight was measured and uterine horns were examined. Fetuses were weighed, measured (crown-rump length), sexed, and subjected to gross and histopathological examinations.

No adverse maternal or fetal effects were noted at 50 ppm, with the exception of a slight increase in crown-rump length that was not observed at 500 ppm. Maternal body weight gain decreased along with food consumption at 500 ppm. At 500 ppm, delayed ossification of the skull and sternebrae was

observed. The increase in resorptions at 500 ppm was considered to have been within historical control limits. Significant changes in the percentage of implantations resorbed, litter size, and fetal body weight would not have been observed at 500 ppm if comparison had been made to the other control group (the sham-exposed group for the 50-ppm concentration). There was frank maternal toxicity at 500 ppm (17% death). The data for delayed ossification are not amenable to benchmark dose (BMD) modeling, because only one of two dose groups showed a response that was different from controls. A LOAEL of 500 ppm and a NOAEL of 50 ppm were identified based on delayed ossification in fetuses.

Selection of the Point of Departure for the MRL: The NOAEL of 50 ppm was selected as the POD.

Adjustment for Intermittent Exposure: The intermittent exposure duration of 7 hours/day was duration-adjusted ($NOAEL_{ADJ}$) to continuous exposure according to the following equation:

$NOAEL_{ADJ}$ = NOAEL (50 ppm) x 7 hours/24 hours per day = 14.58 ppm.

Human Equivalent Concentration: Following EPA (1994) methodology, the human equivalent concentration ($NOAEL_{HEC}$) for an extrarespiratory effect produced by a category 3 gas, such as vinyl chloride, is calculated by multiplying the duration-adjusted animal NOAEL by the ratio of the blood:gas partition coefficients in animals and humans ($[H_{b/g}]_A$ / $[H_{b/g}]_H$). Since the partition coefficient in mice is greater than that in humans a default value of 1 is used for the ratio resulting in a $NOAEL_{HEC}$ of 14.58 ppm.

Uncertainty Factor: The $NOAEL_{HEC}$ was divided by a total uncertainty factor (UF) of 30:

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

$MRL = NOAEL_{HEC} \div (UF)$
$14.58 \text{ ppm} \div (3 \times 10) = 0.486 \text{ ppm} \approx 0.5 \text{ ppm}$

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Delayed ossification (500 ppm, the lowest concentration tested) was the only developmental effect observed in a rabbit developmental study (John et al. 1977, 1981).

Agency Contacts (Chemical Managers): Rae Benedict

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Vinyl chloride
CAS Numbers: 75-01-4
Date: January 2024
Profile Status: Final
Route: Inhalation
Duration: Intermediate
MRL: 0.02 ppm; 0.05 mg/m^3
Critical Effect: Increased incidence of centrilobular hypertrophy
Reference: Thornton et al. 2002
Point of Departure: $BMCL_{10}$: 2.05 ppm ($BMCL_{HEC}$: 0.5 ppm)
Uncertainty Factor: 30
LSE Graph Key: 28
Species: Rat

MRL Summary: An intermediate-duration inhalation MRL of 0.02 ppm (0.05 mg/m^3) was derived for vinyl chloride based on the benchmark concentration lower confidence limit 10% ($BMCL_{10}$) of 2.05 ppm for the increased incidence of centrilobular hypertrophy of the liver in F1 female rats exposed for 16–19 weeks, including exposure during gestation and lactation (Thornton et al. 2002). The $BMCL_{10}$ was adjusted to continuous duration exposure and converted to a human equivalent concentration ($BMCL_{10HEC}$) of 0.5125 ppm. A total uncertainty factor of 30 (3 for species extrapolation using a dosimetric conversion and 10 for human variability) was applied to the $BMCL_{10HEC}$ to derive the MRL of 0.02 ppm.

Selection of the Critical Effect: No dose-response data are available for humans. Available data indicate that the liver is the most sensitive endpoint for toxic effects following intermediate-duration inhalation exposure to vinyl chloride (Table A-2). Liver effects observed at the lowest LOAEL concentration of approximately 10 ppm include increased liver weight (Bi et al. 1985; Thornton et al. 2002) and centrilobular hypertrophy (Thornton et al. 2002). Fatty liver changes were also observed in two studies of rats exposed to 50 ppm for 10 months (Sokal et al. 1980; Wisniewska-Knypl et al. 1980) and one study in mice exposed to 286.7 ppm for 16 weeks (Wang et al. 2019a). Centrilobular degeneration and necrosis was observed in rabbits exposed to 200 ppm for 6 months (Torkelson et al. 1961). Adverse histopathological changes in the liver of rats and mice exposed to 2,000–3,000 ppm were observed in several other intermediate-duration inhalation studies (Lester et al. 1963; Schaffner 1978; Torkelson et al. 1961; Wisniewska-Knypl et al. 1980).

Table A-2. Summary of Candidate Critical Effects for Intermediate-Duration Inhalation MRL for Vinyl Chloride

Species	Duration	NOAEL (ppm)	LOAEL (ppm)	Effect	Reference
Hepatic effects[a]					
Rat (Wistar)	3, 6 months 6 days/week 6 hours/day	ND	11.1	Increased relative liver weight at 6 months	Bi et al. 1985
Rat (Wistar)	10 months 5 days/week 5 hours/day	ND	50	Fatty changes	Sokal et al. 1980
Rat (Sprague-Dawley)	2 generations 16 weeks (M)	ND	10[a]	Centrilobular hypertrophy in F1	Thornton et al. 2002

Table A-2. Summary of Candidate Critical Effects for Intermediate-Duration Inhalation MRL for Vinyl Chloride

Species	Duration	NOAEL (ppm)	LOAEL (ppm)	Effect	Reference
	19 weeks (F) 4-6 hours/day			female rats	
Rat (NS)	6 months 5 days/week 0.5– 7 hours/day	ND	100	Increased relative liver weight	Torkelson et al. 1961
Rabbit (NS)	6 months 5 days/week 7 hours/day	100	200	Centrilobular degeneration and necrosis	Torkelson et al. 1961
Rat (Wistar)	10 months 5 days/week 5 hours/day	ND	50	Fatty changes	Wisniewska-Knypl et al. 1980
Mouse (C57BL/6N)	16 weeks 5 days/week 2 hours/day	57.3	286.7	Fat droplets, eosinophilic changes, nuclear condensation; at 1,433.6 ppm: Steatosis, large lipid droplets, hepatic edema, cytoplasmic loosening, and hepatocyte nuclear fragmentation	Wang et al. 2019a
Reproductive effects					
Rat (Wistar)	3, 6 months 6 days/week 6 hours/day		100	Decreased testes weight with testicular necrosis at 6 months	Bi et al. 1985
Renal effects					
Rat (Wistar)	3, 6 months 6 days/week 6 hours/day		2,918	Increased relative kidney weight at 3 months	Bi et al. 1985
Rat (Wistar)	10 months 5 days/week 5 hours/day	50	500	Increased relative kidney weight	Sokal et al. 1980
Immunological effects					
Rat (Wistar)	10 months 5 days/week 5 hours/day	ND	50	Increased relative spleen weight	Sokal et al. 1980

Table A-2. Summary of Candidate Critical Effects for Intermediate-Duration Inhalation MRL for Vinyl Chloride

Species	Duration	NOAEL (ppm)	LOAEL (ppm)	Effect	Reference
Mouse (CD-1)	2–8 weeks 5 days/week 6 hours/day	ND	10	Increased spontaneous lymphocyte proliferation	Sharma and Gehring 1979
Rabbit (New Zealand)	8 weeks 5 days/week 6 hours/day	ND	10	Increased spontaneous lymphocyte proliferation	Sharma et al. 1980

[a]Selected critical effect.

F = female(s); LOAEL = lowest-observed-adverse-effect level; M = male(s); MRL = Minimal Risk Level; ND = not determined; NOAEL = no-observed-adverse-effect level

Testicular lesions characterized as degenerative seminiferous tubule changes or spermatogenic epithelial necrosis were observed in male rats exposed for 6–10 months to 100–500 ppm vinyl chloride (Bi et al. 1985; Sokal et al. 1980). Decreased white blood cell counts resulted from exposure of rats to 20,000 ppm for 3 months (Lester et al. 1963), while increased lymphocyte proliferation resulted in mice and immunized rabbits exposed to 10 ppm for up to 8 weeks (Sharma and Gehring 1979; Sharma et al. 1980). Exposures of 10–20,000 ppm resulted in increases and decreases in various relative organ weights (Bi et al. 1985; Sokal et al. 1980; Sharma et al. 1980), including the liver (Bi et al. 1985; Sharma and Gehring 1979; Thornton et al. 2002; Torkelson et al. 1961).

Selection of the Principal Study: Thornton et al. (2002) was chosen as the principal study for derivation of the intermediate-duration inhalation MRL. The study identified the lowest LOAEL for critical liver effects including centrilobular hypertrophy and increased liver weight in rats. The study provided data for centrilobular hypertrophy in F1 offspring, a minimally adverse effect in a sensitive subpopulation (offspring) of the target organ (liver) that is sensitive to both inhalation and oral exposures. A hematological effect was also observed at 10 ppm in mice (Sharma and Gehring 1979) and immunized rabbits (Sharma et al. 1980). However, these studies were not selected as a principal study due to the short exposure duration (2–8 weeks) and lack of other study support.

Summary of the Principal Study:

Thornton SR, Schroeder RE, Robison RL, et al. 2002. Embryo-fetal developmental and reproductive toxicology of vinyl chloride in rats. Toxicol Sci 68:207-219.

Groups of male and female Sprague-Dawley rats (30/sex/group) were exposed to vinyl chloride vapor concentrations of 0, 10, 100, or 1,100 ppm, 6 hours/day for 10 weeks prior to mating and during a 3-week mating period. F0 males were exposed during the gestational period and sacrificed following the completion of parturition. F0 females were exposed during gestation and lactation (with the exception of a break in exposure from GD 21 through postnatal day 4 to allow for delivery of litters). All F0 rats were observed twice daily for clinical signs. Body weights and food consumption were monitored. F1 litters were examined for live and dead pups and on lactation day 4, litters were culled to eight pups (equal numbers of male and female pups where possible). All F0 female rats (including those that did not produce offspring) were sacrificed after the F1 rats had been weaned. Reproductive tissues, adrenal glands, brain, kidneys, liver, lungs, spleen, thymus, mammary glands, nasal tissues, pituitary, and trachea

from each of the F0 rats were individually weighed and subjected to histopathologic examinations. At weaning, 15 male and female F1 rats/group were selected for gross and microscopic examinations. Other F1 rats were randomly selected to form groups of 30/sex/group, and these F1 rats were subjected to the same treatment as the F0 rats during the production of an F2 generation. At weaning, 15 male and female F2 rats/group were subjected to gross and microscopic examinations. Sperm parameters were assessed in 15 F0 and 15 F1 male rats of each exposure group.

Absolute and relative mean liver weights were significantly increased at all exposure levels in F0 males and in 100- and 1,100-ppm F1 males. Slight centrilobular hypertrophy, considered to be a minimal adverse effect, was noted in the livers of all 1,100-ppm male and female F0 and F1 rats, most 100-ppm male and female F0 and F1 rats, and in 2/30 and 6/30 of the 10-ppm F0 and F1 female rats, respectively. No incidences of centrilobular hypertrophy were found in any of the control rats. Compared to an incidence of 0/30 for this lesion in controls, the incidence of 6/30 in the 10-ppm F1 female rats exceeded the level of statistical significance ($p<0.05$ according to Fisher's Exact Test performed by ATSDR).

Selection of the Point of Departure for the MRL: The $BMCL_{10}$ value of 2.05 ppm for increased incidence of centrilobular hypertrophy in the liver of F1 female rats was selected as the basis of the MRL.

BMD modeling was performed for the candidate liver endpoints in Table A-3 when data were amenable to modeling. Data modeled are shown in Tables A-4 and A-5. The data were fit to all available dichotomous or continuous models in EPA's Benchmark Dose Software (BMDS) (version 3.2) using a benchmark response (BMR) of 1 standard deviation (liver weight data) or 10% extra risk (centrilobular hypertrophy). Adequate model fit was judged by four criteria: goodness-of-fit statistics (p-value >0.1), visual inspection of the dose-response curve, BMCL that is not 10 times lower than the lowest non-zero dose, and scaled residual within ±2 units at the data point (except the control) closest to the predefined BMR. Among all of the models providing adequate fit to the data, the lowest BMCL (95% lower confidence limit on the BMD) was selected as the POD when the difference between the BMCLs estimated from these models was ≥3 fold; otherwise, the BMCL from the model with the lowest Akaike Information Criterion (AIC) was chosen. ATSDR follows EPA BMD Guidance (EPA 2012) that compares the fold difference in BMCL values of acceptable models to select the most appropriate model.

Table A-3. Summary of Candidate Critical Liver Effects for Intermediate-Duration Inhalation MRL for Vinyl Chloride[a]

Effect	Sex/generation	NOAEC (ppm)	LOAEC (ppm)
Absolute liver weight	F0 males	ND	10
	F1 males	10	100
Relative liver weight	F0 males	10	100
	F1 males	10	100
Centrilobular hypertrophy	F0 females	10	100
	F1 females	ND	10

[a]Thornton et al. (2002); exposure occurred 10 weeks prior to mating and during a 3-week mating period; F0 males were further exposed during the gestational period and F0 females were further exposed during gestation and lactation.

LOAEC = lowest-observed-adverse-effect level; MRL = Minimal Risk Level; NOAEC = no-observed-adverse-effect level; ND = not determined

Table A-4. Absolute and Relative Liver Weight in F0 And F1 Male Rats Following Inhalation Exposure to Vinyl Chloride[a]

	Exposure concentration (ppm)			
Endpoint	0	10	100	1,100
Number of animals	15	15	15	15
Absolute liver weight (g)				
F0 males	14.32±2.13[b]	16.20±2.19[c]	16.22±1.59[d]	16.72±0.86[d]
F1 males	14.13±2.36	15.07±2.74	16.62±2.27[c]	17.01±1.49[d]
Relative liver weight				
F0 males	2.83±0.26	3.05±0.29[c]	3.09±0.20[c]	3.26±0.19[d]
F1 males	2.98±0.33	3.01±0.19	3.32±0.36[d]	3.38±0.19[d]

[a]Exposure for 6 hours/day for 10 weeks prior to mating and during mating and gestation (males and females) and lactation (females).
[b]Mean±standard deviation.
[c]Statistically significantly ($p<0.05$) different from controls.
[d]Statistically significantly ($p<0.01$) different from controls.

Source: Thornton et al. 2002

Table A-5. Incidences of Centrilobular Hypertrophy in the Liver for F0 And F1 Female Rats Following Inhalation Exposure to Vinyl Chloride[a]

	Exposure concentration (ppm)			
	0	10	100	1,100
F0 females	0/30	2/30	26/30[b]	30/30[b]
F1 females	0/30	6/30[b]	30/30[b]	30/30[b]

[a]Exposure for 6 hours/day for 10 weeks prior to mating and during mating and gestation (males and females) and lactation (females).
[b]Statistically significantly ($p<0.05$) different from controls according to Fisher's Exact Test performed by ATSDR.

Source: Thornton et al. 2002

None of the BMD models (with constant variance or nonconstant variance) provided adequate fit to the data for increased absolute liver weight in F0 males or to relative liver weight in F1 males. Therefore, a NOAEL/LOAEL approach was used for these endpoints.

For absolute liver weight in F1 males, the BMD software (BMDS) could not adequately fit the full dataset, but it was able to provide an adequate fit after dropping the highest dose (1,100 ppm). Dropping the highest dose (or doses) is a valid technique in this case. First, the dataset had enough non-zero dose groups with significant responses to remove the highest dosage without loss of BMD trend. Second, the POD for this dataset would visually be in the lower dose groups, but the high dose group is very far away from these lower groups. This situation can lead to models straining to fit the high group (because of leverage) at the cost of losing adequate fit of lower groups. With the highest dose dropped, five frequentist, constant variance models provided adequate fit to the data. BMCLs for models providing adequate fit were sufficiently close (differed by <3-fold), so the simplest model with the lowest AIC was selected (Linear). The restricted linear model estimated a BMC_{1SD} and $BMCL_{1SD}$ of 110 and 68 ppm,

respectively. BMDS states a warning when fitting the reduced dataset, as the estimated BMD was higher than the new highest dose (100 ppm), which normally raises extrapolation error concerns. However, the estimated BMD (109.8) was still less than the removed high dose, so the estimate would not be much of an extrapolation. Since BMD falls well below the dropped dose of 1,100 ppm, the extrapolation warning (BMD>higher dose) may not be a concern. The results of the BMD modeling are summarized in Table A-6.

Table A-6. Model Predictions (Constant Variance) for Absolute Liver Weight in F1 Male Rats Following Inhalation Exposure to Vinyl Chloride[a]

Model	BMC_{1SD}[b] (ppm)	$BMCL_{1SD}$[b] (ppm)	p-Value[c]	AIC	Scaled residuals[d]	
					Dose near BMC	Dose near control
Highest dose dropped from dataset						
Exponential (model 2)[e]	109.69	70.36	0.40	212.52	-0.06	-0.57
Exponential (model 3)[e]	109.72	70.36	0.40	212.52	-0.05	-0.57
Exponential (model 4)[e]			NA	213.80	-3.3×10^{-6}	-4.1×10^{-6}
Exponential (model 5)[e]			NA	213.80	-5.8×10^{-8}	-2.7×10^{-7}
Hill[e]			<0.0001	215.80	-0.00023	-9.7×10^{-5}
Polynomial (2-degree)[e]	109.77	67.61	0.41	212.49	-0.06	-0.55
Power[f]	109.77	67.61	0.41	212.49	-0.06	-0.55
Linear[e,g]	**109.77**	**67.61**	**0.41**	**212.49**	**-0.06**	**-0.55**

[a]Exposure for 6 hours/day for 10 weeks prior to mating and during mating and gestation (males and females) and lactation (females).
[b]BMC and BMCL values for models that do not provide adequate fit are not included in the table.
[c]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[d]Scaled residuals at concentrations immediately below and above the BMC.
[e]Power restricted to ≥1.
[f]Coefficients restricted to be positive.
[g]Selected model. For the full dataset, none of the models provided adequate fit to the variance data (constant or nonconstant). With the highest dose dropped, constant variance models provided adequate fit to the variance data. With constant variance model applied, all models provided adequate fit to the means except for the Hill and Exponential 4 and 5 models. BMCLs for models providing adequate fit were sufficiently close (differed by <3-fold), so the simplest model with the lowest AIC is selected (Linear).

AIC = Akaike Information Criterion; BMC = benchmark concentration (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); NA = not applicable (Goodness of fit test cannot be calculated); SD = standard deviation

Source: Thornton et al. 2002

For relative liver weight in F0 males, no constant variance models provided an adequate fit to the dataset with the nonconstant variance model applied, only the Hill and Exponential 4 and 5 models provided adequate fit to the data. The BMD computation failed for the Hill model; the lower limit included zero and the BMDL was not estimated. BMCLs for models providing adequate fit were sufficiently close (differed by <3-fold), so the model with the lowest AIC was selected (Exponential 4). The Exponential 4 model estimated a BMC_{1SD} and $BMCL_{1SD}$ of 216 and 72 ppm, respectively. The results of the BMD modeling are summarized in Table A-7.

Table A-7. Model Predictions (Nonconstant Variance) for Relative Liver Weight in F0 Male Rats Following Inhalation Exposure to Vinyl Chloride[a]

Model	BMC_{1SD}[b] (ppm)	$BMCL_{1SD}$[b] (ppm)	p-Value[c]	AIC	Scaled residuals[d] Dose near BMC	Scaled residuals[d] Dose near control
Exponential (model 2)[e]			0.02	8.08	-0.07	-2.16
Exponential (model 3)[e]			0.02	8.08	-0.08	-2.16
Exponential (model 4)[e,f]	**216.31**	**71.99**	**0.11**	**5.08**	**-0.40**	**-1.20**
Exponential (model 5)[e]	225.86	70.96	0.11	5.09	-0.38	-1.22
Hill[d]	246.14	0	0.14	4.72	-0.57	-1.04
Polynomial (3-degree)[e]			0.02	8.03	-0.09	-2.15
Polynomial (2-degree)[e]			0.02	8.03	-0.09	-2.15
Power[e]			0.02	8.03	-0.09	-2.15
Linear[g]			0.02	8.03	-0.09	-2.15

[a]Exposure for 6 hours/day for 10 weeks prior to mating and during mating and gestation (males and females) and lactation (females).
[b]BMC and BMCL values for models that do not provide adequate fit are not included in the table.
[c]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[d]Scaled residuals at concentrations immediately below and above the BMC.
[e]Power restricted to ≥1.
[f]Selected model. None of the constant variance models provided adequate fit to the data. With the nonconstant variance model applied, only the Hill and Exponential 4 and 5 models provided adequate fit to the data. The BMC computation failed for the Hill model; the lower limit included zero and the BMCL was not estimated; therefore, the Hill model was unusable. BMCLs for models providing adequate fit were sufficiently close (differed by <3-fold), so the model with the lowest AIC was selected (Exponential 4).
[g]Coefficients restricted to be positive.

AIC = Akaike Information Criterion; BMC = benchmark concentration (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); SD = standard deviation

Source: Thornton et al. 2002

For the incidence of centrilobular hypertrophy in the liver in F0 females, all models provided an adequate fit to the data except for the Probit model. BMCLs for models providing an adequate fit were not sufficiently close (differed by ≥3-fold), so the model with the lowest BMCL was selected (1-degree multistage). The 1-degree multistage model estimated a BMC_{10} and $BMCL_{10}$ of 6.16 and 4.4 ppm, respectively. The results of the BMD modeling are summarized in Table A-8.

Table A-8. Results from BMD Analysis of Incidences of Centrilobular Hypertrophy in the Liver in F0 Female Rats Following Inhalation Exposure to Vinyl Chloride[a]

Model	BMC_{10}[b] (ppm)	$BMCL_{10}$[b] (ppm)	p-Value[c]	Scaled residuals[d]		
				AIC	Dose near BMC	Dose near control
Gamma[e]	13.01	5.89	1.00	44.26	0.0006	-0.0032
Logistic	31.04	20.79	0.54	44.13	0.7257	-0.8500
Log-Logistic[f]	12.64	6.89	0.98	42.34	0.0301	-0.0007
Log-Probit	12.14	7.58	0.97	44.26	0.0028	-0.0007
Multistage (1-degree)[g,h]	**6.16**	**4.40**	**0.31**	**45.03**	**-1.3638**	**-0.0007**
Multistage (2-degree)[h]	14.06	5.78	1.00	44.26	1.71×10^{-5}	-0.0007
Multistage (3-degree)[h]	14.92	5.76	1.00	42.26	2.16×10^{-6}	-0.0007
Probit			0.01	55.73	-1.1734	-1.9041
Weibull[e]	12.79	5.85	0.90	44.27	-0.1025	-0.0017
Dichotomous Hill	12.64	6.89	0.98	42.34	0.0301	-0.0007

[a]Exposure for 6 hours/day for 10 weeks prior to mating and during mating and gestation (males and females) and lactation (females).
[b]BMC and BMCL values for models that do not provide adequate fit are not included in the table.
[c]Values <0.1 fail to meet conventional χ^2 goodness-of-fit criteria.
[d]Scaled residuals at doses immediately below and above the BMC.
[e]Power restricted to ≥1.
[f]Slope restricted to ≥1.
[g]Selected model. All models provided adequate fit to the data except for the Probit model. BMCLs for models providing adequate fit differed by ≥3-fold; therefore, the model with the lowest BMCL was selected (1-degree Multistage).
[h]Betas restricted to ≥0.

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

Source: Thornton et al. 2002

For the incidence of centrilobular hypertrophy in the liver in F1 females, all models provided an adequate fit to the data except for the Probit model. The BMD computation failed for the Weibull model and a BMCL was not estimated; this model was deemed unusable. BMCLs for models providing an adequate fit were not sufficiently close (differed by ≥3-fold), so the model with the lowest BMCL was selected (1-degree multistage). The 1-degree multistage model estimated a BMC_{10} and $BMCL_{10}$ of 3.03 and 2.05 ppm, respectively. The results of the BMD modeling are summarized in Table A-9.

Table A-9. Results from BMD Analysis of Incidences of Centrilobular Hypertrophy in the Liver in F1 Female Rats Following Inhalation Exposure to Vinyl Chloride[a]

Model	BMC_{10}[b] (ppm)	$BMCL_{10}$[b] (ppm)	p-Value[c]	Scaled residuals[d]		
				AIC	Dose near BMC	Dose near control
Gamma[e]	6.53	3.10	0.98	34.11	-0.0241	-0.0007
Logistic	11.34	7.58	0.41	36.75	0.9450	-1.4034
Log-Logistic[f]	8.21	5.21	1.00	32.04	-0.0021	-0.0007
Log-Probit	8.59	5.09	1.00	34.02	7.296×10^{-11}	-0.0007
Multistage (1-degree)[g,h]	**3.03**	**2.05**	**0.33**	**37.28**	**-0.0007**	**-0.0007**
Multistage (2-degree)[h]	6.75	2.72	1.00	34.02	-2.32×10^{-8}	-0.0007
Multistage (3-degree)[h]	6.76	2.61	1.00	36.02	3.527×10^{-8}	-0.0007
Probit			0.001	60.13	-0.4459	-2.6297
Weibull[e]	5.11	0.00	0.84	34.65	-0.2606	-0.0007
Dichotomous Hill	8.21	5.21	1.00	34.04	-0.0021	-0.0007

[a]Exposure for 6 hours/day for 10 weeks prior to mating and during mating and gestation (males and females) and lactation (females).
[b]BMC and BMCL values for models that do not provide adequate fit are not included in the table.
[c]Values <0.1 fail to meet conventional χ^2 goodness-of-fit criteria.
[d]Scaled residuals at doses immediately below and above the BMC.
[e]Power restricted to ≥1.
[f]Slope restricted to ≥1.
[g]Selected model. All models provided adequate fit to the data except for the Probit model and the Weibull model did not estimate a BMCL. BMCLs for models providing adequate fit differed by ≥3-fold; therefore, the model with the lowest BMCL was selected (1-degree Multistage).
[h]Betas restricted to ≥0.

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

Source: Thornton et al. 2002

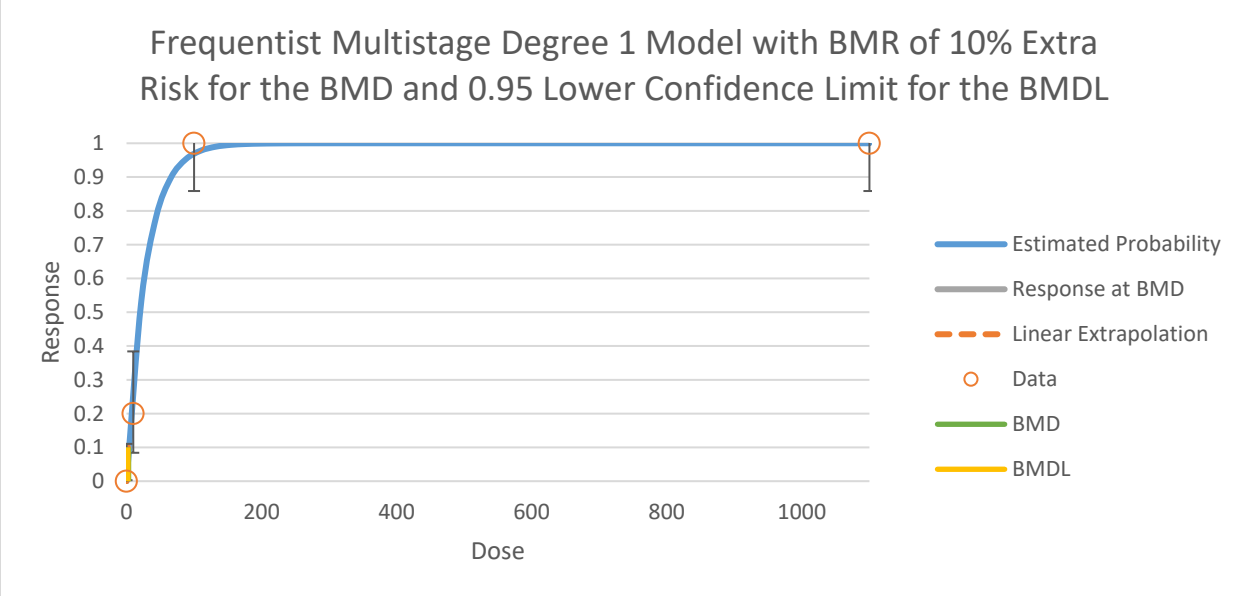
Table A-10 summarizes the potential candidate PODs for the intermediate-duration inhalation MRL for vinyl chloride. Based on the lowest available critical values (BMC, NOAEL), centrilobular hypertrophy (in F1 females) was identified as the critical effect following intermediate-duration inhalation exposure to vinyl chloride. The 1-degree multistage model fit to the centrilobular hypertrophy data in F1 female rats is presented in Figure A-1. The corresponding $BMCL_{10}$ of 2.05 is used as the POD in further calculations.

Table A-10. Candidate Points of Departure for the Intermediate-Duration Inhalation MRL

Endpoint	NOAEC (ppm)	LOAEC (ppm)	BMC_{10} (ppm)	$BMCL_{10}$ (ppm)
Increased absolute liver weight F0 males	ND	10		
Increased absolute liver weight F1 males			110	68
Increased relative liver weight F0 males			216	72
Increased relative liver weight F1 males	10	100		
Centrilobular hypertrophy F0 females			6.16	4.4
Centrilobular hypertrophy F1 females			3.03	2.05

BMC = benchmark concentration; BMCL = 95% lower confidence limit on the BMC; LOAEL = lowest-observed-adverse-effect level; MRL = Minimal Risk Level; NOAEL = no-observed-adverse-effect level

Figure A-1. Fit of 1-Degree Multistage Model to Data for Incidences of Centrilobular Hypertrophy in the Liver in F1 Female Rats Following Inhalation Exposure to Vinyl Chloride (Thornton et al. 2002)



Calculations

Adjustment for Intermittent Exposure: The intermittent exposure duration of 6 hours/day was duration-adjusted ($BMCL_{10ADJ}$) to continuous exposure according to the following equation:

$BMCL_{10ADJ} = BMCL_{10}$ (2.05 ppm) x 6 hours/24 hours per day = 0.5125 ppm

Human Equivalent Concentration: Following EPA (1994) methodology, the human equivalent concentration ($BMCL_{10HEC}$) for an extrarespiratory effect produced by a category 3 gas, such as vinyl chloride, is calculated by multiplying the animal $BMCL_{10ADJ}$ by the ratio of the blood:gas partition coefficients in animals and humans $[(H_{b/g})_A / H_{b/g})_H]$. Since the partition coefficient in rats is greater than that in humans, a default value of 1 is used for the ratio and the animal $BMCL_{10ADJ}$ is equivalent to the $BMCL_{10HEC}$. Several PBPK models are available for vinyl chloride; however, none of these models included an evaluation of exposure during mating, gestation, or lactation. Therefore, PBPK models could not be used to calculate a $BMCL_{10HEC}$ from the Thornton et al. (2002) study. The intermediate-duration inhalation MRL of 0.02 ppm was derived by dividing the $BMCL_{10HEC}$ of 0.5125 ppm for centrilobular hypertrophy in female Sprague-Dawley rats by a factor of 30 (3 for species extrapolation using a dosimetric conversion and 10 for human variability).

Uncertainty Factor: The $BMCL_{10}$ was divided by a total uncertainty factor (UF) of 30:

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

$MRL = BMCL_{10HEC} \div (UF)$
$0.5125 \text{ ppm} \div (3 \times 10) = 0.017 \approx 0.02 \text{ ppm}$

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Liver enlargement and/or histopathological changes have been noted in a number of intermediate-duration inhalation studies in animals (Bi et al. 1985; Lester et al. 1963; Schaffner 1978; Sokal et al. 1980; Torkelson et al. 1961; Wisniewska-Knypl et al. 1980). The studies by Thornton et al. (2002) and Bi et al. (1985) show these effects at a somewhat lower dosage. In support of using an effect level of 10 ppm, there was also a finding of immunostimulation in mice and immunized rabbits at 10 ppm (Sharma and Gehring 1979; Sharma et al. 1980).

Agency Contacts (Chemical Managers): Rae Benedict

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Vinyl chloride
CAS Numbers: 75-01-4
Date: January 2024
Profile Status: Final
Route: Inhalation
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration inhalation MRL for vinyl chloride.

Rationale for Not Deriving an MRL: In the absence of exposure level data, the human database did not provide a suitable LOAEL or NOAEL for derivation of a chronic-duration inhalation MRL. The animal database mostly reported cancer and death. One study (Bi et al. 1985) reported body weight, organ weight, reproductive (histological), and cancer effects. A NOAEL (11.1 ppm) and a LOAEL (105.6 ppm) were identified for testicular effects (increases in the number of degenerative seminiferous tubule changes) in a chronic-duration inhalation study (Bi et al. 1985). However, the results of the Thornton et al. (2002) study for intermediate-duration exposure suggest that liver effects (increased liver weight, centrilobular hypertrophy) would occur at lower concentrations (10 ppm) than the reported testicular effects. Bi et al. (1985) did not report noncancer liver histopathology; therefore, this study cannot be used to derive a chronic-duration inhalation MRL. Though several other chronic-duration studies did report carcinogenicity in rats chronically exposed to 5–250 ppm vinyl chloride (Drew et al. 1983; Lee et al. 1977a, 1978; Maltoni et al. 1981), they did not report the incidence of noncancerous or precancerous histopathological lesions in any tissue. Therefore, no chronic-duration inhalation MRL was derived for vinyl chloride.

Agency Contacts (Chemical Managers): Rae Benedict

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Vinyl chloride
CAS Numbers: 75-01-4
Date: January 2024
Profile Status: Final
Route: Oral
Duration: Acute

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

Rationale for Not Deriving an MRL: No acute-duration oral MRLs was derived for vinyl chloride because of an absence of data on the effects of oral exposure to vinyl chloride for this duration category.

Agency Contacts (Chemical Managers): Rae Benedict

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Vinyl chloride
CAS Numbers: 75-01-4
Date: January 2024
Profile Status: Final
Route: Oral
Duration: Intermediate

MRL Summary: There are insufficient data for derivation of an intermediate-duration oral MRL for vinyl chloride.

Rationale for Not Deriving an MRL: No intermediate-duration oral MRLs was derived for vinyl chloride because of an absence of data on the effects of oral exposure to vinyl chloride for this duration category.

Agency Contacts (Chemical Managers): Rae Benedict

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Vinyl chloride
CAS Numbers: 75-01-4
Date: January 2024
Profile Status: Final
Route: Oral
Duration: Chronic
MRL: 0.003 mg/kg/day (3 µg/kg/day)
Critical Effect: Liver cell polymorphisms
References: Til et al. 1983, 1991
Point of Departure: NOAEL of 0.17 mg/kg/day ($NOAEL_{HED}$ of 0.09 mg/kg/day)
Uncertainty Factor: 30
LSE Graph Key: 5
Species: Rat

MRL Summary: A chronic-duration oral MRL of 0.003 mg/kg/day (3 µg/kg/day) is proposed for vinyl chloride based on a NOAEL of 0.17 mg/kg/day and a LOAEL of 1.7 mg/kg/day for liver cell polymorphisms in rats administered vinyl chloride for 149 weeks (Til et al. 1983,1991). The PBPK-modeled equivalent human NOAEL associated with the rat NOAEL ($NOAEL_{HED}$) of 0.17 mg/kg/day was 0.09 mg/kg/day. The $NOAEL_{HED}$ was divided by a total uncertainty factor of 30 (3 for species extrapolation using a dosimetric conversion and 10 for human variability) to arrive at an MRL of 0.003 mg/kg/day.

Selection of the Critical Effect: No dose-response data are available for humans. Available data indicate that the liver is the most sensitive endpoint for toxic effects following chronic-duration oral exposure to vinyl chloride (Table A-11). A number of effects were observed in rats given 1.7 mg/kg/day, including hepatocellular alterations (Feron et al. 1981), liver cell polymorphisms, and increased mortality (Til et al. 1983, 1991). Liver cell polymorphism is related to cytotoxicity and is considered a nonneoplastic lesion (Schoental and Magee 1957, 1959). The LOAEL of 1.7 mg/kg/day for liver cell polymorphism (in both sexes) and hepatic cysts in female rats was the lowest identified LOAEL and was associated with the lowest identified NOAEL (0.17 mg/kg/day) for any chronic effect. Chronic gavage doses of 3 mg/kg/day vinyl chloride in rats resulted in increased mottled appearance and hemorrhagic liver patches (Knight and Gibbons 1987). Doses of 14.1 mg/kg/day in female rats resulted in extensive hepatic necrosis, 100% early mortality, humpback position, lethargy, and emaciation (Feron et al. 1981). Decreased blood clotting time was also observed in rats given 14.1 mg/kg/day (Feron et al. 1981). Increased collagen deposition and skin thickness were seen in rats chronically gavaged with 30 mg/kg/day (Knight and Gibbons 1987).

Table A-11. Summary of Candidate Critical Effects for Chronic-Duration Oral MRL for Vinyl Chloride

Species	Duration/route	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Hepatic effects					
Rat (Wistar)	84 weeks–2.7 years 5 days/week 4 hours/day (F), (GO)	ND	1.7	Cellular alteration	Feron et al. 1981

Table A-11. Summary of Candidate Critical Effects for Chronic-Duration Oral MRL for Vinyl Chloride

Species	Duration/route	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Rat (Wistar)	149 weeks 4 hours/day (F)	0.17[a]	1.7	Liver cell polymorphism	Til et al. 1983, 1991
Rat (Wistar)	2 years 1 time/day (GO)		3	Mottled appearance and hemorrhagic patches	Knight and Gibbons 1987
Hematological					
Rat (Wistar)	84 weeks–2.7 years 5 days/week 4 hours/day (F), (GO)	5	14.1	Decreased clotting time	Feron et al. 1981
Neurological					
Rat (Wistar)	84 weeks–2.7 years 5 days/week 4 hours/day (F), (GO)	5	14.1	Humpback position, lethargy, emaciation	Feron et al. 1981
Dermal effects					
Rat (Wistar)	2 years 1 time/day (GO)		30	Increased skin thickness, collagen	Knight and Gibbons 1987

F = female(s); G = gavage (no vehicle); GO = gavage (oil vehicle); LOAEL = lowest-observed-adverse-effect level; M = male(s); MRL = Minimal Risk Level; NOAEL = no-observed-adverse-effect level; ND = not determined

Selection of the Principal Study: The study by Til et al. (1983,1991) was selected as the principal study for the derivation of a chronic-duration oral MRL based on the NOAEL of 0.17 mg/kg/day for liver cell polymorphisms. This study identified the lowest LOAEL (1.7 mg/kg/day) for the critical effect.

Summary of the Principal Study:

Til HP, Immel HR, Feron VJ. 1983. Lifespan oral carcinogenicity study of vinyl chloride in rats. Final report. Civo Institutes, TNO. Report No. V 93.285/291099.

Til HP, Feron VJ, Immel HR. 1991. Lifetime (149-week) oral carcinogenicity study of vinyl chloride in rats. Food Chem Toxicol 29:713-718.

Groups of Wistar rats (100/sex/group in controls and the two lowest exposure groups; 50/sex at the highest exposure level) were administered vinyl chloride in the daily diet at intended initial dietary concentrations of 0, 0.46, 4.6, or 46 ppm for 149 weeks. Due to rapid evaporative loss of vinyl chloride from the food, liquid vinyl chloride was mixed with PVC granules to produce a mixture in which vinyl chloride was effectively encapsulated in PVC granules (Feron et al. 1975). The study authors trained the rats to a feeding schedule of 4 hours/day prior to the initiation of exposure to vinyl chloride in the diet. The authors noted that food consumption per hour was fairly constant during the 4-hour feeding period. Loss of vinyl chloride from food during the first hour, the second hour, and the final 2 hours was calculated. Periodic food intake measurements were made for the first hour, the second hour, and the

final 2 hours. Based on these measurements, the study authors calculated the average oral intake of the combined sexes during the daily 4-hour feeding periods to be 0, 0.018, 0.17, and 1.7 mg/kg/day for the 0-, 0.49-, 4.49-, and 44.1-ppm groups, respectively. Measurements of vinyl chloride in the feces were made periodically at 1 hour prior to the feeding period, the end of the 4-hour feeding period, and 4 and 9 hours later. The study authors considered the vinyl chloride content in the feces to have remained encapsulated in the PVC granules and thus not to have been available for absorption from the gastrointestinal tract. The amount of vinyl chloride in the feces was subtracted from the calculated daily oral intake of vinyl chloride to arrive at what the study authors termed "actual oral exposure levels" of 0, 0.014, 0.13, and 1.3 mg/kg/day for the 0-, 0.49-, 4.49-, and 44.1-ppm groups, respectively. The incidence of cell polymorphism was recorded by sex and estimated absorbed dose group (Table A-12). Results of toxicokinetic assessments for vinyl chloride indicate that, following absorption, vinyl chloride and its metabolites are not excreted in appreciable amounts in the feces. Types and incidences of neoplastic and nonneoplastic liver lesions were determined at the end of the study.

Effects noted in study and corresponding doses: The critical nonneoplastic effect was determined to be liver cell polymorphism, which was classified by severity (slight, moderate, severe). The incidences of this lesion are listed in Table A-12.

Table A-12. Incidences of Male and Female Wistar Rats Exhibiting Slight, Moderate, or Severe Liver Cell Polymorphism Following Daily Oral Exposure to Vinyl Chloride in the Diet for 149 Weeks

	Estimated oral intake, absorbed (mg/kg/day)							
	Males				Females			
	0	0.014	0.13	1.3	0	0.014	0.13	1.3
Number of rats examined	99	99	99	49	98	100	96	49
Slight	27	23	26	19	46	41	49	23
Moderate	4	4	7	10[a]	14	13	8	15[b]
Severe	1	1	1	3	2	3	4	9[c]

[a]Significantly different from controls according to Fisher's exact test ($p<0.001$).
[b]Significantly different from controls according to Fisher's exact test ($p<0.05$).
[c]Significantly different from controls according to Fisher's exact test ($p<0.0001$).

Source: Til et al. 1983, 1991

Selection of the Point of Departure for the MRL: A LOAEL of 1.7 mg/kg/day was identified for statistically significantly increased incidences of liver cell polymorphism in male and female rats. The NOAEL for nonneoplastic liver effects is 0.17 mg/kg/day. An increase in the incidence of female rats with many hepatic cysts was also observed at the highest dose (1.7 mg/kg/day). Other histopathologic lesions, described as hepatic foci of cellular alteration, were observed at all dose levels in female rats and in high-dose male rats, but were not used to derive an MRL because they are considered to be preneoplastic lesions. MRLs are protective only for non-neoplastic effects and do not reflect cancer risk.

EPA (2000) applied the Clewell et al. (1995) PBPK model for vinyl chloride to the low-, mid-, and high-dose groups (estimated absorbed doses of 0.014, 0.13, and 1.3 mg/kg/day, respectively) to generate dose metrics of 0.3, 3, and 30 mg vinyl chloride metabolites/L liver, respectively. The EPA approach was reviewed and was considered appropriate for deriving the chronic-duration oral MRL.

The dose metric, "number of rats examined," and the "moderate" and "severe" polymorphism categories (Table A-12) were used in modeling. The "number of rats examined" were summed, regardless of sex, for each dose group, resulting in a low-dose, mid-dose, and high-dose groups. For example, the low-dose group males numbered 99 and the low-dose females numbered 100 to result in 199 rats that were examined in that group (Tables A-12 and A-13). Likewise, the "moderate" and "severe" cell polymorphism incidence data were combined (i.e., summed) for each group, regardless of sex, resulting in one data category of moderate+severe (Table A-13). The moderate+severe polymorphism data had one control group and three exposure groups (low-dose, mid-dose, and high-dose). These combinations resulted in the following cell polymorphism data that were used for modeling: 21/197 controls, 21/199 low-dose, 20/196 mid-dose, and 37/98 high-dose rats) (Til et al. 1983, 1991).

Table A-13. Incidences of Male and Female Wistar Rats Exhibiting Moderate or Severe Liver Cell Polymorphism Following Daily Oral Exposure to Vinyl Chloride in the Diet for 149 Weeks

	Estimated oral intake, absorbed (mg/kg/day)			
	0	0.014	0.13	1.3
	Dose metric (mg metabolite/L liver)			
	0	0.3	3	30
Number of rats examined	197 (99, 98)[a]	199 (99, 100)	195 (99, 96)	98 (49, 49)
Moderate+severe cell polymorphism	21 (4, 1, 14, 2)[b]	21 (4, 1, 13, 3)	20 (7, 1, 8, 4)	37 (10, 3, 15, 9)

[a]Data in parentheses are the incidence numbers for males and females taken from Table A-12.
[b]Data in parentheses are moderate and severe cell polymorphism incidence numbers for males and females.

Source: Til et al. 1983, 1991

The resulting incidence data for each dose metric (0.3, 3, and 30 mg metabolite/L liver) were subjected to BMD modeling in order to statistically identify a threshold response for vinyl chloride-induced effects. The resulting dose metric values are shown in Table A-14.

Table A-14. LED_{10} Values Generated from Various Models to Liver Cell Polymorphism Incidence Data from Oral Exposure of Male and Female Rats to Vinyl Chloride in the Diet for 149 Weeks in the Study of Til et al. (1991)

Model	LED_{10} (mg/L liver)[a]	p-Value
Weibull (power ≥1)	24.0	0.88
Gammahit	21.4	0.88
Quantal quadratic	13.8	0.96
Logistic	12.9	0.47
Multistage	11.8	0.79
Probit	11.6	0.44
Quantal linear	6.5	0.46
NOAEL	3.00 (0.13 mg/kg/day)	
LOAEL	29.9 (1.3 mg/kg/day)	

[a]LED_{10} is the lower 95% confidence limit of a 10% change in numbers exhibiting polymorphism evaluated as either moderate or severe. The NOAEL and LOAEL are shown for comparison.

Source: EPA 2000

Although all models provided adequate fit to the data, the LED_{10} values ranged from 6.5 to 24.01 mg/L liver (nearly a 4-fold range) and all modeled LED_{10} values were higher than the NOAEL of the study. Because there was no biological reason to choose the results of one model over another and the dose-response characteristics present additional uncertainty due to the large gaps between dose levels, the BMD modeling results were not used to derive the POD. Assuming that all dietary vinyl chloride was absorbed, the human equivalent dose of 0.09 mg/kg/day, calculated from the rat NOAEL of 0.17 mg/kg/day (Til et al. 1983, 1991), served as the basis for the chronic-duration oral MRL for vinyl chloride. The chronic-duration oral MRL of 0.003 mg/kg/day was derived by dividing the PBPK-modeled equivalent human NOAEL of 0.09 mg/kg/day for liver cell polymorphisms by a factor of 30 (3 for species extrapolation using a dosimetric conversion and 10 for human variability).

Human Equivalent Concentration: In deriving the MRL, the rat NOAEL of 0.17 mg/kg/day was converted to a human equivalent dose using the PBPK models described in Clewell et al. (2001) and EPA (2000) to extrapolate from rats to humans. Source code and parameter values for running the rat and human models in ACSL were transcribed from Appendix C of EPA (2000). Parameter values used in the interspecies extrapolation are presented in Table A-15. Accuracy of the implementation of the model in ACSL (v. 11.8.4) was checked against observations reported in Gehring et al. (1978), also reported in Clewell et al. (2001) (results shown in Figure A-2). The visual fit of the observed and predicted values appears adequately good at low doses. The total amount of vinyl chloride metabolized in 24 hours per L of liver volume was the rat internal dose metric that was used in determining the human dose that would result in an equivalent human dose metric. One kilogram of liver was assumed to have an approximate volume of 1 L. Exposures in the Til et al. (1983, 1991) rat dietary study were simulated as 4-hour oral exposures, for which the average daily dose (ADD) was equivalent to the NOAEL dose for liver effects (ADD=0.17 mg/kg/day). This dose was uniformly distributed over a 4-hour period (i.e., 0.0425 mg/kg/hour for 4 hours, followed by 16 hours at 0 mg/kg/hour). Dose metrics reflect the cumulative amount of vinyl chloride metabolized over the 24-hour period.

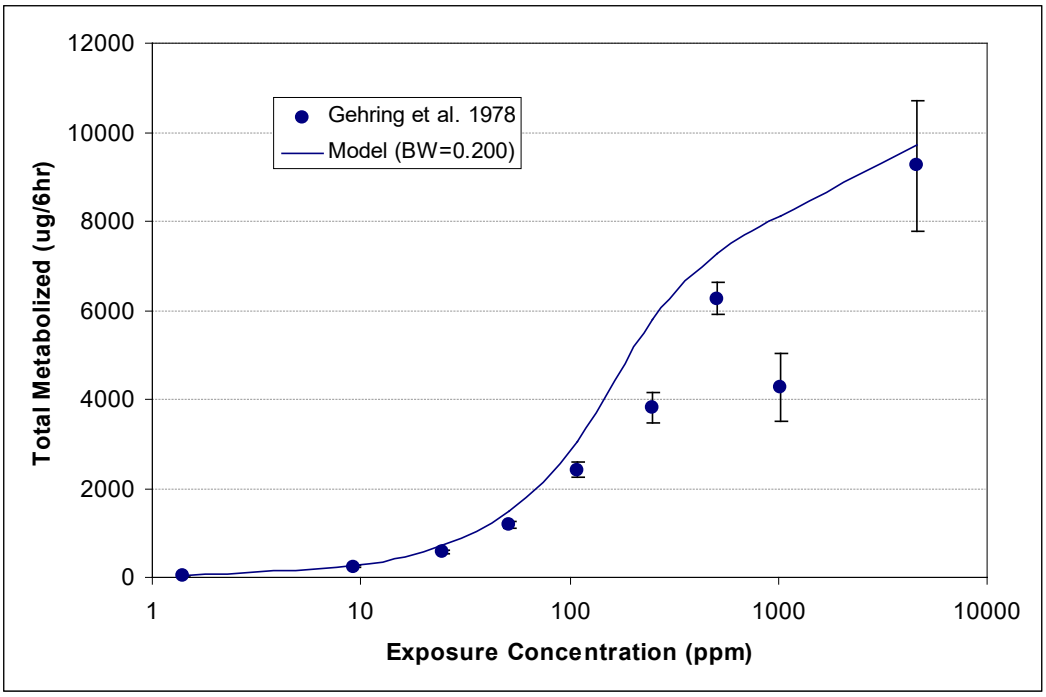
Table A-15. Parameter Values for Rat and Human Models

Parameter	Definition	Model	
		Rat	Human
BW	Body weight (kg)	0.377 (M) 0.204 (F)	70
VLC	Liver volume (fraction of body)	0.05	0.026
VFC	Fat volume (fraction of body)	0.12	0.19
VSC	Slowly-perfused tissue volume (fraction of body)	0.75	0.63
VRC	Rapidly-perfused tissue volume (fraction of body)	0.05	0.064
QCC	Cardiac output (L/hour-kg body weight)	18.0	16.5
QPC	Alveolar ventilation rate (L/hour-kg body weight)	21.0	24.0
QLC	Liver blood flow (fraction of cardiac output)	0.25	0.26
QFC	Fat blood flow (fraction of cardiac output)	0.09	0.05
QSC	Slowly-perfused blood flow (fraction of cardiac output)	0.15	0.19
QRC	Rapidly-perfused blood flow (fraction of cardiac output)	0.51	0.5
PB	Blood:air partition coefficient	2.4	1.16
PL	Liver:blood partition coefficient	0.7	1.45
PF	Fat:blood partition coefficient	10.0	20.7
PS	Slowly-perfused partition coefficient	4.0	0.83
PR	Rapidly-perfused partition coefficient	0.7	1.45
VMAX1C	Maximum rate of oxidative metabolism (mg/hour-kg body weight)	4.0	4.0
VMAX2C	Maximum rate of oxidative metabolism (mg/hour-kg body weight)	2.0	0.1
KM1	Michaelis-Menten coefficient for oxidative metabolism (mg/L)	0.1	0.1
KM2	Michaelis-Menten coefficient for oxidative metabolism (mg/L)	10.0	10.0
KCO2C	Rate constant for formation of CO_2 from oxidative metabolite ($hour^{-1}$)	1.6	1.6
KGSMC	Rate constant for conjugation with GSH ($hour^{-1}$)	0.13	0.13
KFEEC	Rate constant for conjugation, not with GSH ($hour^{-1}$)	35.0	35.0
CGSZ	Initial GSH concentration in liver (µmol/L)	5,800	5,800
KBC	Rate constant for GSH catabolism ($hour^{-1}$)	0.12	0.12
KS	Coefficient controlling resynthesis of GSH (µmol/L)	2,000	2,000
KZC	Zero-order rate constant for resynthesis of GSH (µmol/hour)	28.5	28.5
Ka	Gastrointestinal absorption rate constant ($hour^{-1}$)	3.0	

F= female; GSH = glutathione; M = male

Source: EPA 2000

Figure A-2. Predicted and Observed Relationship Between Air Exposure Concentration and Rate Metabolism of Vinyl Chloride in Rats*



*Measurements of metabolites (non-volatile ^{14}C in carcass) were made immediately following a 6-hour exposure to [^{14}C]vinyl chloride in air. Circles represent observations (±standard deviation); the line shows the corresponding simulations.

The human model was run iteratively, varying the ADD, until the model converged with the internal dose estimate shown in row 1 in Table A-7 (rat, male). The value for the Km1 for oxidative metabolism in humans was assumed to be equal to the Km1 value for rats (0.1 mg/L) (EPA 2000). The human ADD was assumed to be uniformly distributed over a 24-hour period. The resulting HED was 0.09 mg/kg/day (Table A-16). Additional simulations were performed assuming that the ADD was distributed over a 12-hour period (to simulate exposure from drinking water or food during the day only). The resulting dose metrics were very similar to the 24-hour estimates (data not shown).

Table A-16. Summary of Internal Dose Predictions and Corresponding Human and Rat Equivalent Doses

Species	BW (kg)	Km1 mg/L	ED (week)	EF1 (day/week)	EF2 (hour/day)	ADD (mg/kg/day)	DM (mg/L)
Wistar rat							
Male	0.377	0.1	149	7	4	0.17	3.16
Female	0.204	0.1	149	7	4	0.17	3.16
Human	70	0.1	3,640	7	24	0.09	3.16

ADD = average daily administered dose; BW = body weight; DM = dose metric equals the total amount of metabolite formed in 24 hours per L of liver; ED = exposure duration; EF = exposure frequency; Km1 = Michaelis-Menten constant for oxidative metabolism

The $NOAEL_{HED}$ of 0.09 mg/kg/day, associated with the rat NOAEL of 0.17 mg/kg/day (Til et al. 1983, 1991), served as the basis for the chronic-duration oral MRL for vinyl chloride; the $LOAEL_{HED}$ is 1.07 mg/kg/day.

Uncertainty Factor: The PBPK-modeled equivalent human NOAEL of 0.09 mg/kg/day was divided by a total uncertainty factor (UF) of 30:

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

$MRL = NOAEL_{HED} \div (UF)$
$0.09 \text{ mg/kg/day} \div (3 \times 10) = 0.003 \text{ mg/kg/day}$

Other Additional Studies or Pertinent Information that Lend Support to this MRL: This MRL is reinforced by a study by Feron et al. (1981) in which rats were fed diets containing PVC powder. Increased areas of cellular alteration (consisting of clear foci, basophilic foci, and eosinophilic foci) were observed in the liver of rats at an oral intake of vinyl chloride monomer of 1.8 mg/kg/day.

Agency Contacts (Chemical Managers): Rae Benedict

APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR VINYL CHLORIDE

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 vinyl chloride.

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 vinyl chloride. ATSDR primarily focused on peer-reviewed articles without publication date or language restrictions. Foreign language studies are reviewed based on available English-language abstracts and/or tables (or summaries in regulatory assessments, such as International Agency for Research on Cancer [IARC] documents). If the study appears critical for hazard identification or MRL derivation, translation into English is requested. Non-peer-reviewed studies that were considered relevant to the assessment of the health effects of vinyl chloride 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 vinyl chloride are presented in Table B-1.

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

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

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

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

B.1.1 Literature Search

The current literature search was intended to update the draft toxicological profile for vinyl chloride released for public comment in February 2023; thus, the literature search was restricted to studies published between January 2020 and May 2023. The following main databases were searched in May 2023:

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

The search strategy used the chemical names, Chemical Abstracts Service (CAS) numbers, synonyms, Medical Subject Headings (MeSH) headings, and keywords for vinyl chloride. 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 vinyl chloride 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	
05/2023	(("Vinyl Chloride"[mh] OR 75-01-4[rn] OR (("1-Chloroethene"[tw] OR "1-Chloroethylene"[tw] OR "Chlorethene"[tw] OR "Chlorethylene"[tw] OR "Chloroethene"[tw] OR "Chloroethylene"[tw] OR "Ethene, chloro-"[tw] OR "Ethylene monochloride"[tw] OR "Ethylene, chloro-"[tw] OR "F 1140"[tw] OR "Monochloroethene"[tw] OR "Monochloroethylene"[tw] OR "Monovinyl chloride"[tw] OR "Trovidur"[tw] OR "Vinyl C monomer"[tw] OR "Vinyl chloride"[tw] OR "Vinyl chlorine"[tw] OR "Vinylchloride"[tw]) AND (to[sh] OR po[sh] OR ae[sh] OR pk[sh] OR ai[sh] OR ci[sh] OR bl[sh] OR cf[sh] OR ur[sh] OR "pharmacology"[sh:noexp] OR "environmental exposure"[mh] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR "Computational biology"[mh] OR "Medical Informatics"[mh] OR Genomics[mh] OR Genome[mh] OR Proteomics[mh] OR Proteome[mh] OR Metabolomics[mh] OR Metabolome[mh] OR Genes[mh] OR "Gene expression"[mh] OR Phenotype[mh] OR genetics[mh] OR genotype[mh] OR Transcriptome[mh] OR ("Systems Biology"[mh] AND ("Environmental Exposure"[mh] OR "Epidemiological Monitoring"[mh] OR analysis[sh])) OR "Transcription, Genetic "[mh] OR "Reverse transcription"[mh] OR "Transcriptional activation"[mh] OR "Transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, Messenger"[mh] OR "RNA, Transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "Reverse Transcriptase Polymerase Chain Reaction"[mh] OR "Base Sequence"[mh] OR "Trans-activators"[mh] OR "Gene Expression Profiling"[mh] OR (("Neoplasms"[mh] OR "Carcinogens"[mh] OR "Lymphoproliferative disorders"[mh] OR "Myeloproliferative disorders"[mh] OR "Toxicity Tests"[mh] OR ((cancer*[tiab] OR carcinogen*[tiab]) AND (risk*[tiab] OR health[tiab]) AND assessment*[tiab]) OR "Mutagens"[mh] OR "Mutagenicity Tests"[mh] OR "Chromosome Aberrations"[mh] OR "DNA Damage"[mh] OR "DNA Repair"[mh] OR "DNA Replication/drug effects"[mh] OR "DNA/drug effects"[mh] OR "DNA/metabolism"[mh] OR "Genomic Instability"[mh] OR "Salmonella typhimurium/drug effects"[mh] OR "Salmonella typhimurium/genetics"[mh] OR "Sister Chromatid Exchange"[mh] OR strand-break*[tiab])) OR (me[sh] AND ("humans"[mh] OR "animals"[mh])) OR toxicokinetics[mh:noexp]))) AND (2020/10/01:3000[mhda] OR 2020:3000[dp])) OR ((("1-Chloroethene"[tw] OR "1-Chloroethylene"[tw] OR "Chlorethene"[tw] OR "Chlorethylene"[tw] OR "Chloroethene"[tw] OR "Chloroethylene"[tw] OR "Ethene, chloro-"[tw] OR "Ethylene monochloride"[tw] OR "Ethylene, chloro-"[tw] OR "F 1140"[tw] OR "Monochloroethene"[tw] OR "Monochloroethylene"[tw] OR "Monovinyl chloride"[tw] OR "Trovidur"[tw] OR "Vinyl C monomer"[tw] OR "Vinyl chloride"[tw] OR "Vinyl chlorine"[tw] OR "Vinylchloride"[tw]) NOT medline[sb]) AND (2020/10/01:3000[crdt] OR 2020/10/01:3000[edat] OR 2020:3000[dp]))

Table B-2. Database Query Strings

Database search date	Query string
	OR ("vinyl chloride"[mh] AND 2022/04/01:2023/05/18[mhda])
NTRL	
05/2023	Date limit 2020-2023 Search Titles OR Keywords; "Chlorethene" OR "Chlorethylene" OR "Chloroethene" OR "Chloroethylene" OR "Ethene, chloro-" OR "Ethylene monochloride" OR "Ethylene, chloro-" OR "Monochloroethene" OR "Monochloroethylene" OR "Monovinyl chloride" OR "Trovidur" OR "Vinyl C monomer" OR "Vinyl chloride" OR "Vinyl chlorine" OR "Vinylchloride" OR "F 1140"
Toxcenter	
05/2023	FILE 'TOXCENTER' ENTERED AT 13:34:16 ON 18 MAY 2023 L1 11624 SEA FILE=TOXCENTER 75-01-4 L2 11449 SEA FILE=TOXCENTER L1 NOT TSCATS/FS L3 10101 SEA FILE=TOXCENTER L2 NOT PATENT/DT L4 441 SEA FILE=TOXCENTER L3 AND ED>=20201001 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 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

Table B-2. Database Query Strings

Database search date	Query string
	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 235 SEA FILE=TOXCENTER L4 AND L37 L39 235 SEA FILE=TOXCENTER L4 AND L37 L40 36 SEA FILE=TOXCENTER L38 AND MEDLINE/FS L41 199 SEA FILE=TOXCENTER L38 NOT MEDLINE/FS L42 207 DUP REM L40 L41 (28 DUPLICATES REMOVED) L*** DEL 36 S L38 AND MEDLINE/FS L*** DEL 36 S L38 AND MEDLINE/FS L43 36 SEA FILE=TOXCENTER L42 L*** DEL 199 S L38 NOT MEDLINE/FS L*** DEL 199 S L38 NOT MEDLINE/FS L44 171 SEA FILE=TOXCENTER L42 L45 171 SEA FILE=TOXCENTER (L43 OR L44) NOT MEDLINE/FS D SCAN L45

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS via ChemView	
05/2023	Compounds searched: 75-01-4
NTP	
05/2023	Date limit 2020-2023 "75-01-4" "Vinyl chloride" "Chloroethene" "Chloroethylene" "Ethylene, chloro-" "Vinyl C monomer" "Vinyl chlorine" "Vinylchloride" "1-Chloroethene" "1-Chloroethylene" "Chlorethene" "Chlorethylene" "Ethene, chloro-" "Ethylene monochloride" "Monochloroethene" "Monochloroethylene" "Monovinyl chloride" "F 1140" "Trovidur"
Regulations.gov	
05/2023	"Vinyl chloride" "75-01-4" "Chloroethene" "Chloroethylene"
NIH RePORTER	
07/2023	Search Criteria Fiscal Year: Active Projects; Text Search: "1-Chloroethene" OR "1-Chloroethylene" OR "Chlorethene" OR "Chlorethylene" OR "Chloroethene" OR "Chloroethylene" OR "Ethene, chloro-" OR "Ethylene monochloride" OR "Ethylene, chloro-" OR "F 1140" OR "Monochloroethene" OR "Monochloroethylene" OR "Monovinyl chloride" OR "Trovidur" OR "Vinyl C monomer" OR "Vinyl chloride" OR "Vinyl chlorine" OR "Vinylchloride" (advanced); Limit to: Project Title, Project Terms, Project Abstracts
Other	Identified throughout the assessment process

The 2023 results were:

- Number of records identified from PubMed, NTRL, and TOXCENTER (after duplicate removal): 469
- Number of records identified from other strategies: 48
- Total number of records to undergo literature screening: 517

B.1.2 Literature Screening

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

- Title and abstract screen
- Full text screen

Title and Abstract Screen. Within the reference library, titles and abstracts were screened manually for relevance. Studies that were considered relevant (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.

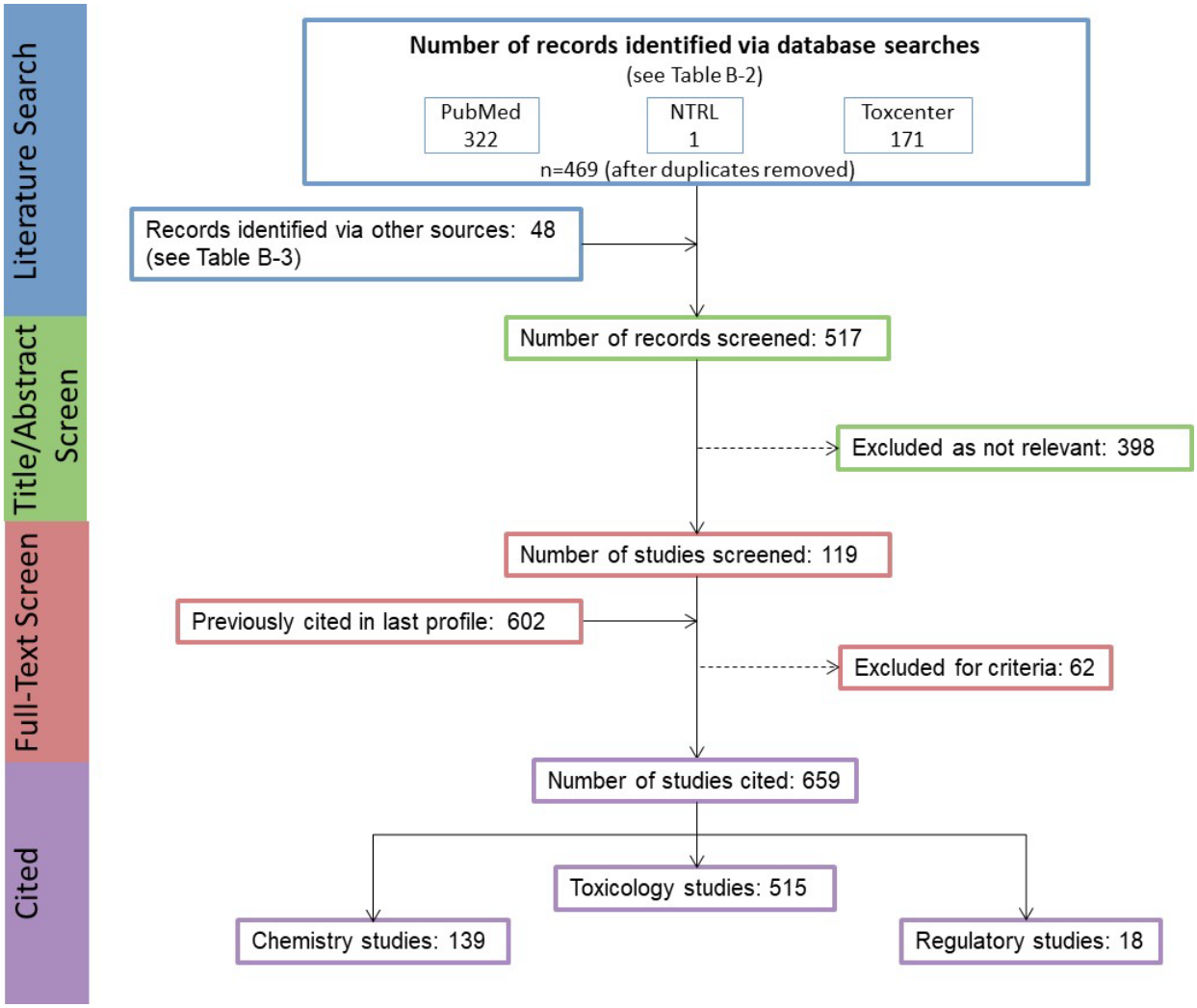
- Number of titles and abstracts screened: 517
- Number of studies considered relevant and moved to the next step: 119

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: 119
- Number of studies cited in the pre-public draft of the toxicological profile: 602
- Total number of studies cited in the profile: 659

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

Figure B-1. May 2023 Literature Search Results and Screen for Vinyl Chloride



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

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 vinyl chloride, 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 vinyl chloride:

- 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 vinyl chloride. The inclusion criteria used to identify relevant studies examining the health effects of vinyl chloride 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

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

Cardiovascular effects
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 vinyl chloride. The literature search framework for the toxicological profile is discussed in detail in Appendix B.

C.2.1 Literature Search

As noted in Appendix B, the current literature search was intended to update the draft toxicological profile for vinyl chloride released for public comment in January 2023. See Appendix B for the databases searched and the search strategy.

A total of 517 records relevant to all sections of the toxicological profile were identified (after duplicate removal).

C.2.2 Literature Screening

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

Title and Abstract Screen. In the Title and Abstract Screen step, 517 records were reviewed; 10 documents were considered to meet the health effects inclusion criteria in Table C-1 and were moved to the next step in the process.

Full Text Screen. In the second step in the literature screening process for the systematic review, a full text review of 208 health effect documents (documents identified in the update literature search and documents cited in older versions of the profile) was performed. From those 208 documents (234 studies), 77 documents (89 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 Vinyl Chloride and overviews of the results of the inhalation and oral exposure studies (no dermal exposure studies were identified) are presented in Sections 2.2–2.18 of the profile and in the Levels Significant Exposures tables in Section 2.1 of the profile (Tables 2-1 and 2-2, respectively).

C.4 IDENTIFY POTENTIAL HEALTH EFFECT OUTCOMES OF CONCERN

Overviews of the potential health effect outcomes for vinyl chloride identified in human and animal studies are presented in Tables C-3 and C-4, respectively. The available human studies evaluating noncancer effects examined a comprehensive set of endpoints for the inhalation route (no oral or dermal human studies were located). Occupational studies of inhalation exposure provide a thorough evaluation of respiratory, cardiovascular, hematological, musculoskeletal, hepatic, dermal, immunological, neurological, and developmental outcomes with health effects being observed for each outcome (except developmental). Animal inhalation studies examined a comprehensive set of endpoints, oral animal studies examined a limited number of health outcomes, and no dermal animal studies were available. Hepatic, immunological, neurological, developmental, and other noncancer (insulin resistance) effects

were considered sensitive noncancer 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. Human studies that did not estimate exposure or include a comparison group (i.e., occupational health studies and case reports/series) were not included in the systematic review. Available cohort, case-control and cross-sectional studies were adequate for evaluating the sensitive health outcomes. There were 89 studies (published in 77 documents) examining these potential outcomes were carried through to Steps 4–8 of the systematic review.

APPENDIX C

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

	Body weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological	Neurological	Reproductive	Developmental	Other Noncancer	Cancer
Inhalation studies																	
Cohort	1	9	11	1	8	5	15		5		1	5	9	4	3		49
	1	6	10	1	6	5	14		5		1	5	9	4	0		39
Case control		1	1				5					4			5	1	11
		1	1				5					4			0	1	7
Population		1	3				9	1				6	3		4	1	3
		0	3				9	1				6	3		0	1	3
Case series		4	6	3	3	6	6		8	4		3	8				12
		4	6	3	2	6	6		8	4		2	8				12
Oral studies																	
Cohort																	
Case control																	
Population																	
Case series																	
Dermal studies																	
Cohort																	
Case control																	
Population																	
Case series																	

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

APPENDIX C

Table C-4. Overview of the Health Outcomes for Vinyl Chloride 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	Cancer
Inhalation studies																	
Acute-duration	6	5	4	1	2	1	13	4		2	1	2	9		5		1
	1	5	2	0	2	0	7	3			0	0	7		4		1
Intermediate-duration	18	1	4		6	1	19	9	1		1	6	2	5	2	4	11
	3	1	1		3	0	14	3	1		0	3	0	3	2	1	11
Chronic-duration	1	2	1		1	1	1	2	1		1		3	1			12
	1	2	1		1	1	1	2	1		1		2	1			12
Oral studies																	
Acute-duration																	
Intermediate-duration																	
Chronic-duration	1	1			2		2		1				1				4
	0	1			1		2		1				1				4
Dermal studies																	
Acute-duration																	
Intermediate-duration																	
Chronic-duration																	

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

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 vinyl chloride health effects studies (observational epidemiology and animal experimental studies) are presented in Tables C-8, C-9, and C-10, respectively.

Table C-8. Summary of Risk of Bias Assessment for Vinyl Chloride—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: Hepatic Effects							
Inhalation—cohort							
Fedeli et al. 2019a	+	+	+	+	++	++	Second
Mundt et al. 2017	++	++	+	+	+	++	First
Hsieh et al. 2007	+	++	+	+	++	++	First
Maroni and Fanetti 2006	+	++	+	+	+	++	First
Zhu et al. 2005a	++	+	+	++	+	+	First
Hsiao et al. 2004	+	++	+	+	++	++	First
Maroni et al. 2003	+	++	+	+	+	++	First
Ward et al. 2001	+	+	+	+	+	+	First
Inhalation—cross-sectional							
Lee et al. 2020	–	+	++	++	++	++	First
Yuan et al. 2020	–	++	++	+	++	++	First
Wang et al. 2019b	+	++	+	+	++	++	First
Attarchi et al. 2007	++	+	–	++	+	++	First
Cheng et al. 1999b	–	++	+	+	++	++	First
Du et al. 1995	+	++	+	+	+	++	First
Tamburro et al. 1984	+	–	+	+	+	+	Second
Vihko et al. 1984	– –	– –	–	+	+	++	Second
NIOSH 1977	+	+	–	+	+	++	Second

Table C-8. Summary of Risk of Bias Assessment for Vinyl Chloride—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?	
Inhalation—case-control							
Cave et al. 2010	++	– –	+	+	+	++	Second
Mastrangelo et al. 2004	++	++	+	+	++	++	First
Du and Wang 1998	+	– –	+	–	+	+	Second
Liss et al. 1985	+	– –	–	–	+	+	Second
Outcome: Immunological Effects							
Inhalation—cross-sectional							
Saad et al. 2017	++	–	+	–	+	+	Second
Fucic et al. 1998	++	–	+	+	++	++	Second
Fucic et al. 1995	++	–	+	+	+	– –	Second
Bencko et al. 1988	–	–	+	–	+	+	Second
Wagnerova et al. 1988	+	–	+	–	+	–	Second
Bogdanikowa and Zawilska 1984	+	–	+	–	+	–	Second
Inhalation—case-control							
Cave et al. 2010	++	– –	+	+	++	++	Second
Black et al. 1983, 1986	++	–	+	–	+	+	Second
Grainger et al. 1980	+	–	+	–	+	+	Second
Outcome: Neurological Effects							
Inhalation—cohort							
Bove et al. 2014	++	+	+	++	++	++	First
Zhu et al. 2005a	++	+	+	++	–	+	First

Table C-8. Summary of Risk of Bias Assessment for Vinyl Chloride—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?	
Inhalation—cross-sectional							
Perticoni et al. 1986	+	–	–	–	++	++	Second
NIOSH 1977	+	+	–	–	+	++	Second
Spirtas et al. 1975	+	+	–	+	+	+	First
Outcome: Developmental Effects							
Inhalation—cohort							
Bao et al. 1988	+	–	+	+	+	–	Second
Inhalation—cross-sectional							
Infante et al. 1976a, 1976b; NIOSH 1977	+	+	–	–	+	++	Second
Inhalation—case-control							
Swartz et al. 2015	++	++	+	+	++	++	First
Talbott et al. 2015	++	++	+	+	++	++	First
Ruckart et al. 2013	+	+	+	+	+	++	First
Rosenman et al. 1989	+	–	+	–	+	+	Second
Theriault et al. 1983	+	–	+	–	–	+	Third
Edmonds et al. 1978	+	–	+	–	+	+	Second
Inhalation—ecological							
Infante 1976	+	–	+	–	+	+	Second
Edmonds et al. 1975	+	–	+	–	+	+	Second

Table C-8. Summary of Risk of Bias Assessment for Vinyl Chloride—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: Other Noncancer (Insulin Resistance)							
Inhalation—cross-sectional							
Lee et al. 2020	–	+	++	++	++	++	First
Inhalation—case-control							
Cave et al. 2010	++	– –	+	+	+	++	Second

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

Table C-9. Summary of Risk of Bias Assessment for Vinyl Chloride— Human-Controlled Exposure Studies

Reference	Risk of bias criteria and ratings							Risk of bias tier
	Selection bias		Performance Bias	Attrition / exclusion bias	Detection bias		Selective reporting bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	**Were the research personnel and human subjects blinded to the study group during the study?***	Outcome data complete without attrition or exclusion from analysis?	**Confidence in exposure characterization?***	**Confidence in outcome assessment?***	All measured outcomes reported?	
Outcome: Neurological Effects								
Inhalation								
Lester et al. 1963	++		+	+	+	+	–	First
Patty et al. 1930	– –		–	+	+	+	–	Second

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

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

Reference	Risk of bias criteria and ratings									
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	Other 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?	Did the study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Outcome: Hepatic Effects										
Inhalation acute-duration exposure										
Jaeger et al. 1974 (rat; 1, 5 days)	–	–	+	+	–	–	+	++	NA	Second
John et al. 1977, 1981 (rat; 10 days)	–	–	+	+	++	–	+	++	NA	First
Mastromatteo et al. 1960 (rat; 30 minutes)	–	–	+	+	++	+	+	++	NA	First
Reynolds et al. 1975a (rat; 1, 5 days)	–	–	+	+	–	–	–	++	NA	Third
Reynolds et al. 1975b (rat; 1 day)	–	–	+	+	–	–	+	++	NA	Second
John et al. 1977, 1981 (mouse; 10 days)	–	–	+	+	++	–	+	++	NA	First
Mastromatteo et al. 1960 (mouse; 30 minutes)	–	–	+	+	++	+	+	++	NA	First
Mastromatteo et al. 1960 (guinea pig; 30 minutes)	–	–	+	+	++	+	+	++	NA	First
John et al. 1977, 1981 (rabbit; 13 days)	–	–	+	+	++	–	+	++	NA	First
Ungvary et al. 1978 (rat; 7–9 days)	–	–	+	+	++	–	+	++	NA	First
Hehir et al. 1981 (rat; 1-hour)	–	–	+	+	+	–	+	++	NA	First
Inhalation intermediate-duration exposure										
Bi et al. 1985 (rat; 3, 6 months)	+	+	+	+	+	++	+	++	NA	First
Jia et al. 2022 (mice; 13 weeks)	+	+	+	+	++	–	+	+	NA	First

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

Reference	Risk of bias criteria and ratings									
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	Other 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?	Did the study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Lester et al. 1963 (rat; 19 days)	–	–	++	+	+	++	+	++	NA	First
Lester et al. 1963 (rat; 92 days)	+	+	++	+	+	++	+	++	NA	First
Liu et al. 2023 (mice; 12 weeks)	–	–	+	+	++	–	+	+	NA	First
Sokal et al. 1980 (rat; 10 months)	–	–	++	+	–	++	+	++	NA	First
Thornton et al. 2002 (rat; 2-generation)	++	+	++	+	++	–	+	++	NA	First
Torkelson et al. 1961 (rat; 6 months)	–	–	++	+	+	+	+	++	NA	First
Wisniewska-Knypl et al. 1980 (rat; 10 months)	–	–	++	+	–	++	+	++	NA	First
Chen et al. 2019 (mouse; 12 weeks)	–	–	++	+	–	–	+	++	NA	Second
Lang et al. 2018 (mouse; 12 weeks)	–	–	++	+	–	–	+	++	NA	Second
Lang et al. 2020 (mouse; 12 weeks)	–	–	++	+	–	–	+	++	NA	Second
Schaffner 1978 (mouse; 6 months)	–	–	+	+	–	–	–	++	NA	Third
Sharma and Gehring 1979 (mouse; 2–8 weeks)	–	–	+	+	–	–	+	++	NA	Second
Wahlang et al. 2020 (mouse; 12 weeks)	–	–	++	+	–	–	+	++	NA	Second
Wang et al. 2019a (mouse; 16 weeks)	–	–	++	+	–	– –	+	++	NA	Second
Torkelson et al. 1961 (rabbit; 6 months)	–	–	++	+	+	+	+	++	NA	First
Du et al. 1979 (rat; 2–4 weeks)	+	+	++	+	–	– –	+	++	NA	First

Table C-10. Summary of Risk of Bias Assessment for Vinyl Chloride—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	Other 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?	Did the study design or analysis account for important confounding and modifying variables?		
Inhalation chronic-duration exposure											
Bi et al. 1985 (rat; 12 months)	+	+	+	+	+	++	+	++	NA		First
Oral chronic-duration exposure											
Til et al. 1983 (rat; 149 weeks)	++	+	++	+	++	++	+	++	NA		First
Feron et al. 1981 (rat; 2 years)	++	+	++	+	++	++	+	++	NA		First
Outcome: Immunological Effects											
Inhalation acute-duration exposure											
Mastromatteo et al. 1960 (guinea pig; 30 minutes)	–	–	+	+	++	+	+	++	NA		First
Inhalation intermediate-duration exposure											
Bi et al. 1985 (rat; 3, 6 months)	+	+	+	+	+	++	+	++	NA		First
Sharma and Gehring 1979 (mouse; 2–8 weeks)	–	–	+	+	–	–	+	++	NA		Second
Sharma et al. 1980 (rabbit; 8 weeks)	–	–	+	+	+	–	+	+	NA		First
Sokal et al. 1980 (rat; 10 months)	–	–	++	+	–	++	+	++	NA		Second
Outcome: Neurological Effects											
Inhalation acute-duration exposure											
Jaeger et al. 1974 (rat; 1, 5 days)	–	–	+	+	–	–	+	++	NA		Second
Lester et al. 1963 (rat; 2 hours)	–	–	++	+	+	++	–	++	NA		Third

Table C-10. Summary of Risk of Bias Assessment for Vinyl Chloride—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	Other 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?	Did the study design or analysis account for important confounding and modifying variables?	
Mastromatteo et al. 1960 (rat; 30 minutes)	–	–	+	+	++	+	+	++	NA	First
Hehir et al. 1981 (rat; 2 weeks)	–	–	+	+	+	–	+	++	NA	First
Hehir et al. 1981 (rat; 1 hour)	–	–	+	+	+	–	+	++	NA	First
Hehir et al. 1981 (mouse; 1 hour)	–	–	+	+	+	–	+	++	NA	First
Mastromatteo et al. 1960 (mouse; 30 minutes)	–	–	+	+	++	+	+	++	NA	First
Mastromatteo et al. 1960 (guinea pig; 30 minutes)	–	–	+	+	++	+	+	++	NA	First
Patty et al. 1930 (guinea pig; up to 8 hours)	–	–	+	+	+	–	+	++	NA	First
Inhalation intermediate-duration exposure										
Hehir et al. 1981 (rat; 20 weeks)	–	–	+	+	+	–	+	++	NA	First
Inhalation chronic-duration exposure										
Viola 1970 (rat; 12 months)	–	–	–	+	+	–	+	++	NA	Second
Viola et al. 1971 (rat; 12 months)	–	–	+	+	+	+	+	++	NA	First
Feron and Kroes 1979 (rat; 12 months)	–	–	+	+	–	–	+	++	NA	Second

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

Reference	Risk of bias criteria and ratings									
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	Other 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?	Did the study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Outcome: Developmental Effects										
Inhalation acute-duration exposure										
Thornton et al. 2002 (rat; GDs 6–19)	++	+	++	+	++	–	+	+	NA	First
John et al. 1977, 1981 (rat; 10 days)	–	–	+	+	++	–	+	++	NA	First
John et al. 1977, 1981 (mouse; 10 days)	–	–	+	+	++	–	+	++	NA	First
John et al. 1977, 1981 (rabbit; 13 days)	–	–	+	+	++	–	+	++	NA	First
Ungvary et al. 1978 (rat; 7-9 days)	–	–	+	+	++	–	+	++	NA	First
Inhalation intermediate-duration exposure										
Sal'nikova and Kotsovskaya 1980 (rat; 21 days)	–	–	+	+	–	–	+	++	NA	Second
Mirkova et al. 1978	–	–	–	+	–	–	–	–	NA	Third

Table C-10. Summary of Risk of Bias Assessment for Vinyl Chloride—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	Other 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?	Did the study design or analysis account for important confounding and modifying variables?		
Outcome: Other Noncancer (Insulin Resistance)											
Inhalation intermediate-duration exposure											
Chen et al. 2019 (mouse; 12 weeks)	–	–	++	+	–	–	+	++	NA		Second
Lang et al. 2018 (mouse; 12 weeks)	–	–	++	+	–	+	+	++	NA		First
Wahlang et al. 2020 (mouse; 12 weeks)	–	–	++	+	–	–	+	++	NA		Second

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

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

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

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

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

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

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

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

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

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

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

The presence or absence of the key features and the initial confidence levels for studies examining hepatic, immunological, neurological, developmental and other noncancer (insulin resistance) observed in the observational epidemiology, human controlled-exposure and animal experimental studies are presented in Tables C-14, C-15, and C-16, respectively.

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

	Key features				
Reference	Controlled exposure	Exposure prior to outcome	Outcomes assessed on an individual level	Comparison group	Initial study confidence
Outcome: Hepatic effects					
Inhalation—cohort					
Fedeli et al. 2019a	No	Yes	Yes	Yes	Moderate
Mundt et al. 2017	No	Yes	Yes	Yes	Moderate
Hsieh et al. 2007	No	Yes	Yes	Yes	Moderate

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

Reference	Key features				Initial study confidence
	Controlled exposure	Exposure prior to outcome	Outcomes assessed on an individual level	Comparison group	
Maroni and Fanetti 2006	No	Yes	Yes	Yes	Moderate
Zhu et al. 2005a	No	Yes	Yes	Yes	Moderate
Hsiao et al. 2004	No	Yes	Yes	Yes	Moderate
Maroni et al. 2003	No	Yes	Yes	Yes	Moderate
Ward et al. 2001	No	Yes	Yes	Yes	Moderate
Inhalation—cross-sectional					
Lee et al. 2020	No	No	Yes	Yes	Low
Yuan et al. 2020	No	No	Yes	Yes	Low
Wang et al. 2019b	No	No	Yes	Yes	Low
Attarchi et al. 2007	No	No	Yes	Yes	Low
Cheng et al. 1999b	No	No	Yes	Yes	Low
Du et al. 1995	No	No	Yes	Yes	Low
Tamburro et al. 1984	No	No	Yes	Yes	Low
Vihko et al. 1984	No	No	Yes	No	Very low
NIOSH 1977	No	No	Yes	Yes	Low
Inhalation—case-control					
Cave et al. 2010	No	Yes	Yes	Yes	Moderate
Mastrangelo et al. 2004	No	Yes	Yes	Yes	Moderate
Du and Wang 1998	No	Yes	Yes	Yes	Moderate
Liss et al. 1985	No	Yes	Yes	Yes	Moderate
Outcome: Immunological effects					
Inhalation—cross-sectional					
Saad et al. 2017	No	No	Yes	Yes	Moderate
Fucic et al. 1998	No	No	Yes	Yes	Moderate
Fucic et al. 1995	No	No	Yes	Yes	Moderate
Bencko et al. 1988	No	No	Yes	Yes	Moderate
Wagnerova et al. 1988	No	No	Yes	Yes	Moderate
Bogdanikowa and Zawilska 1984	No	No	Yes	Yes	Moderate
Inhalation—case-control					
Cave et al. 2010	No	No	Yes	Yes	Low
Black et al. 1983, 1986	No	Yes	Yes	Yes	Moderate
Grainger et al. 1980	No	Yes	Yes	Yes	Moderate

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

Reference	Key features				Initial study confidence
	Controlled exposure	Exposure prior to outcome	Outcomes assessed on an individual level	Comparison group	
Outcome: Neurological effects					
Inhalation—cohort					
Bove et al. 2014	No	Yes	Yes	Yes	Moderate
Zhu et al. 2005a	No	Yes	Yes	Yes	Moderate
Inhalation—cross-sectional					
Perticoni et al. 1986	No	No	Yes	Yes	Low
NIOSH 1977	No	No	Yes	Yes	Low
Spirtas et al. 1975	No	No	Yes	Yes	Low
Outcome: Developmental effects					
Inhalation—cohort					
Bao et al. 1988	No	Yes	Yes	Yes	Moderate
Inhalation—cross-sectional					
Infante et al. 1976a, 1976b; NIOSH 1977	No	No	Yes	Yes	Low
Inhalation—case-control					
Swartz et al. 2015	No	Yes	Yes	Yes	Moderate
Talbott et al. 2015	No	Yes	Yes	Yes	Moderate
Ruckart et al. 2013	No	Yes	Yes	Yes	Moderate
Rosenman et al. 1989	No	Yes	Yes	Yes	Moderate
Theriault et al. 1983	No	Yes	Yes	Yes	Moderate
Edmonds et al. 1978	No	Yes	Yes	Yes	Moderate
Inhalation—ecological					
Infante 1976	No	Yes	Yes	Yes	Moderate
Edmonds et al. 1975	No	Yes	Yes	Yes	Moderate
Other noncancer (insulin resistance)					
Inhalation—cross-sectional					
Lee et al. 2020	No	No	Yes	Yes	Low
Inhalation—case-control					
Cave et al. 2010	No	Yes	Yes	Yes	Moderate

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

Reference	Key features: Comparison group	Sufficient number of subjects	Outcomes assessed with appropriate methods	Statistical analysis	Initial study confidence
Outcome: Neurological effects					
Inhalation					
Lester et al. 1963	Yes	Yes	Yes	No	Moderate
Patty et al. 1930	No	No	Yes	No	Very low

Table C-16. Presence of Key Features of Study Design for Vinyl Chloride—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: Hepatic effects					
Inhalation acute-duration exposure					
Jaeger et al. 1974 (rat; 1, 5 days)	Yes	No	Yes	No	Low
John et al. 1977, 1981 (rat; 10 days)	Yes	Yes	Yes	Yes	High
Mastromatteo et al. 1960 (rat; 30 minutes)	Yes	Yes	Yes	No	Moderate
Reynolds et al. 1975a (rat; 1, 5 days)	No	No	Yes	No	Low
Reynolds et al. 1975b (rat; 1 day)	Yes	No	Yes	No	Low
John et al. 1977, 1981 (mouse; 10 days)	Yes	Yes	Yes	Yes	High
Mastromatteo et al. 1960 (mouse; 30 minutes)	Yes	Yes	Yes	No	Moderate
Mastromatteo et al. 1960 (guinea pig; 30 minutes)	Yes	Yes	Yes	No	Moderate
John et al. 1977, 1981 (rabbit; 13 days)	Yes	Yes	Yes	Yes	High
Ungvary et al. 1978 (rat; 7–9 days)	Yes	Yes	Yes	Yes	High
Hehir et al. 1981 (rat; 1 hour)	Yes	Yes	Yes	No	Moderate

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

Reference	Key feature				Initial study confidence
	Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	
Inhalation intermediate-duration exposure					
Bi et al. 1985 (rat; 3, 6 months)	Yes	Yes	Yes	Yes	High
Jia et al. 2022 (mice; 13 weeks)	Yes	Yes	Yes	Yes	High
Lester et al. 1963 (rat; 19 days)	Yes	Yes	Yes	Yes	High
Lester et al. 1963 (rat; 92 days)	Yes	Yes	Yes	Yes	High
Liu et al. 2023 (mice; 12 weeks)	Yes	Yes	Yes	Yes	High
Sokal et al. 1980 (rat; 10 months)	Yes	Yes	Yes	Yes	High
Thornton et al. 2002 (rat; 2-generation)	Yes	Yes	Yes	Yes	High
Torkelson et al. 1961 (rat; 6 months)	Yes	Yes	Yes	Yes	High
Wisniewska-Knypl et al. 1980 (rat; 10 months)	Yes	Yes	Yes	Yes	High
Chen et al. 2019 (mouse; 12 weeks)	Yes	Yes	Yes	Yes	High
Lang et al. 2018 (mouse; 12 weeks)	Yes	Yes	Yes	Yes	High
Lang et al. 2020 (mouse; 12 weeks)	Yes	Yes	Yes	Yes	High
Schaffner 1978 (mouse; 6 months)	No	Yes	Yes	No	Low
Sharma and Gehring 1979 (mouse; 2–8 weeks)	Yes	No	Yes	Yes	Moderate
Wahlang et al. 2020 (mouse; 12 weeks)	Yes	No	Yes	Yes	Moderate
Wang et al. 2019a (mouse; 16 weeks)	Yes	Yes	Yes	Yes	High
Torkelson et al. 1961 (rabbit; 6 months)	Yes	No	Yes	Yes	Moderate
Du et al. 1979 (rat; 2–4 weeks)	Yes	No	Yes	Yes	Moderate
Inhalation chronic-duration exposure					
Bi et al. 1985 (rat; 12 months)	Yes	Yes	Yes	Yes	High
Oral chronic-duration exposure					
Til et al. 1983 (rat; 149 weeks)	Yes	Yes	Yes	Yes	High
Feron et al. 1981 (rat; 2 years)	Yes	Yes	Yes	Yes	High
Outcome: Immunological effects					
Inhalation acute-duration exposure					
Mastromatteo et al. 1960 (guinea pig; 30 minutes)	Yes	Yes	Yes	No	Moderate

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

Reference	Key feature				Initial study confidence
	Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	
Inhalation intermediate-duration exposure					
Bi et al. 1985 (rat; 3, 6 months)	Yes	Yes	Yes	Yes	High
Sharma and Gehring 1979 (mouse; 2–8 weeks)	Yes	No	Yes	Yes	Moderate
Sharma et al. 1980 (rabbit; 8 weeks)	Yes	Yes	Yes	Yes	High
Sokal et al. 1980 (rat; 10 months)	Yes	Yes	Yes	Yes	High
Outcome: Neurological effects					
Inhalation acute-duration exposure					
Jaeger et al. 1974 (rat; 1, 5 days)	Yes	No	Yes	No	Low
Lester et al. 1963 (rat; 2 hours)	No	No	Yes	No	Low
Mastromatteo et al. 1960 (rat; 30 minutes)	Yes	Yes	Yes	No	Moderate
Hehir et al. 1981 (rat; 2 weeks)	Yes	Yes	Yes	No	Moderate
Hehir et al. 1981 (rat; 1 hour)	Yes	Yes	Yes	No	Moderate
Hehir et al. 1981 (mouse; 1 hour)	Yes	Yes	Yes	No	Moderate
Mastromatteo et al. 1960 (mouse; 30 minutes)	Yes	Yes	Yes	No	Moderate
Mastromatteo et al. 1960 (guinea pig; 30 minutes)	Yes	Yes	Yes	No	Moderate
Patty et al. 1930 (guinea pig; up to 8 hours)	Yes	Yes	Yes	No	Moderate
Inhalation intermediate-duration exposure					
Hehir et al. 1981 (rat; 20 weeks)	Yes	Yes	Yes	No	Moderate
Inhalation chronic-duration exposure					
Viola 1970 (rat; 12 months)	Yes	Yes	Yes	No	Moderate
Viola et al. 1971 (rat; 12 months)	Yes	Yes	Yes	No	Moderate
Feron and Kroes 1979 (rat; 12 months)	Yes	Yes	Yes	No	Moderate
Outcome: Developmental effects					
Inhalation acute-duration exposure					
Thornton et al. 2002 (rat; GDs 6–19)	Yes	Yes	Yes	Yes	High
John et al. 1977, 1981 (rat; 10 days)	Yes	Yes	Yes	Yes	High
John et al. 1977, 1981 (mouse; 10 days)	Yes	Yes	Yes	Yes	High
John et al. 1977, 1981 (rabbit;	Yes	Yes	Yes	Yes	High

Table C-16. Presence of Key Features of Study Design for Vinyl Chloride—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
13 days)					
Ungvary et al. 1978 (rat; 7–9 days)	Yes	Yes	Yes	Yes	High
Inhalation intermediate-duration exposure					
Sal'nikova and Kotsovskaya 1980 (rat; 21 days)	Yes	Yes	Yes	Yes	High
Mirkova et al. 1978 (rat; 21 days)	Yes	Yes	Yes	Yes	High
Other noncancer (insulin resistance)					
Inhalation intermediate-duration exposure					
Chen et al. 2019 (mouse; 12 weeks)	Yes	Yes	Yes	Yes	High
Lang et al. 2018 (mouse; 12 weeks)	Yes	Yes	Yes	Yes	High
Wahlang et al. 2020 (mouse; 12 weeks)	Yes	No	Yes	Yes	Moderate

A summary of the initial confidence ratings for each outcome is presented in Table C-17. If individual studies for a particular outcome and study type had different study quality ratings, then the highest confidence rating for the group of studies was used to determine the initial confidence rating for the body of evidence; any exceptions were noted in Table C-17.

Table C-17. Initial Confidence Rating for Vinyl Chloride Health Effects Studies

	Initial study confidence	Initial confidence rating
Outcome: Hepatic effects		
Inhalation acute-duration exposure		
Animal studies		
Jaeger et al. 1974 (rat; 1, 5 days)	Low	High
John et al. 1977, 1981 (rat; 10 days)	High	
Mastromatteo et al. 1960 (rat; 30 minutes)	Moderate	
Reynolds et al. 1975a (rat; 1, 5 days)	Low	
Reynolds et al. 1975b (rat; 1 day)	Low	
John et al. 1977, 1981 (mouse; 10 days)	High	
Mastromatteo et al. 1960 (mouse; 30 minutes)	Moderate	
Mastromatteo et al. 1960 (guinea pig; 30 minutes)	Moderate	
John et al. 1977, 1981 (rabbit; 13 days)	High	
Ungvary et al. 1978 (rat; 7–9 days)	High	

Table C-17. Initial Confidence Rating for Vinyl Chloride Health Effects Studies

	Initial study confidence	Initial confidence rating
Hehir et al. 1981 (rat; 1 hour)	Moderate	
Inhalation intermediate-duration exposure		
Animal studies		
Bi et al. 1985 (rat; 3, 6 months)	High	High
Jia et al. 2022 (mice; 13 weeks)	High	
Lester et al. 1963 (rat; 19 days)	High	
Lester et al. 1963 (rat; 92 days)	High	
Liu et al. 2023 (mice; 12 weeks)	High	
Sokal et al. 1980 (rat; 10 months)	High	
Thornton et al. 2002 (rat; 2-generation)	High	
Torkelson et al. 1961 (rat; 6 months)	High	
Wisniewska-Knypl et al. 1980 (rat; 10 months)	High	
Chen et al. 2019 (mouse; 12 weeks)	High	
Lang et al. 2018 (mouse; 12 weeks)	High	
Lang et al. 2020 (mouse; 12 weeks)	High	
Schaffner 1978 (mouse; 6 months)	Low	
Sharma and Gehring 1979 (mouse; 2–8 weeks)	Moderate	
Wahlang et al. 2020 (mouse; 12 weeks)	Moderate	
Wang et al. 2019a (mouse; 16 weeks)	High	
Torkelson et al. 1961 (rabbit; 6 months)	Moderate	
Du et al. 1979 (rat; 2-4 weeks)	Moderate	
Inhalation chronic-duration exposure		
Human studies		
NIOSH 1977	Low	Moderate
Zhu et al. 2005a	Moderate	
Liss et al. 1985	Moderate	
Tamburro et al. 1984	Low	
Vihko et al. 1984	Very low	
Du et al. 1995	Low	
Cheng et al. 1999b	Low	
Ward et al. 2001	Moderate	
Du and Wang 1998	Moderate	
Mastrangelo et al. 2004	Moderate	
Maroni et al. 2003	Moderate	
Cave et al. 2010	Moderate	
Hsieh et al. 2007	Moderate	
Attarchi et al. 2007	Low	
Maroni and Fanetti 2006	Moderate	
Hsiao et al. 2004	Moderate	
Mundt et al. 2017	Moderate	
Fedeli et al. 2019a	Moderate	

Table C-17. Initial Confidence Rating for Vinyl Chloride Health Effects Studies

	Initial study confidence	Initial confidence rating
Wang et al. 2019b	Low	
Lee et al. 2020	Low	
Yuan et al. 2020		
Animal studies		
Bi et al. 1985 (rat; 12 months)	High	High
Oral chronic-duration exposure		
Animal studies		
Til et al. 1983 (rat; 149 weeks)	High	High
Feron et al. 1981 (rat; 2 years)	High	
Outcome: Immunological effects		
Inhalation acute-duration exposure		
Animal studies		
Mastromatteo et al. 1960 (guinea pig; 30 minutes)	Moderate	Moderate
Inhalation intermediate-duration exposure		
Animal studies		
Bi et al. 1985 (rat; 3, 6 months)	High	High
Sharma and Gehring 1979 (mouse; 2–8 weeks)	Moderate	
Sharma et al. 1980 (rabbit; 8 weeks)	High	
Sokal et al. 1980 (rat; 10 months)	High	
Inhalation chronic-duration exposure		
Human studies		
Cave et al. 2010	Low	Moderate
Fucic et al. 1995	Moderate	
Fucic et al. 1998	Moderate	
Wagnerova et al. 1988	Moderate	
Bogdanikowa and Zawilska 1984	Moderate	
Grainger et al. 1980	Moderate	
Black et al. 1983, 1986	Moderate	
Saad et al. 2017	Moderate	
Bencko et al. 1988	Moderate	
Outcome: Neurological effects		
Inhalation acute-duration exposure		
Human studies		
Patty et al. 1930	Very low	Moderate
Lester et al. 1963	Moderate	
Animal studies		
Jaeger et al. 1974 (rat; 1, 5 days)	Low	Moderate
Lester et al. 1963 (rat; 2 hours)	Low	
Mastromatteo et al. 1960 (rat; 30 minutes)	Moderate	
Hehir et al. 1981 (rat; 2 weeks)	Moderate	

Table C-17. Initial Confidence Rating for Vinyl Chloride Health Effects Studies

	Initial study confidence	Initial confidence rating
Hehir et al. 1981 (rat; 1 hour)	Moderate	
Hehir et al. 1981 (mouse; 1 hour)	Moderate	
Mastromatteo et al. 1960 (mouse; 30 minutes)	Moderate	
Mastromatteo et al. 1960 (guinea pig; 30 minutes)	Moderate	
Patty et al. 1930 (guinea pig; up to 8 hours)	Moderate	
Inhalation intermediate-duration exposure		
Animal studies		
Hehir et al. 1981 (rat; 20 weeks)	Moderate	Moderate
Inhalation chronic-duration exposure		
Human studies		
NIOSH 1977	Low	
Zhu et al. 2005a	Moderate	
Spirtas et al. 1975	Low	Moderate
Perticoni et al. 1986	Low	
Bove et al. 2014	Moderate	
Animal studies		
Viola 1970 (rat; 12 months)	Moderate	
Viola et al. 1971 (rat; 12 months)	Moderate	Moderate
Feron and Kroes 1979 (rat; 12 months)	Moderate	
Outcome: Developmental effects		
Inhalation acute-duration exposure		
Animal studies		
Thornton et al. 2002 (rat; GDs 6–19)	High	
John et al. 1977, 1981 (rat; 10 days)	High	
John et al. 1977, 1981 (mouse; 10 days)	High	High
John et al. 1977, 1981 (rabbit; 13 days)	High	
Ungvary et al. 1978 (rat; 7–9 days)	High	
Inhalation intermediate-duration exposure		
Human studies		
Swartz et al. 2015	Moderate	
Talbott et al. 2015	Moderate	Moderate
Ruckart et al. 2013	Moderate	
Animal studies		
Sal'nikova and Kotsovskaya 1980 (rat; 21 days)	High	High
Mirkova et al. 1978 (rat; 21 days)	High	
Inhalation chronic-duration exposure		
Human studies		
NIOSH 1977	Low	
Edmonds et al. 1975, 1978	Moderate	Moderate
Infante 1976	Moderate	
Rosenman et al. 1989	Moderate	

Table C-17. Initial Confidence Rating for Vinyl Chloride Health Effects Studies

	Initial study confidence	Initial confidence rating
Theriault et al. 1983	Moderate	
Infante et al. 1976a, 1976b	Low	
Bao et al. 1988	Moderate	
Outcome: Other noncancer (insulin resistance)		
Inhalation intermediate-duration exposure		
Animal studies		
Chen et al. 2019 (mouse; 12 weeks)	High	
Lang et al. 2018 (mouse; 12 weeks)	High	High
Wahlang et al. 2020 (mouse; 12 weeks)	Moderate	
Inhalation chronic-duration exposure		
Human studies		
Lee et al. 2020	Low	Moderate
Cave et al. 2010	Moderate	

C.6.2 Adjustment of the Confidence Rating

The initial confidence rating was then downgraded or upgraded depending on whether there were substantial issues that would decrease or increase confidence in the body of evidence. The nine properties of the body of evidence that were considered are listed below. The summaries of the assessment of the confidence in the body of evidence for hepatic, immunological, neurological, developmental, and other noncancer (insulin resistance) effects are presented in Table C-18. If the confidence ratings for a particular outcome were based on more than one type of human study, then the highest confidence rating was used for subsequent analyses. An overview of the confidence in the body of evidence for all health effects associated with vinyl chloride exposure is presented in Table C-19.

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

- **Risk of bias.** Evaluation of whether there is substantial risk of bias across most of the studies examining the outcome. This evaluation used the risk of bias tier groupings for individual studies examining a particular outcome (Tables C-8, C-9, and C-10). Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for risk of bias:
  - No downgrade if most studies are in the risk of bias first tier
  - Downgrade one confidence level if most studies are in the risk of bias second tier
  - Downgrade two confidence levels if most studies are in the risk of bias third tier

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

  - Downgrade one confidence level if there is variability across studies in the magnitude or direction of the effect
  - Downgrade two confidence levels if there is substantial variability across studies in the magnitude or direct of the effect

- **Indirectness.** Evaluation of four factors that can affect the applicability, generalizability, and relevance of the studies:
  - Relevance of the animal model to human health—unless otherwise indicated, studies in rats, mice, and other mammalian species are considered relevant to humans
  - Directness of the endpoints to the primary health outcome—examples of secondary outcomes or nonspecific outcomes include organ weight in the absence of histopathology or clinical chemistry findings in the absence of target tissue effects
  - Nature of the exposure in human studies and route of administration in animal studies—inhalation, oral, and dermal exposure routes are considered relevant unless there are compelling data to the contrary
  - Duration of treatment in animal studies and length of time between exposure and outcome assessment in animal and prospective human studies—this should be considered on an outcome-specific basis

  Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for indirectness:
  - No downgrade if none of the factors are considered indirect
  - Downgrade one confidence level if one of the factors is considered indirect
  - Downgrade two confidence levels if two or more of the factors are considered indirect

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

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

Table C-18. Adjustments to the Initial Confidence in the Body of Evidence

	Initial confidence	Adjustments to the initial confidence rating	Final confidence
Outcome: Hepatic			
Human studies	Moderate	+1 consistency	High
Animal studies	High	-1 inconsistency	Moderate
Outcome: Immunological			
Human studies	Moderate	-1 risk of bias, +1 consistency	Moderate
Animal studies	High	-1 inconsistency, -1 indirectness	Low
Outcome: Neurological			
Human Studies	Moderate	None	Moderate
Animal Studies	Moderate	None	Moderate
Outcome: Developmental			
Human studies	Moderate	-1 risk of bias	Low
Animal studies	High	None	High
Outcome: Other noncancer (insulin resistance)			
Human studies	Moderate	-1 indirectness	Low
Animal studies	High	-1 risk of bias	Moderate

Table C-19. Confidence in the Body of Evidence for Vinyl Chloride

	Confidence in body of evidence	
Outcome	Human studies	Animal studies
Hepatic	High	Moderate
Immunological	Moderate	Low
Neurological	Moderate	Moderate
Developmental	Low	High
Other Noncancer (Insulin resistance)	Low	Moderate

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 vinyl chloride, 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 vinyl chloride is presented in Table C-20.

Table C-20. Level of Evidence of Health Effects for Vinyl Chloride

Outcome	Confidence in body of evidence	Direction of health effect	Level of evidence for health effect
Human studies			
Hepatic	High	Health effect	High
Immunological	Moderate	Health effect	Moderate
Neurological	Moderate	Health effect	Moderate
Developmental	Low	No health effect	Inadequate
Other noncancer (insulin resistance)	Low	Health effect	Low
Animal studies			
Hepatic	Moderate	Health effect	Moderate
Immunological	Low	No health effect	Inadequate
Neurological	Moderate	Health effect	Moderate
Developmental	High	Health effect	High
Other noncancer (insulin resistance)	Moderate	No health effect	Inadequate

C.8 INTEGRATE EVIDENCE TO DEVELOP HAZARD IDENTIFICATION CONCLUSIONS

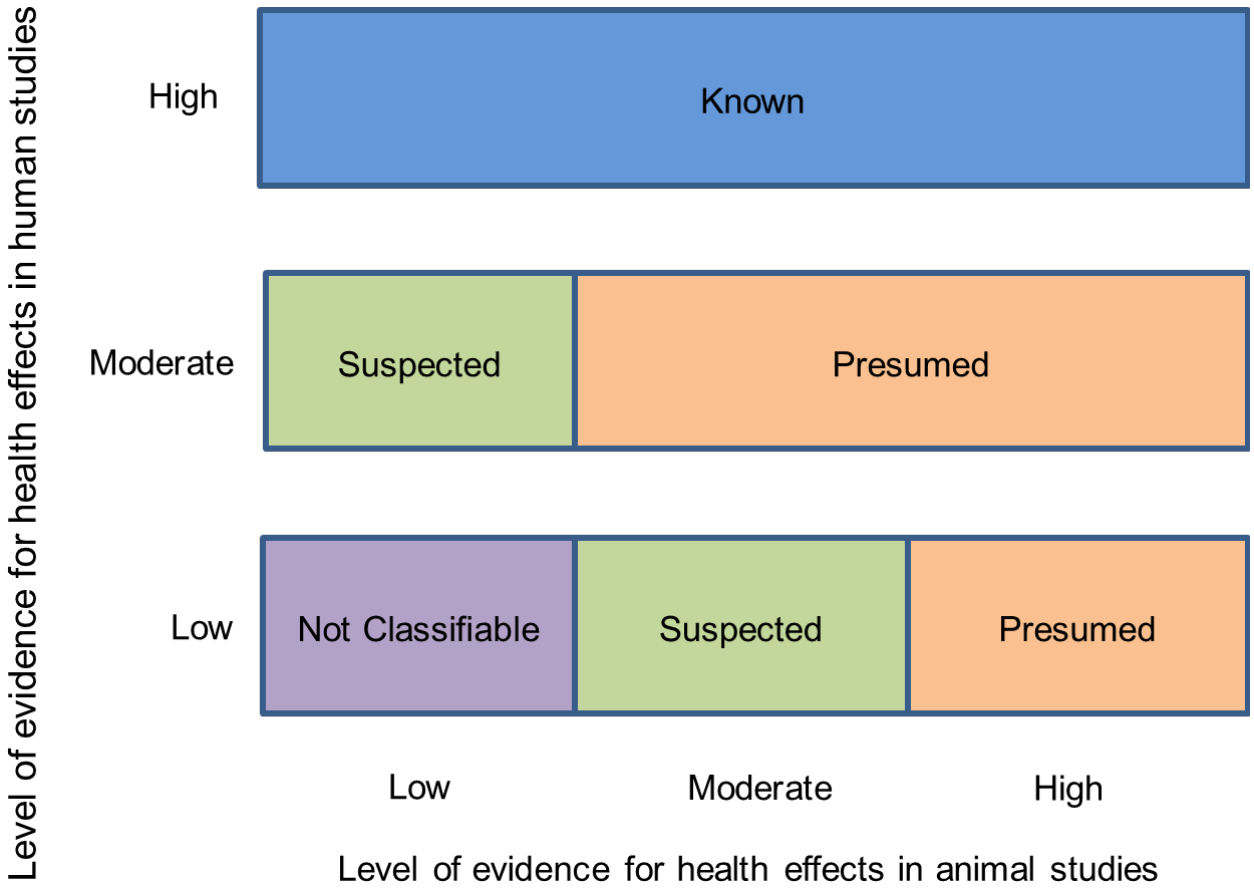
The final step involved the integration of the evidence streams for the human studies and animal studies to allow for a determination of hazard identification conclusions. For health effects, there were four hazard identification conclusion categories:

- **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 vinyl chloride are listed below and summarized in Table C-21.

Presumed Health Effects

- Hepatic
  - High level of evidence of hepatic effects in humans based on fibrosis, cirrhosis, and steatosis observed in vinyl chloride workers (Cave et al. 2010; Du and Wang 1998; Fedeli et al. 2019a; Hsiao et al. 2004; Hsieh et al. 2007; Maroni et al. 2003; Mastrangelo et al. 2004; Mundt et al. 2017; Ward et al. 2001; Yuan et al. 2020).
  - Moderate evidence level in animals including increased liver weight and histopathological liver lesions in rats and mice following inhalation (Bi et al. 1985; Jia et al. 2022; Lester et al. 1963; Sokal et al. 1980; Thornton et al. 2002; Torkelson et al. 1961; Wisniewska-Knypl et al. 1980) and oral exposure (Feron et al. 1981; Til et al. 1983, 1991).
- Neurological
  - Moderate level of evidence in humans based on neurological symptoms reported in human studies (Lester et al. 1963; NIOSH 1977; Patty et al. 1930; Spirtas et al. 1975; Zhu et al. 2005a) and a single report of peripheral neuropathy (Perticoni et al. 1986).
  - Moderate level of evidence in animals based on clinical signs in multiple acute-duration inhalation studies (Hehir et al. 1981; Jaeger et al. 1974; Lester et al. 1963; Mastromatteo et al. 1960; Patty et al. 1930)

Suspected Health Effects

- Immunological
  - Moderate level of evidence in humans based on occupational worker studies demonstrating an increase in circulating immune complexes, immunoglobulins, complement factors, and levels of inflammatory cytokines (Bencko et al. 1988, Bogdanikowa and Zawilska 1984; Cave et al. 2010; Grainger et al. 1980; Saad et al. 2017; Wagnerova et al. 1988; Ward 1976).
  - Inadequate evidence in animals due to limited information available on increased spleen weight in rats (Bi et al. 1985; Sokal et al. 1980) and a splenic lymphocyte proliferation assay in mice and rabbits (Sharma and Gehring 1979, Sharma et al. 1980)
- Developmental
  - Inadequate evidence in humans due to the absence of demonstrated developmental effects in a small number of ecological and case-control studies of birth defects (Edmonds et al. 1978; Infante 1976; Infante et al. 1976a, 1976b; NIOSH 1977; Rosenman et al. 1989; Ruckart et al. 2013; Swartz et al. 2015; Talbott et al. 2015; Theriault et al. 1983).
  - High level of evidence in animals based on developmental effects occurring at low concentrations in inhalation studies (John et al. 1977, 1981).

Not Classifiable

- Other noncancer (insulin resistance)
  - Low level of evidence level in humans based on two epidemiology studies with serum markers of increased insulin resistance (Cave et al. 2010; Lee et al. 2020).
  - Several intermediate-duration inhalation studies using glucose, insulin, and pyruvate tolerance tests (Chen et al. 2019; Lang et al. 2018) and measures of fasting blood glucose and glycogen storage (Wahlang et al. 2020). These studies used a single low concentration of vinyl chloride (0.85 ppm) and did not evaluate effects at higher concentrations.

Table C-21. Hazard Identification Conclusions for Vinyl Chloride

Outcome	Hazard identification
Hepatic	Presumed health effect
Immunological	Suspected health effect
Neurological	Presumed health effect
Developmental	Suspected health effect
Other noncancer (insulin resistance)	Not classifiable

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.

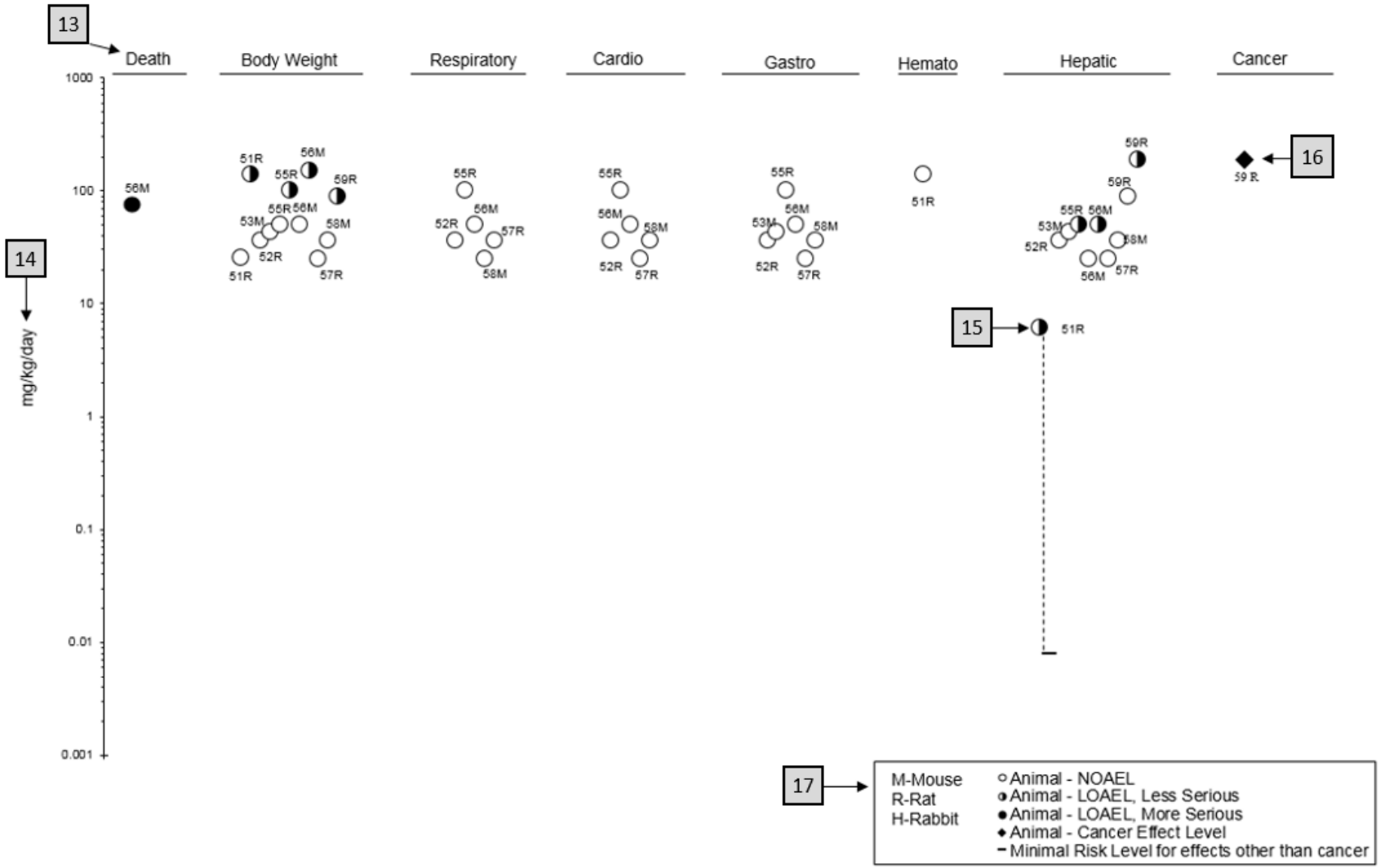
(17) Key to LSE figure. The key provides the abbreviations and symbols used in the figure.

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

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

(11)
[a]The number corresponds to entries in Figure 2-x.
[b]Used to derive an acute-duration oral minimal risk level (MRL) of 0.1 mg/kg/day based on the $BMDL_{05}$ of 10 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).
[c]Used to derive a chronic-duration oral MRL of 0.008 mg/kg/day based on the $BMDL_{10}$ of 0.78 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

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



APPENDIX E. QUICK REFERENCE FOR HEALTH CARE PROVIDERS

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

Primary Chapters/Sections of Interest

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

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

Pediatrics:

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

ATSDR Information Center

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

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

Clinician Briefs and Overview discuss health effects and approaches to patient management in a brief/factsheet style. They are narrated PowerPoint presentations with Continuing Education credit available (see https://www.atsdr.cdc.gov/emes/health_professionals/clinician-briefs-overviews.html).

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

Fact Sheets (ToxFAQs™) provide answers to frequently asked questions about toxic substances (see https://www.atsdr.cdc.gov/toxfaqs/Index.asp).

Other Agencies and Organizations

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

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 395 E Street, S.W., Suite 9200, Patriots Plaza Building, Washington, DC 20201 • Phone: 202-245-0625 or 1-800-CDC-INFO (800-232-4636) • Web Page: https://www.cdc.gov/niosh/.

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

Clinical Resources (Publicly Available Information)

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

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

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

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

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

APPENDIX F. GLOSSARY

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

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

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

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

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

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

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

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

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

Carcinogen—A chemical capable of inducing cancer.

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

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

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

Ceiling Value—A concentration that must not be exceeded.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Metabolism—Process in which chemical substances are 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
FEMA	Federal Emergency Management Agency
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
JECFA	Joint FAO/WHO Expert Committee on Food Additives
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 level-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