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 acetate
CAS Numbers: 108-05-4
Date: January 2025
Profile Status: Final
Route: Inhalation
Duration: Acute
MRL 1 ppm (3.5 mg/m^3)
Critical Effect: Nasal lesions
Reference: Bogdanffy et al. 1997
Point of Departure: NOAEL of 199.6 ppm ($NOAEL_{HEC}$ of 29.1 ppm)
Uncertainty Factor: 30
LSE Graph Key: 2
Species: Rat

MRL Summary: An acute-duration inhalation MRL of 1 ppm was derived for vinyl acetate based on nasal lesions in male rats exposed to concentrations ≥598.5 ppm for 6 hours/day for 5 days; a NOAEL of 199.6 ppm was identified (Bogdanffy et al. 1997). The MRL is based on a $NOAEL_{HEC}$ of 29.1 ppm derived using the PBPK model by Bogdanffy et al. (1999). The $NOAEL_{HEC}$ was divided by a total uncertainty factor of 30 (3 for extrapolation from animals to humans after dosimetric adjustment and 10 for human variability).

Selection of the Critical Effect: Available acute-duration inhalation studies report vinyl acetate-related effects at LOAELs in the range of 598.5–1,007.3 ppm, including respiratory effects in rats and mice and body weight and developmental effects in rats (Table A-1). The lowest identified LOAEL is for damage to the upper respiratory tract in rats, with 100% incidence of nasal lesions in rats exposed to ≥598.5 ppm for 6 hours/day for 1 or 5 days (Bogdanffy et al. 1997). While this study did not look at a comprehensive set of endpoints, data from intermediate- and chronic-duration studies, as well as mechanistic data, support that the nasal cavity is the most sensitive target following inhalation exposure (see ***Other Additional Studies of Pertinent Information that Lend Support to this MRL*** below). Based on these data, the nasal cavity lesions are selected as the critical effect.

Selection of the Principal Study: Bogdanffy et al. (1997) was selected as the principal study because it provided the lowest point of departure (POD) for the critical effect (nasal cavity lesions). The 5-day study was selected over the 1-day study since observed severity of nasal lesions increased over the 5-day exposure period.

Table A-1. Select NOAEL and LOAEL Values in Animals Following Acute-Duration Inhalation Exposure to Vinyl Acetate

Species	Duration	NOAEL/LOAEL (ppm) NOAEL	LOAEL	Effect	Reference
Respiratory					
Rat (SD)	6 hours (WB)	199.6	598.5	Minimal-to-moderate nasal cavity lesions, cell proliferation in nasal epithelium	Bogdanffy et al. 1997
Rat (SD)	5 days 6 hours/day (WB)	199.6	598.5	Mild-to-severe nasal cavity lesions[a]	Bogdanffy et al. 1997
Rat (SD)	6 hours (WB)	201.6	604.8	Slight-to-marked degeneration/ necrosis of nasal tissue (primarily proximal olfactory epithelium)	Krieger et al. 2020
Rat (SD)	5 days 6 hours/day (WB)	201.6	604.8	Slight-to-moderate atrophy and necrosis of nasal tissue	Krieger et al. 2020
Mouse (NS)	4 hours (WB)	410	820	Labored breathing	Union Carbide 1973
Body weight					
Rat (SD)	10 days GDs 6–15 6 hours/day (WB)	197.5	1,005	9–12% decrease in maternal body weight on GDs 10–20	Hurtt et al. 1995; Hazleton 1980d
Rat (SD)	5 days 6 hours/day (WB)	598.5	1,007.3	14% decrease in body weight	Bogdanffy et al. 1997
Developmental					
Rat (SD)	10 days GDs 6–15 6 hours/day (WB)	197.5	1,005	28% decrease in fetal weight; 12% decrease in crown-to-rump-length, delayed ossification; associated with maternal body weight decreases	Hurtt et al. 1995; Hazleton 1980d

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

GD = gestation day; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; NS = not specified; SD = Sprague-Dawley; (WB) = whole-body exposure

Summary of the Principal Study:

Bogdanffy MS, Gladnick NL, Kegelman T, et al. 1997. Four-week inhalation cell proliferation study of the effects of vinyl acetate on rat nasal epithelium. Inhal Toxicol 9(4):331-350. http://doi.org/10.1080/089583797198178.

Groups of male Sprague-Dawley (Crl:CD BR) rats (5/group) were exposed to 0, 50, 200, 600, or 1,000 ppm for 5 consecutive days (6 hours/day); analytical concentrations (± standard error [SE]) were 0±0, 50.8±0.7, 199.6±5.3, 598.5±6.4, and 1,007.3±11.0 ppm, respectively. Rats were observed for

clinical signs and weighed 3 times/week. Sixteen hours after exposure, rats were injected with bromodeoxyuridine (BrdU) to assess cell proliferation and sacrificed 2 hours later. Respiratory tract tissues were examined for gross alterations, and nasal cavities were dissected and cut into five cross sections for histopathological analysis. Immunocytochemistry was performed for BrdU analysis of Level 2, the region with the most observed damage.

Body weights were statistically significantly decreased by 14% on day 5. No gross lesions were observed. Olfactory epithelium regenerative hyperplasia was observed in Levels 2, 3, and 5 in all rats at 598.5 and 1,007.3 ppm and 4/5 and 5/5 rats in Level 4. The most severe lesions were observed in the second and third levels (mild to severe). Increased incidence of minimal degeneration/necrosis of the olfactory epithelium were also observed in Levels 4 and 5. Incidence and severity of respiratory epithelium lesions were low across all groups. No significant changes in cell proliferation were observed.

Selection of the Point of Departure for the MRL: Bogdanffy et al. (1997) identified a NOAEL of 199.6 ppm for nasal lesions in rats following exposure to vinyl acetate for 5 days (6 hours/day). The available data in Bogdanffy et al. (1997) are not amenable to benchmark dose (BMD) modeling because incidences go from 0% at the NOAEL to 100% at the LOAEL for the most sensitive nasal lesions. Therefore, the NOAEL of 199.6 ppm is selected as the POD.

Adjustment for Intermittent Exposure: Exposure over time is accounted for in the PBPK model (HEC simulations are for continuous exposure, see details below); therefore, no additional duration adjustment is needed.

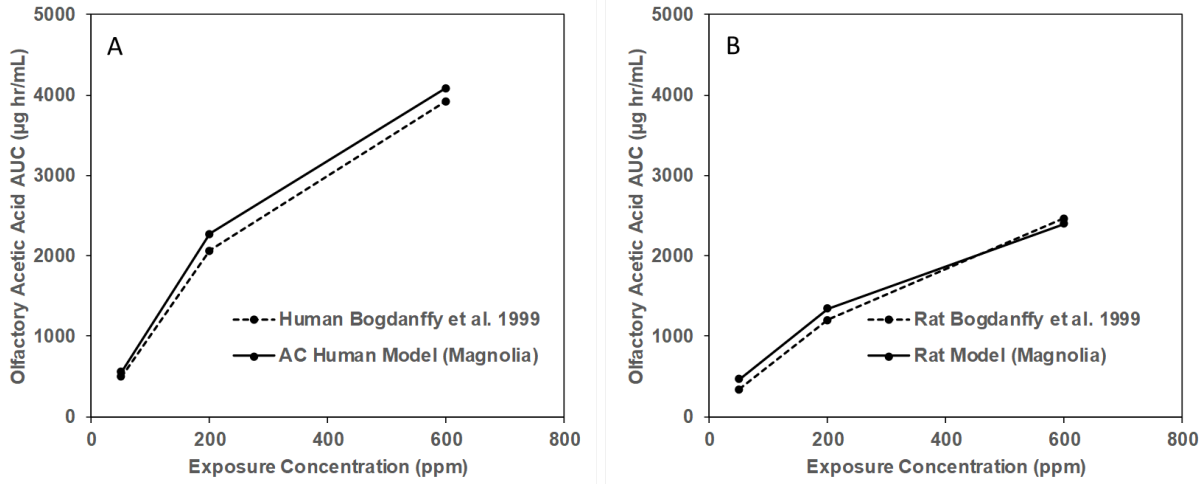
Conversion to Human Equivalent Concentration: A PBPK model (Bogdanffy et al. 1999; Hinderliter et al. 2005) was used for rat-to-human dosimetry extrapolation in deriving the acute-duration inhalation MRL for vinyl acetate. A description of the model can be found in Section 3.1.5 of the profile. This model was selected for dosimetry extrapolation because it has been shown to reliably simulate the kinetics of vinyl acetate uptake and metabolism in the nasal cavity of rats and humans (Bogdanffy et al. 1999; Hinderliter et al. 2005). Important features of vinyl acetate-induced nasal lesions and vinyl acetate kinetics that are relevant to interspecies dosimetry extrapolation include: (1) regional gradients of nasal lesions to the olfactory epithelium, with more severe lesions occurring in the anterior regions (Bogdanffy et al. 1994a, 1997); (2) nearly 100% first-pass extraction of vinyl acetate from inspired air at low concentrations which saturates at higher concentrations (Plowchalk et al. 1997); and (3) intracellular acidification resulting from metabolism of vinyl acetate to acetic acid (Bogdanffy 2002). In the derivation of inhalation MRLs, the PBPK model was used to simulate the acetic acid dose to the surficial layers of the olfactory epithelium in the anterior region of the rat and human nasal cavities. The dose metric used for interspecies dosimetry extrapolation was the area under the curve (AUC) for the acetic acid concentration. The AUC was selected based on evidence that the nature and severity of the nasal lesions in rats change with increasing duration of exposure to vinyl acetate (Bogdanffy et al. 1997; see further discussion of the selection of the dose metric below).

Implementation of the Bogdanffy et al. (1999; Hinderliter et al. 2005) Model

Source and verification of model code. Code for implementing the human vinyl acetate model in Advance Continuous Simulation Language (ASCL) was reported in Hinderliter et al. (2005). For simulations run to support derivation of MRLs, the ACSL code was migrated to Magnolia (v1.3.9 beta). Performance of the Magnolia code was confirmed by comparing predictions with those from the ACSL code reported in Table 2 of Bogdanffy et al. (1999). Examples of these comparisons are presented in Figure A-1, Panel A. The code for the rat model described in Bogdanffy et al. (1999) has not been published; however, the human model was revised to recreate the rat model via addition of a second (posterior) olfactory compartment that is present in rats, but not in humans. Parameter values for the rat

model were based on those reported in Bogdanffy et al. (1999) and Plowchalk et al. (1997). Performance of the Magnolia code for the rat model was confirmed by comparing predictions with those from the ACSL model reported in Table 2 of Bogdanffy et al. (1999). Examples of these comparisons are presented in Figure A-1, Panel B. Figure A-1 shows the non-linear relationship between the vinyl acetate exposure concentration and the AUC for the acetic acid concentration in olfactory tissue that results from capacity limited metabolism of vinyl acetate (see Section 3.1.3 of the profile).

Figure A-1. Area Under the Curve for Acetic Acid Concentration in Human (A) and Rat (B) Olfactory Epithelium Predicted by the Physiologically Based Pharmacokinetic (PBPK) Model*



*Shown are predictions from the ACSL model reported in Table 2 of Bogdanffy et al. (1999) and from the Magnolia version of the model. The simulations are of a continuous 60-hour exposure to vinyl acetate and an inspiratory flow of 197 mg/minute for rats and 7.5 L/minute for humans.

Revisions to the rat model. In addition to including the second olfactory compartment in the rat model, parameters were introduced into the rat model to simulate body weight-dependence of the nasal cavity air flow (model variable *qin*). The Bogdanffy et al. (1999) model parameter value for nasal air flow was the air inspiration rate for a 0.25 kg body weight male rat (197 mL/minute; 11,820 mL/hour). However, in deriving MRLs, simulations were needed for rats having different body weights. The inspiration rate (mL/hour) in rats is dependent on body weight. Therefore, body weight dependence of nasal cavity air flow was simulated in the Magnolia code using an allometric relationship derived for inspiration rate in the male Fischer rat (EPA 1988):

$$qin = 0.80 \cdot bw^{0.8206}$$

where *qin* is the modal parameter for nasal air flow (m^3/day) and *bw* is body weight (kg). The conversion to mL/hour for use in the model is 1,000,000/24. This yields a value for *qin* of 0.271 m^3/day and 11,279 mL/hour for a 0.25-kg rat, which is 4.5% lower than the value used in Bogdanffy et al. (1999).

Uncertainties regarding relationship between body weight and size of nasal tissue compartments. In simulations run to support derivation of inhalation MRLs, dimensions of nasal cavity tissue compartments (surface area, depth) in the rat were assumed to be independent of body weight over the range of body weights simulated in derivation of MRLs (0.2–0.6 kg). This assumption precluded having to develop a model for nasal cavity tissue growth. The assumption appears to be reasonable for simulating rats having body weights >0.25 kg. Viscerocranial growth (nose length) in *hooded* laboratory rats was shown to be

complete by age 80 days postconception (~58 days postpartum), with relatively little growth beyond age 50 days (see Figure 3 of Hughes et al. 1978). At age 50 days (postpartum), the average body weight of male and female Sprague-Dawley is approximately 0.26 kg (Timchalk et al. 2007), which is close to the value assumed in the Bogdanffy et al. (1997) model (0.25 kg). The Hughes et al. (1978) observations are for viscerocranial length, and do not necessarily reflect growth of the nasal cavity tissues; it is possible that surface area or depth of nasal cavity tissues could change independently of viscerocranial length. The assumption of independence of nasal cavity dimensions and body weight introduces some uncertainty into predictions of nasal olfactory tissue doses, particularly in simulations of rats having body weights <0.25 kg (e.g., rat body weights during the first two weeks of exposure in the Bogdanffy et al. 1997 inhalation toxicity studies).

Simulation of olfactory tissue dosimetry in derivation of MRLs. The dose metric used in dosimetry extrapolation was the AUC for the acetic acid concentration in the surficial layers of the anterior olfactory epithelium. This dose metric was selected for the following reasons:

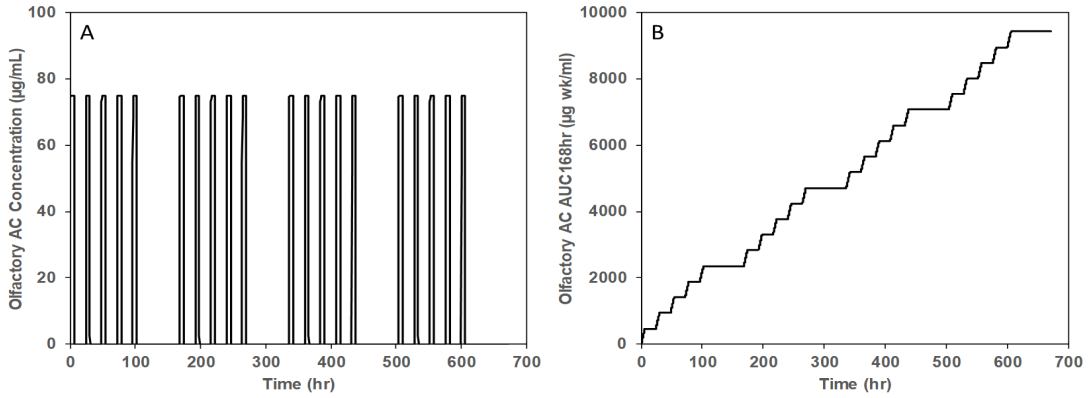
1. Acetic acid was selected because it is considered to be crucial in the mode of action of vinyl acetate. The mode of action is thought to be intracellular acidification resulting from metabolism of vinyl acetate to acetic acid (Bogdanffy 2002).
2. The AUC for acetic acid concentration was selected based on evidence that the severity of lesions in the olfactory epithelium of rats exposed to vinyl acetate is affected by exposure concentration and duration (Bogdanffy et al. 1994a, 1997). Therefore, a cumulative dose metric was considered to be a more appropriate internal dose metric for olfactory tissue than a mean or peak tissue concentration. The PBPK model predicts a steady state acetic acid concentration in olfactory tissue after 1 hour of exposure. As a result, the predicted olfactory concentration is independent of exposure duration for exposures >1 hour, while the AUC increases with increasing exposure duration.
3. The anterior olfactory tissue compartment was selected because it is predicted to receive the highest acetic acid doses during inhalation as a result of anterior-to-posterior air flow and clearance of vinyl acetate and metabolites along the air pathway. This pattern of internal dose is consistent with observations of regional gradients of lesions to the olfactory epithelium, with more severe lesions occurring in the anterior regions (Bogdanffy et al. 1994a, 1997).
4. The surficial region of the rat olfactory epithelium was selected because it is predicted to receive the highest tissue dose as a result of diffusive clearance and metabolism of acetic acid in the surficial layer which limits the concentration experienced by irrepressibly deeper layers (Bogdanffy et al. 1999).

Due to the complexity of the PBPK model to estimate the HEC value, it is impractical to list all the equations and parameters used in the simulations. ATSDR can provide the Magnolia source code and parameter values (based on Bogdanffy et al. 1999 and Plowchalk et al. 1997) upon request. An example of a simulation of the acetic acid concentration in the surficial layer of olfactory epithelium in rats exposed to vinyl acetate, 6 hours/day, 5 days/week for 4 weeks (Bogdanffy et al. 1997) is presented in Figure A-2 (Panel A). The model predicts two patterns of periodicity in the olfactory tissue concentration during this toxicity study. The first pattern appears daily with the attainment of steady state and complete clearance following cessation of each daily exposure. This daily pattern is repeated during each week of exposure (168 hours, inclusive of exposed plus unexposed hours during each weekly interval). The AUC for the acetic acid concentration shows a corresponding pattern of step increases in the AUC during each week of exposure (Figure A-2, Panel B). Because of the complete clearance of acetic acid between exposures, there is no accumulation of acetic acid with increasing exposure duration. As a result, the AUC for durations of more than 1 week ($AUC_{x\ wks}$) at the same exposure frequency (6 hours/day, 5 day/week) is predicted by the AUC for the first week (AUC_{168hr}) times the number of weeks:

$$AUC_{x\ wks} = AUC_{168\ hr} \cdot x$$

This equation indicates that, for exposures that have durations of multiple weeks, the number of weeks included in the calculation of the AUC will transform the dose axis of the dose-response relationship without changing its shape on the response axis. Therefore, the AUC_{168hr} can be used as the dose-response metric in continuous-exposure dosimetry extrapolation for studies of any duration in which the exposure frequency was 6 hours/day, 5 days/week, including a single-week (5-day) study (Bogdanffy et al. 1994a, 1997).

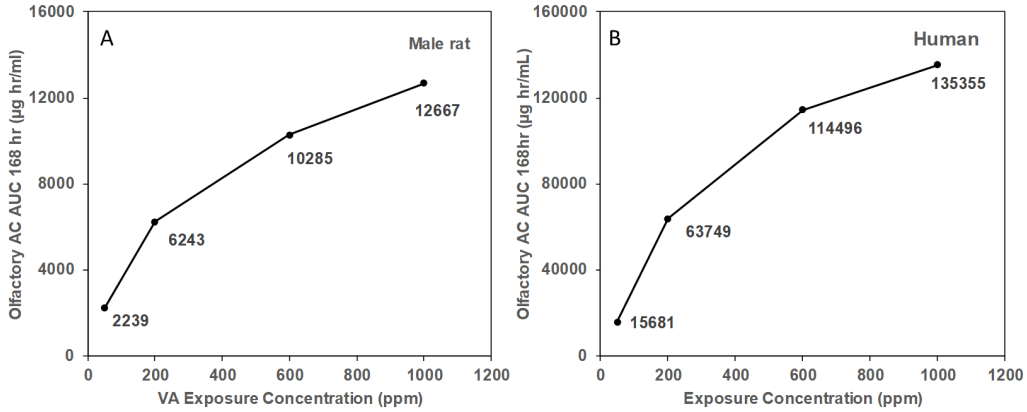
Figure A-2. Concentration (A) and AUC_{168hr} (B) for Acetic Acid (AC) in Olfactory Epithelium for Rats Predicted by the Physiologically Based Pharmacokinetic Model*



*The simulations are of 4 weeks of exposure to 50 ppm vinyl acetate for 6 hours/day, 5 days/week (Bogdanffy et al. 1997).

Figure A-3 (Panel A) shows the AUC_{168hr} predicted for rats exposed 6 hours/day, 5 days/week in the Bogdanffy et al. (1997) 4-week toxicity study. Figure A-3 (Panel B) shows the corresponding AUC_{168hr} predicted for humans exposed continuously to the same concentrations of vinyl acetate based on the PBPK model developed by Bogdanffy et al. (1999; Hinderliter et al. 2005). Using this model, the human is predicted to experience a 10-fold higher AUC for acetic acid concentration in olfactory tissue than the rat. This prediction applies only to exposures that occur when ventilation is restricted to nasal breathing and reflects the higher ratio of the nasal passage surface area to ventilation volume in the rat compared to the adult human. The Bogdanffy et al. (1997) model cannot be used to predict dosimetry in infants or children without reevaluating all parameters and assigning values (e.g., ventilation rate) that represent specific pre-adult life stages. It is also noted that this model does not account for situations in which nasal exposure would be lower when ventilation in the human occurs from a mix of nasal and oral breathing (e.g., during moderate to heavy exercise or in people who habitually breathe through their mouth) (ICRP 1994). This introduces some uncertainty in animal-to-human extrapolations since rodents are obligate nasal breathers (EPA 1994).

Figure A-3. AUC_{168hr} for Acetic Acid (AC) in Olfactory Epithelium for Rats (A) and Humans (B) Predicted by the Physiologically Based Pharmacokinetic Model*



*The simulations are of 4 weeks of exposure for 6 hours/day, 5 days/week in rats (Bogdanffy et al. 1997) and continuous exposure in humans.

HECs that are pharmacokinetically equivalent to PODs (e.g., AUC_{168hr} POD) were computed by reverse dosimetry simulations using the human PBPK model. In these simulations, the human model was run over a range of vinyl acetate exposure concentrations to determine the exposure concentration that corresponded to the AUC_{168hr} POD. The study-specific parameters utilized in the PBPK model to calculate a $NOAEL_{HEC}$ of 29.1 ppm for the selected POD are shown in Table A-2. As previously indicated, all model parameters were based on values reported by Bogdanffy et al. (1999) and Plowchalk et al. (1997), with the exception of body weights, which were based on TWA body weights calculated for the principal study.

Table A-2. HECs Corresponding to the Rat POD Selected for Acute-Duration Inhalation MRL for Vinyl Acetate

Study	Exposure (ppm)	Duration and frequency	POD basis	POD metric	POD (hour µg/mL)	HEC[a] (ppm)
Bogdanffy et al. (1997)	0, 50.8, 199.6, 598.5, 1,007.3	5 days 6 hours/day	NOAEL (199.6 ppm)	$AUC_{168\ hr}$	6,175	29.1

[a]Calculated for continuous human exposure.

AUC = area under the curve for acetic acid concentration in olfactory epithelium; HEC = human equivalent exposure concentration; MRL = Minimal Risk Level; NOAEL = no-observed adverse effect level; POD = dose-response point of departure

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

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

$$MRL = \frac{NOAEL_{HEC}}{UFs} = \frac{29.1\ ppm}{30} = 1\ ppm$$

Other Additional Studies of Pertinent Information that Lend Support to this MRL: Limited evidence from humans has shown that the respiratory tract is a sensitive target of acute-duration vinyl acetate exposure, with irritation of throat mucous membranes from acute-duration exposure levels as low as 4 ppm and persistent irritation at 74 ppm (Deese and Joyner 1969; Union Carbide 1973). The intermediate- and chronic-duration databases confirm that the respiratory system, particularly the extrathoracic region, is the most sensitive target of toxicity following inhalation exposure to vinyl acetate. Nasal lesions are observed in rats following intermediate-duration exposure to ≥598.5 ppm (Bogdanffy et al. 1997; Krieger et al. 2020) and in rats and mice following chronic-duration exposure to ≥200.5 ppm (Bogdanffy et al. 1994a; Hazleton 1988). Lower respiratory tract lesions are also seen in rats and mice following intermediate-duration exposure to 998.9 ppm (Hazleton 1980b, 1980c) and mice following chronic-duration exposure to ≥200.5 ppm (Bogdanffy et al. 1994a; Hazleton 1988). In acute-duration inhalation lethality studies, deaths were attributed to lung damage in rats, mice, guinea pigs, and rabbits (Union Carbide 1973). Mechanistic data predict portal-of-entry effects (i.e., respiratory tract lesions) based on rapid hydrolysis of vinyl acetate into acetaldehyde and acetic acid following contact with mucosal surfaces, resulting in irritation due to tissue acidification (Bogdanffy et al. 1999, 2001, 2004; Slikker et al. 2004).

Agency Contacts (Chemical Managers): Rae T. Benedict

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Vinyl acetate
CAS Numbers: 108-05-4
Date: January 2025
Profile Status: Final
Route: Inhalation
Duration: Intermediate
MRL 0.7 ppm (2.5 mg/m^3)
Critical Effect: Nasal lesions
Reference: Bogdanffy et al. 1997
Point of Departure: NOAEL of 199.6 ppm ($NOAEL_{HEC}$ of 21.6 ppm)
Uncertainty Factor: 30
LSE Graph Key: 11
Species: Rat

MRL Summary: An intermediate-duration inhalation MRL of 0.7 ppm was derived for vinyl acetate based on nasal lesions in male rats exposed to concentrations ≥598.5 ppm for 4 weeks (6 hours/day, 5 days/week); a NOAEL of 199.6 ppm was identified (Bogdanffy et al. 1997). The MRL is based on a $NOAEL_{HEC}$ of 21.6 ppm derived using the PBPK model by Bogdanffy et al. (1999). The $NOAEL_{HEC}$ was divided by a total uncertainty factor of 30 (3 for extrapolation from animals to humans after dosimetric adjustment and 10 for human variability).

Selection of the Critical Effect: Available intermediate-duration inhalation studies for vinyl acetate consistently report exposure-related respiratory and body weight effects in rats and mice at LOAELs in the range of 497.6–998.9 and 998.9 –1,007.3 ppm, respectively (Table A-3). One study in rats reported neurological effects (degeneration/atrophy of olfactory nerve bundles) at 598.8 ppm; however, this effect was not noted in other studies in rats and mice (Table A-3). Respiratory effects are considered the most sensitive effect, with clinical signs (intermittent respiratory distress) at ≥497.6 ppm, nasal lesions at ≥598.5 ppm, and lower respiratory tract lesions at 998.9 ppm. While intermittent respiratory distress is reported at a slightly lower administered concentration, compared to nasal lesions, confidence in this endpoint is low due to intermittent nature (decreasing over the course of treatment), lack of incidence data, lack of concurrent histopathological evaluation, and lack of observation in chronic-duration studies. In contrast, the upper respiratory system (nasal cavity) is a clear target of vinyl acetate toxicity following acute-, intermediate-, and chronic-duration inhalation exposure. Therefore, nasal cavity lesions were selected as the critical effect for derivation of the intermediate-duration inhalation MRL.

Selection of the Principal Study: The 4-week rat study (Bogdanffy et al. 1997) was selected as the principal study because it provides the lowest LOAEL for the critical effect (nasal lesions) following intermediate-duration inhalation exposure. While the NOAEL for nasal lesions is similar in rats and mice, the rat is more sensitive to nasal toxicity, showing higher incidence (100%) and more severe effects (atrophy, hyperplasia) at the LOAEL of 598.5 ppm compared to mice (70% incidence of rhinitis at the LOAEL of 998.9 ppm). Additionally, a PBPK model estimating olfactory epithelium exposure metrics in rats and humans is available (Bogdanffy et al. 1999; Hinderliter et al. 2005). Use of a PBPK model will result in a higher confidence in the HEC calculation in rats, compared to use of a default HEC concentration for mice based on the regional gas dose ratio (RGDR) recommended by the EPA (1994).

Table A-3. Select NOAEL and LOAEL Values in Animals Following Intermediate-Duration Inhalation Exposure to Vinyl Acetate

Species	Duration	NOAEL/LOAEL (ppm) NOAEL	LOAEL	Effect	Reference
Respiratory					
Rat (SD)	4 weeks 5 days/week 6 hours/day (WB)	150.5	497.6	Intermittent respiratory distress (histology not evaluated)	Hazleton 1979c
Mouse (CD-1)	4 weeks 5 days/week 6 hours/day (WB)	150.5	497.6	Intermittent respiratory distress (histology not evaluated)	Hazleton 1979b
Rat (SD)	4 weeks 5 days/week 6 hours/day (WB)	199.6	598.5	Nasal lesions[a]	Bogdanffy et al. 1997
Rat (SD)	4 weeks 5 days/week 6 hours/day (WB)	201.6	604.8	Slight-to-marked atrophy of the olfactory epithelium; minimal-to-mild transitional hyperplasia and slight respiratory metaplasia of nasal tissue	Krieger et al. 2020
Rat (SD)	13 weeks 5 days/week 6 hours/day (WB)	201.6	604.8	Slight-to-marked atrophy and necrosis/degeneration of the olfactory epithelium; slight respiratory metaplasia of nasal tissue	Krieger et al. 2020
Rat (SD)	3 months 5 days/week 6 hours/day (WB)	199.9	998.9	Intermittent respiratory distress, focal histiocytic alveolitis	Hazleton 1980c
Mouse (CD-1)	3 months 5 days/week 6 hours/day (WB)	199.8	998.9	Intermittent respiratory distress, focal and diffuse rhinitis, mild multifocal bronchitis, hyperplasia, and metaplasia of the trachea.	Hazleton 1980b
Body weight					
Rat (SD)	3 months 5 days/week 6 hours/day (WB)	199.9	998.9	18–22% decrease in body weight	Hazleton 1980c
Mouse (CD-1)	3 months 5 days/week 6 hours/day (WB)	199.8	998.9	20–24% decrease in body weight	Hazleton 1980b
Mouse (CD-1)	4 weeks 5 days/week 6 hours/day (WB)	497.6	1,000.2	16% decrease in body weight in males	Hazleton 1979b

Table A-3. Select NOAEL and LOAEL Values in Animals Following Intermediate-Duration Inhalation Exposure to Vinyl Acetate

Species	Duration	NOAEL/LOAEL (ppm) NOAEL	LOAEL	Effect	Reference
Rat (SD)	4 weeks 5 days/week 6 hours/day (WB)	598.5	1,007.3	>10% decrease in body weight	Bogdanffy et al. 1997
Neurological effects					
Rat (SD)	4 weeks 5 days/week 6 hours/day (WB)	199.6	598.5	Degeneration/atrophy of olfactory nerve bundle	Bogdanffy et al. 1997
Rat (SD)	3 months 5 days/week 6 hours/day (WB)	998.9	ND	No adverse effects	Hazleton 1980c
Mouse (CD-1)	3 months 5 days/week 6 hours/day (WB)	998.9	ND	No adverse effects	Hazleton 1980b

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

LOAEL = lowest-observed-adverse-effect level; ND = not determined; NOAEL = no-observed-adverse-effect level; SD = Sprague-Dawley; (WB) = whole-body exposure

Summary of the Principal Study:

Bogdanffy MS, Gladnick NL, Kegelman T, et al. 1997. Four-week inhalation cell proliferation study of the effects of vinyl acetate on rat nasal epithelium. Inhal Toxicol 9(4):331-350. http://doi.org/10.1080/089583797198178.

Groups of male rats (5/group) were exposed to 0, 50, 200, 600, or 1,000 ppm for 4 weeks (5 days/week, 6 hours/day); analytical concentrations (±SE) were 0±0, 50.8±0.7, 199.6±5.3, 598.5±6.4, and 1,007.3±11.0 ppm, respectively. Rats were observed for clinical signs, and for the 5-day study, weighed 3 times/week. Sixteen hours after exposure rats were injected with BrdU to assess cell proliferation and sacrificed 2 hours later. Respiratory tract tissues were examined for gross alterations and nasal cavities were dissected and cut into five cross sections for histopathological analysis. Immunocytochemistry was performed for BrdU analysis of Level 2, the region with the most observed damage.

Body weights were statistically decreased >10% at 1,007.3 ppm from day 3 through 26 (maximal reduction of 15% on day 5). No gross lesions were observed. Microscopic lesions were observed in several nasal cavity levels in all rats at ≥598.5 ppm, including olfactory epithelium regenerative hyperplasia and degeneration/necrosis and nerve bundle degeneration/atrophy. The most severe lesions were observed in the second and third levels (mild to severe). Incidence and severity of respiratory epithelium lesions were low across all groups. Increased cell proliferation was observed in the olfactory epithelium at ≥598.5 ppm, but not the respiratory epithelium.

Selection of the Point of Departure for the MRL: Bogdanffy et al. (1997) identified a NOAEL of 199.6 ppm for nasal lesions in rats following exposure to vinyl acetate for 4 weeks (6 hours/day; 5 days/week). The available data in Bogdanffy et al. (1997) are not amenable to BMD modeling because incidences go from 0% at the NOAEL to 100% at (and above) the LOAEL for the most sensitive nasal lesions. Therefore, the NOAEL of 199.6 ppm is selected as the POD.

Adjustment for Intermittent Exposure: Exposure over time is accounted for in the PBPK model (HEC simulations are for continuous exposure, see details below); therefore, no additional duration adjustment is needed.

Conversion to Human Equivalent Concentration: The PBPK model (Bogdanffy et al. 1999; Hinderliter et al. 2005) was used for rat-to-human dosimetry extrapolation in deriving inhalation MRLs for vinyl acetate as described in the acute-duration inhalation MRL worksheet. The study-specific parameters utilized in the PBPK model to calculate a $NOAEL_{HEC}$ of 21.6 ppm for the selected POD are shown in Table A-4. As previously indicated, model parameters were based on values reported by Bogdanffy et al. (1999) and Plowchalk et al. (1997), with the exception of body weights, which were based on TWA body weights calculated for the principal study. The difference in the acute- and intermediate-duration $NOAEL_{HEC}$ values (based on identical administered concentrations) is due to different TWA body weight values.

Table A-4. HECs Corresponding to the Rat POD Selected for Intermediate-Duration Inhalation MRL for Vinyl Acetate

Study	Exposure (ppm)	Duration and frequency	POD basis	POD metric	POD (hour µg/mL)	HEC[a] (ppm)
Bogdanffy et al. (1997)	0, 50.8, 199.6, 598.5, 1,007.3	4 weeks 5 days/week 6 hours/day	NOAEL (199.6 ppm)	$AUC_{168\ hr}$	6,243	21.6

[a]Calculated for continuous human exposure.

AUC = area under the curve for acetic acid concentration in olfactory epithelium; HEC = human equivalent exposure concentration; MRL = Minimal Risk Level; NOAEL = no-observed adverse effect level; POD = dose-response point of departure

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

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

$$MRL = \frac{NOAEL_{HEC}}{UFs} = \frac{21.6\ ppm}{30} = 0.7\ ppm$$

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Limited evidence from humans has shown that the respiratory tract is a sensitive target of acute-duration vinyl acetate exposure, with irritation of throat mucous membranes from acute-duration exposure levels as low as 4 ppm and persistent irritation at 74 ppm (Deese and Joyner 1969; Union Carbide 1973). The acute-, intermediate-, and chronic-duration databases confirm that the respiratory system, particularly the extrathoracic region, is the most sensitive target of toxicity following inhalation exposure to vinyl acetate. Nasal lesions are observed in rats following acute- or intermediate-duration exposure to ≥598.5 ppm (Bogdanffy et al. 1997; Krieger et al. 2020) and in rats and mice following chronic-duration exposure to

≥200.5 ppm (Bogdanffy et al. 1994a; Hazleton 1988). Lower respiratory tract lesions are also seen in rats and mice following intermediate-duration exposure to 998.9 ppm (Hazleton 1980b, 1980c) and mice following chronic-duration exposure to ≥200.5 ppm (Bogdanffy et al. 1994a; Hazleton 1988). In acute-duration inhalation lethality studies, deaths were attributed to lung damage in rats, mice, guinea pigs, and rabbits (Union Carbide 1973). Mechanistic data predict portal-of-entry effects (i.e., respiratory tract lesions) based on rapid hydrolysis of vinyl acetate into acetaldehyde and acetic acid following contact with mucosal surfaces, resulting in irritation due to tissue acidification (Bogdanffy et al. 1999, 2001, 2004; Slikker et al. 2004).

Agency Contacts (Chemical Managers): Rae T. Benedict

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Vinyl acetate
CAS Numbers: 108-05-4
Date: January 2025
Profile Status: Final
Route: Inhalation
Duration: Chronic
MRL 0.3 ppm (1.1 mg/m^3)
Critical Effect: Nasal lesions
References: Bogdanffy et al. 1994a; Hazleton 1988
Point of Departure: NOAEL of 49.4 ppm ($NOAEL_{HEC}$ of 8.52 ppm)
Uncertainty Factor: 30
LSE Graph Key: 19
Species: Rat

MRL Summary: A chronic-duration inhalation MRL of 0.3 ppm was derived for vinyl acetate based on nasal lesions in male rats exposed to concentrations ≥200.5 ppm for 104 weeks (6 hours/day, 5 days/week); a NOAEL of 49.4 ppm was identified (Bogdanffy et al. 1994a; Hazleton 1988). The MRL is based on a $NOAEL_{HEC}$ of 8.52 ppm derived using the PBPK model by Bogdanffy et al. (1999). The $NOAEL_{HEC}$ was divided by a total uncertainty factor of 30 (3 for extrapolation from animals to humans after dosimetric adjustment and 10 for human variability).

Selection of the Critical Effect: Available chronic-duration inhalation studies for vinyl acetate report exposure-related respiratory and body weight effects in rats and mice at LOAELs of 200.5 and 594.7 ppm, respectively (Table A-5). Respiratory effects are considered the most sensitive effect, with nasal lesions in rats and mice and pulmonary lesions in mice at ≥200.5 ppm. Therefore, respiratory lesions were selected as the critical effect for derivation of the chronic-duration inhalation MRL.

Selection of the Principal Study: While both rats and mice are similarly sensitive to the development of respiratory lesions, the chronic-duration rat study (Bogdanffy et al. 1994a; Hazleton 1988) was selected as the principal study due to the availability of a PBPK model estimating olfactory epithelium exposure metrics in rats and humans (Bogdanffy et al. 1999). Use of a PBPK model will result in higher confidence in the HEC calculation, compared to use of a default HEC concentration based on the RGDR recommended by EPA (1994).

Table A-5. Select NOAEL and LOAEL Values in Animals Following Chronic-Duration Inhalation Exposure to Vinyl Acetate

		NOAEL/LOAEL (ppm)			
Species	Duration	NOAEL	LOAEL	Effect	Reference
Respiratory					
Rat (SD)	104 weeks 5 days/week 6 hours/day (WB)	49.4	200.5	Nasal lesions[a]	Bogdanffy et al. 1994a; Hazleton 1988
Mouse (CD-1)	104 weeks 5 days/week 6 hours/day (WB)	49.4	200.5	Nasal lesions	Bogdanffy et al. 1994a; Hazleton 1988

Table A-5. Select NOAEL and LOAEL Values in Animals Following Chronic-Duration Inhalation Exposure to Vinyl Acetate

Species	Duration	NOAEL/LOAEL (ppm) NOAEL	LOAEL	Effect	Reference
Body weight					
Rat (SD)	104 weeks 5 days/week 6 hours/day (WB)	200.5	594.7	14% decrease in terminal body weight in females	Bogdanffy et al. 1994a; Hazleton 1988
Mouse (CD-1)	104 weeks 5 days/week 6 hours/day (WB)	200.5	594.7	11–15% decrease in terminal body weight	Bogdanffy et al. 1994a; Hazleton 1988

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

LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; SD = Sprague-Dawley; (WB) = whole-body exposure

Summary of the Principal Study:

Bogdanffy MS, Dreef-van der Meulen HC, Beems RB, et al. 1994a. Chronic toxicity and oncogenicity inhalation study with vinyl acetate in the rat and mouse. Fundam Appl Toxicol 23(2):215-229. http://doi.org/10.1006/faat.1994.1100.

Hazleton. 1988. Vinyl acetate: 104 week inhalation combined chronic toxicity and carcinogenicity study in the rat and mouse (Vol. I, II, IV & Vol. I of Amendment to final report, with cover letter 01/31/89). The Society of the Plastics Industry Inc. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8e. OTS0510582. 890000088. 8EHQ01890642.

Groups of Crl:CD(SD)BR Sprague-Dawley rats (60/sex/group) were exposed whole-body to vinyl acetate at concentrations of 0, 50, 200, or 600 ppm for 6 hours/day, 5 days/week for 104 weeks. Analytical concentrations for the exposure groups were 49.4±2.4, 200.5±9.7, and 594.7±16.8 ppm, respectively. Body weights were recorded at weekly intervals to Week 28 and every 4 weeks thereafter. All animals were observed briefly for clinical abnormalities before each exposure, received a detailed examination 1 time/week, and were examined twice daily for morbidity and mortality. Blood was collected from 10/sex/group in Week 104 for clinical chemistry and hematology. Urine samples were collected overnight. All animals underwent gross necropsy at sacrifice. The adrenals, gonads, kidneys, lungs, spleen, brain, heart, liver, pituitary, and thyroids were weighed. Histopathology was conducted on a complete set of tissues in control and high-exposure group. The respiratory tract tissues, including the nasal cavity, were examined in all animals. The respiratory tract histology was conducted in two independent labs, while one lab evaluated the nasal cavity in four cross sections.

Additional animals were used in satellite groups. One satellite group (10/sex/group) was used for clinical laboratory evaluation at Week 51 and interim sacrifice at Weeks 52–53. A second satellite group (10/sex/group) was used for clinical laboratory evaluation at Week 81 and interim sacrifice at Weeks 85–86. A third satellite group (10/sex/group) was used to evaluate recovery after 70 weeks of exposure followed by 15–16 weeks exposure-free.

No adverse treatment-related effects or mortality were observed. The study authors mentioned treatment-related clinical signs of rough haircoat and hunched posture at all concentrations; however, these findings were not uncommon in the control group and no exposure-related findings were observed when weekly incidence data were reviewed. Body weight gain was significantly decreased at 594.7 ppm during the study and absolute body weight in the high exposure group was decreased ~10%. No clear exposure-related hematological changes were observed. Blood glucose was decreased in 594.7-ppm females and urine volume was significantly reduced at 594.7 ppm in males at Week 51 and both sexes at Weeks 81 and 104. These findings were attributed by the study author to reductions in food and water intake (although these parameters were not specifically measured). Relative lung weight was significantly increased in all exposure groups at terminal sacrifice by 12–17% in females; this effect was reversed in the satellite recovery group. Elevated relative lung weight in males was only observed at the 53-week interim sacrifice at 594.7 ppm (20–30%). The biological relevance of reversible elevated relative lung weight in the absence of histopathological changes is unclear, especially considering body weight effects. The unpublished study (Hazleton 1988) also reported decreased relative spleen weight; this is not mentioned in the published report (Bogdanffy et al. 1994a), nor is it accompanied by histopathological changes.

Treatment-related nonneoplastic nasal lesions were observed in animals exposed to 200.5 or 594.7 ppm (olfactory epithelial atrophy, olfactory epithelial squamous metaplasia, olfactory epithelial regeneration, olfactory epithelial inflammatory cell infiltrate, epithelial nest-like infolds, olfactory epithelial leukocytic exudate, basal cell hyperplasia, turbinate leukocytic exudate, submucosal inflammatory cell infiltrate). Nonneoplastic lesions in the lungs were observed at 594.7 ppm (bronchial exfoliation, intraluminal fibrous projections, pigmented macrophages, peribronchiolar/ perivascular lymphoid aggregates). The total incidence of neoplastic nasal tumors (combined) was significantly elevated in male rats at 594.7 ppm (7/59) compared with controls (0/59) and nonsignificantly elevated in females (4/59 compared with 0/59 controls). Only squamous cell carcinoma was observed in females at 594.7 ppm. Nasal tumors observed in 594.7-ppm males included inverted papilloma, two squamous cell carcinomas, carcinoma *in situ* (4/59 total incidence of benign tumors and 3/59 total incidence of malignant tumors). One 200-ppm male had a nasal papilloma. No exposure-related lung tumors were observed in either sex. One squamous cell carcinoma of the larynx was observed in a 594.7-ppm female. The study author attributed the observed olfactory atrophy and tumors in the nasal cavity and lung lesions to chronic irritation.

Selection of the Point of Departure for the MRL: In order to identify the POD, BMD modeling was attempted for nasal lesions (atrophy, basal cell hyperplasia) in male and female rats reported by Bogdanffy et al. (1994a). Male and female rat nasal lesion data modeled are shown in Tables A-6 and A-7, respectively. Prior to modeling, the PBPK model described in the acute-duration inhalation MRL section was utilized to convert administered concentrations to acetic acid concentration overtime (AUC) in rat nasal olfactory epithelial tissue. Conversion to tissue dosimetry was performed prior to BMD modeling due to nonlinear relationship observed between external concentration and tissue concentration (attributed to metabolic saturation). The data were fit to all available dichotomous models in EPA's Benchmark Dose Software (BMDS) (version 3.2) using a benchmark response (BMR) of 10% extra risk. Adequate model fit was judged by four criteria: goodness-of-fit statistics (p-value >0.1), visual inspection of the dose-response curve, BMCL (95% lower confidence limit on the benchmark concentration [BMC]) 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 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.

Table A-6. Incidence of Select Nasal Lesions in the Olfactory Epithelium of Male Sprague-Dawley Rats Following Inhalation Exposure to Vinyl Acetate for 104 Weeks (5 Days/Week, 6 Hours/Day)

	Analytical concentration in ppm (AC AUC in week µg/mL[a])			
	0 (0)	49.4 (2,295)	200.5 (5,975)	594.7 (9,715)
Atrophy	0/59 (0%)	0/60 (0%)	53/60[b] (88%)	50/60[b] (83%)
Basal cell hyperplasia	2/59 (3%)	5/60 (8%)	54/60[b] (92%)	46/60[b] (78%)

[a]Calculated using the PBPK model by Bogdanffy et al. (1999), described in the acute-duration inhalation MRL worksheet.
[b]Statistically significant ($p<0.05$) based on Fisher's Exact Probability test conducted for this review.

AC = acetic acid; AUC = area under the curve; PBPK = physiologically based pharmacokinetic

Source: Bogdanffy et al. 1994a

Table A-7. Incidence of Select Nasal Lesions in the Olfactory Epithelium of Female Sprague-Dawley Rats Following Inhalation Exposure to Vinyl Acetate for 104 Weeks (5 Days/Week, 6 Hours/Day)

	Analytical concentration in ppm (AC AUC in week µg/mL[a])			
	0 (0)	49.4 (2,267)	200.5 (6,224)	594.7 (10,140)
Atrophy	0/60 (0%)	1/60 (2%)	27/60[b] (45%)	51/59[b] (86%)
Basal cell hyperplasia	0/60 (0%)	0/60 (0%)	34/60[b] (57%)	51/59[b] (86%)

[a]Calculated using the PBPK model by Bogdanffy et al. (1999), described in the acute-duration inhalation MRL worksheet.
[b]Statistically significant ($p<0.05$) based on Fisher's Exact Probability test conducted for this review.

AC = acetic acid; AUC = area under the curve; PBPK = physiologically based pharmacokinetic

Source: Bogdanffy et al. 1994a

Details of the modeling results for atrophy in male rats are provided in Table A-8. The only model that provided an adequate statistical fit was the Dichotomous Hill model. However, this model was considered unstable due to overparameterization for this dataset (only four exposure groups) and a mid-range p-value ($p=0.41$). Additionally, graphing the cumulative distribution function plot did not result in the characteristic sigmoidal shape expected for a viable model (Figure A-4). None of the models tested adequately fit the data for basal cell hyperplasia in male rats.

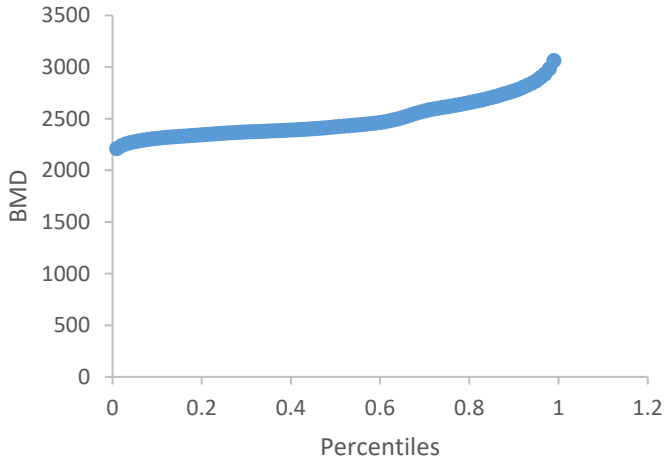
Table A-8. BMD Model Predictions for Olfactory Epithelium Atrophy in Male Sprague-Dawley Rats Following Inhalation to Vinyl Acetate for 104 Weeks (5 Days/Week, 6 Hours/Day) (Bogdanffy et al. 1994a)

Model	BMC_{10}[a] (week µg/mL)	$BMCL_{10}$[a] (week µg/mL)	p-value[b]	AIC	Scaled residuals[c]	
					Dose below BMC	Dose above BMC
Dichotomous Hill	2,419.085	2275.090	0.407	119.708	-0.0001	-0.001
Gamma[d]			<0.0001	143.918	-1.637	-0.001
Log-Logistic[e]			<0.0001	136.008	-1.249	-0.001
Multistage Degree 3[f]			<0.0001	147.915	-2.117	-0.001
Multistage Degree 2[f]			<0.0001	145.915	-2.117	-0.001
Multistage Degree 1[f]			<0.0001	163.073	-0.001	-0.001
Weibull[d]			<0.0001	149.646	-2.416	-0.001
Logistic			<0.0001	155.779	-1.792	-1.284
Log-Probit			<0.0001	138.181	-1.282	-0.001
Probit			<0.0001	159.273	-1.889	-1.186

[a]BMC and BMCLs values for models that do not provide adequate fit are not included in this table.
[b]Values <0.1 fail to meet conventional χ^2 goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the BMC.
[d]Power restricted to ≥1.
[e]Slope restricted to ≥1.
[f]Betas restricted to ≥0.

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

Figure A-4. Cumulative Distribution Function of Dichotomous Hill Model for Olfactory Epithelium Atrophy in Male Sprague-Dawley Rats Following Inhalation Exposure to Vinyl Acetate for 104 Weeks (Bogdanffy et al. 1994a)



Details of the modeling results for olfactory epithelium atrophy in female rats are in Table A-9. All models except the Multistage (1-Degree) provided adequate fit to the incidence data. The Gamma model was recommended by BMDS; however, the *p*-value of approximately 1 and scaled residuals of 0.0 suggest that the Gamma model is overfit, so it was not considered further. In accordance with the selection criteria mentioned above, the models with the next lowest AIC value were reviewed (Dichotomous Hill and Log-Logistic). From these, the model with the slightly lower BMCL was selected (frequentist, restricted Log-Logistic model) for olfactory epithelium atrophy in female rats.

Table A-9. BMD Model Predictions for Olfactory Epithelium Atrophy in Female Sprague-Dawley Rats Following Inhalation to Vinyl Acetate for 104 Weeks (6 Hours/Day) (Bogdanffy et al. 1994a)

					Scaled residuals[c]	
Model	BMC_{10}[a] (week µg/mL)	$BMCL_{10}$[a] (week µg/mL)	p-Value[b]	AIC	Dose below BMC	Dose above BMC
Dichotomous Hill	3,768.407	3,036.528	0.805	145.640	0.174	-0.001
Gamma[d]	3,607.948	2,909.137	0.995	145.581	0.004	-0.001
Log-Logistic[e,f]	**3,768.406**	**3,036.527**	**0.805**	**145.640**	**0.174**	**-0.001**
Multistage Degree 3[g]	3,573.788	2,713.506	0.303	146.685	-0.569	-0.001
Multistage Degree 2[g]	2,527.031	2,197.032	0.224	147.522	-1.832	-0.001
Multistage Degree 1[g]			<0.0001	175.866	-0.001	-0.001
Weibull[d]	3,480.679	2,746.145	0.365	146.482	-0.649	-0.015
Logistic	3,843.494	3,187.257	0.184	147.591	-0.900	-0.718
Log-Probit	3,572.231	2,930.895	0.481	146.060	0.411	-0.001
Probit	3,725.311	3,047.144	0.328	146.067	-0.716	-0.442

[a]BMC and BMCLs values for models that do not provide adequate fit are not included in this table.
[b]Values <0.1 fail to meet conventional χ^2 goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the BMC.
[d]Power restricted to ≥1.
[e]Selected model. All models except the Multistage (1-degree) provided adequate statistical fit to the data. The Gamma model was overfit to the data and was not considered further. BMCLs for the remaining models differed by <3-fold; therefore, the models with the next lowest AIC were reviewed (Dichotomous Hill, Log-Logistic). Since these models have identical AIC values, the model with the (slightly) lower BMCL (Log-Logistic) was selected.
[f]Slope restricted to ≥1.
[g]Betas restricted to ≥0.

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

Details of the modeling results for basal cell hyperplasia in female rats in female rats are in Table A-10. The Dichotomous Hill, Log-Logistic, and Log-Probit models provided adequate fit to the incidence data for atrophy. The Dichotomous Hill model was recommended by BMDS; however, the p-value of approximately 1 and scaled residuals of 0.0 suggest that the Dichotomous Hill model is overfit, so it was not considered further. In accordance with the selection criteria mentioned above, the next lowest AIC was selected (frequentist, restricted Log-Probit model) for basal cell hyperplasia in female rats.

Table A-10. BMD Constant Variance Model Predictions for Olfactory Epithelium Basal Cell Hyperplasia in Female Sprague-Dawley Rats Following Inhalation to Vinyl Acetate for 104 Weeks (6 Hours/Day) (Bogdanffy et al. 1994a)

					Scaled residuals[c]	
Model	BMC_{10}[a] (week µg/mL)	$BMCL_{10}$[a] (week µg/mL)	p-Value[b]	AIC	Dose below BMC	Dose above BMC
Dichotomous Hill	4,943.384	3,326.149	0.977	134.942	0.0005	-0.001
Gamma[d]			0.079	138.960	-1.014	-0.003
Log-Logistic[e]	3,631.587	2,933.453	0.154	137.815	-0.952	-0.001
Multistage Degree 3[f]			0.007	144.070	-1.481	-0.001
Multistage Degree 2[f]			0.081	143.161	-2.460	-0.001
Multistage Degree 1[f]			<0.0001	174.279	-0.001	-0.001
Weibull[d]			0.016	143.239	-1.630	-0.001
Logistic			0.005	146.229	-1.717	-0.769
Log-Probit[g]	**3,576.574**	**2,929.227**	**0.232**	**136.868**	**-0.724**	**-0.001**
Probit			0.009	144.601	-1.585	-0.488

[a]BMC and BMCLs values for models that do not provide adequate fit are not included in this table.
[b]Values <0.1 fail to meet conventional χ^2 goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the BMC.
[d]Power restricted to ≥1.
[e]Slope restricted to ≥1.
[f]Betas restricted to ≥0.
[g]Selected model. Only the Dichotomous Hill, Log-Logistic, and Log-Probit models provided adequate statistical fit. However, the Dichotomous Hill model was considered unstable due to low number of dose groups and a p-value near unity; it was not considered further. BMCLs for the remaining two models providing adequate fit differed by <3-fold; therefore, the model with the lowest AIC of these models was selected (Log-Probit).

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

To select the POD for the chronic-duration inhalation MRL, the POD values for olfactory epithelial lesions in male and female rats were compared (Table A-11). The increased incidence for olfactory epithelial lesions in male rats was selected because it is the most sensitive POD for the critical effect (nasal lesions). Incidence data also support that the male rat is more sensitive to nasal toxicity associated with vinyl acetate exposure, compared to the female rat. The apparent (slight) decrease in the incidence of atrophy and basal cell hypertrophy in male rats at the highest exposure concentration is likely attributable to progression to lesions of increased severity (e.g., metaplasia) that are only observed at the highest exposure level.

Table A-11. Summary of Candidate Effects and POD Values Considered for Derivation of a Chronic-Duration Inhalation MRL for Vinyl Acetate

Species	Duration	Effect	Candidate POD (week µg/mL)	POD type	Reference
Sprague-Dawley rat (male)	104 weeks	Olfactory epithelial atrophy and basal cell hypertrophy	2,295[a]	NOAEL	Bogdanffy et al. 1994a; Hazleton 1988
Sprague-Dawley rat (female)	104 weeks	Olfactory epithelial atrophy	3,037	$BMCL_{10}$	Bogdanffy et al. 1994a; Hazleton 1988
Sprague-Dawley rat (female)	104 weeks	Olfactory epithelial basal cell hypertrophy	2,929	$BMCL_{10}$	Bogdanffy et al. 1994a; Hazleton 1988

[a]Selected POD for derivation of chronic-duration inhalation MRL.

BMC = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; $BMCL_{10}$ = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., 10 = dose associated with 10% extra risk); MRL = Minimal Risk Level; NOAEL = no-observed-adverse-effect level; POD = point of departure

Adjustment for Intermittent Exposure: Exposure over time is accounted for in the PBPK model (HEC simulations are for continuous exposure, see details below); therefore, no additional duration adjustment is needed.

Conversion to Human Equivalent Concentration: The PBPK model (Bogdanffy et al. 1999; Hinderliter et al. 2005) was used for rat-to-human dosimetry extrapolation in deriving the chronic-duration inhalation MRL for vinyl acetate as described in the acute-duration inhalation MRL section. The study-specific parameters utilized in the PBPK model to calculate a $NOAEL_{HEC}$ of 8.52 ppm for the selected POD are shown in Table A-12. As previously indicated, all model parameters were based on values reported by Bogdanffy et al. (1999) and Plowchalk et al. (1997), with the exception of body weights, which were based on TWA body weights calculated for the principal study.

Table A-12. HECs Corresponding to Rat POD Selected for Chronic-Duration Inhalation MRL for Vinyl Acetate

Study	Exposure (ppm)	Duration and frequency	POD basis	POD metric	POD (hour µg/mL)	HEC[a] (ppm)
Bogdanffy et al. (1994a)	0, 49.4, 200.5, 594.7	4 weeks 5 days/week 6 hours/day	NOAEL (49.4 ppm)	$AUC_{168\ hr}$	2,295	8.52

[a]Calculated for continuous human exposure.

AUC = area under the curve for acetic acid concentration in olfactory epithelium; HEC = human equivalent exposure concentration; MRL = Minimal Risk Level; NOAEL = no-observed adverse effect level; POD = dose-response point of departure

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

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

$$MRL = \frac{NOAEL_{HEC}}{UFs} = \frac{8.52\ ppm}{30} = 0.3\ ppm$$

Other Additional Studies of Pertinent Information that Lend Support to this MRL: Limited evidence from humans has shown that the respiratory tract is a sensitive target of acute-duration vinyl acetate exposure, with irritation of throat mucous membranes from acute-duration exposure levels as low as 4 ppm and persistent irritation at 74 ppm (Deese and Joyner 1969; Union Carbide 1973). One cross-sectional study reported subjective respiratory complaints and mild reductions in pulmonary function at an average vinyl acetate concentration of 3.61 ppm (range of 0.02–11.71 ppm) in carpet manufacturers (Khoshakhlagh et al. 2023). However, another occupational study suggests that repeated occupational exposure to vinyl acetate is generally without adverse respiratory effect at levels <10 ppm (Deese and Joyner 1969).

In rodents, the acute-, intermediate- and chronic-duration databases confirm that the respiratory system, particularly the extrathoracic region, is the most sensitive target of toxicity following inhalation exposure to vinyl acetate. Nasal lesions are observed in rats following acute- or intermediate-duration exposure to ≥598.5 ppm (Bogdanffy et al. 1997; Krieger et al. 2020) and in rats and mice following chronic-duration exposure to ≥200.5 ppm (Bogdanffy et al. 1994a; Hazleton 1988). Lower respiratory tract lesions are also seen in rats and mice following intermediate-duration exposure to 998.9 ppm (Hazleton 1980b, 1980c) and mice following chronic-duration exposure to ≥200.5 ppm (Bogdanffy et al. 1994a; Hazleton 1988). In acute-duration inhalation lethality studies, deaths were attributed to lung damage in rats, mice, guinea pigs, and rabbits (Union Carbide 1973). Mechanistic data predict portal-of-entry effects (i.e., respiratory tract lesions) based on rapid hydrolysis of vinyl acetate into acetaldehyde and acetic acid following contact with mucosal surfaces, resulting in irritation due to tissue acidification (reviewed by Bogdanffy et al. 1999, 2001, 2004; Slikker et al. 2004).

Agency Contacts (Chemical Managers): Rae T. Benedict

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Vinyl acetate
CAS Numbers: 108-05-4
Date: January 2025
Profile Status: Final
Route: Oral
Duration: Acute

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

Rationale for Not Deriving an MRL: The acute oral database is limited to acute-duration lethality studies (Goeva 1966; Smyth and Carpenter 1948), a developmental exposure study that does not identify adverse effects at maternal doses up to 477 mg/kg/day (Hurtt et al. 1995), and a study reporting a lack of gastrointestinal lesions in rats and mice exposed to doses up to 1,400 mg/kg/day and 5,300 mg/kg/day, respectively, for 1–8 days (no other organ systems were evaluated) (Valentine et al. 2002).

Agency Contacts (Chemical Managers): Rae T. Benedict

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Vinyl acetate
CAS Numbers: 108-05-4
Date: January 2025
Profile Status: Final
Route: Oral
Duration: Intermediate

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

Rationale for Not Deriving an MRL: No intermediate-duration oral MRL was derived for vinyl acetate because effects potentially associated with intermediate-duration oral exposure to vinyl acetate are of questionable biological significance and/or human relevance:

1. Body weight effects noted in drinking water studies at ≥165 mg/kg/day in F1 rats and 697 mg/kg/day in F0 rats in a 2-generation study and at 1,040 mg/kg/day in mice exposed for 4 weeks were associated with decreased water consumption during some or all of the exposure period (attributed to palatability issues) (Hazleton 1979d; Mebus et al. 1995). Since decreased water consumption can result in body weight loss even in the absence of clinical dehydration (Vasilev et al. 2021), it is difficult to distinguish compound-related effects on body weight from direct effects of decreased water consumption.
2. The developmental serious LOAEL of 697 mg/kg/day based on decreased F1 weanling body weight in a 2-generation study in rats (Mebus et al. 1995) is thought to be secondary to a significant decrease in maternal water intake, attributed to unpalatability of drinking water (which could impair milk supply); F0 dams also showed significant decreases in body weight gain during lactation at 669 mg/kg/day. Therefore, these effects are of questionable biological significance and therefore, not an appropriate basis for the MRL.
3. All of the remaining available intermediate-duration oral NOAELs are "free-standing" and are thus not an appropriate basis for the calculation of an MRL (Hazleton 1979d, 1980e, 1980f; Valentine et al. 2002).

Agency Contacts (Chemical Managers): Rae T. Benedict

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Vinyl acetate
CAS Numbers: 108-05-4
Date: January 2025
Profile Status: Final
Route: Oral
Duration: Chronic

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

Rationale for Not Deriving an MRL: No chronic-duration oral MRL was derived for vinyl acetate. Only one reliable, comprehensive chronic-duration study was identified (Bogdanffy et al. 1994b). In this study, the only potentially adverse effect reported was decreased body weight at ≥202 mg/kg/day in rats. However, as observed in intermediate-duration drinking water studies, findings were associated with decreased water consumption (attributed to palatability issues). Since decreased water consumption can result in body weight loss even in the absence of clinical dehydration (Vasilev et al. 2021), it is difficult to distinguish compound-related effects on body weight from direct effects of decreased water consumption. Additionally, male rats also showed decreased food intake, further confounding body weight findings. The remaining reliable chronic-duration studies focused on neoplastic changes. Exposure-related effects in these studies were limited to serious LOAELs, including death and cancer (Belpoggi et al. 2002; Maltoni et al. 1997; Minardi et al. 2002).

A second comprehensive chronic-duration study reported pre-neoplastic and neoplastic lesions in the upper gastrointestinal tract of rats and mice (Umeda et al. 2004). However, this study is not listed in the LSE tables as there are quality issues with this study precluding accurate dose estimation. The drinking-water solution was only mixed twice weekly (instead of daily, as found in other drinking water studies for vinyl acetate). The study authors reported that the test solution stabilities at 4 days were 72–80% in the rat study and 86–96% in the mouse study. The lost concentration was attributed mainly to evaporation. Acetic acid concentration after 4 days was 9.2, 4.7, and 263 ppm at 400, 2,000, or 10,000 ppm, respectively. It is unclear if acetic acid in the drinking water and/or decreased pH contributed to the observed effects. Therefore, while discussed in the profile, this study was not considered as the basis for the MRL.

Agency Contacts (Chemical Managers): Rae T. Benedict

APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR VINYL ACETATE

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 acetate.

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 acetate. ATSDR primarily focused on peer-reviewed articles without language restrictions. Foreign language studies are reviewed based on available English-language abstracts and/or tables (or summaries in regulatory assessments, such as 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 acetate 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 acetate are presented in Table B-1.

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

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

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

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

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

B.1.1 Literature Search

The literature search was conducted to update the Toxicological Profile for Vinyl Acetate released in 1992. All literature cited in the previous (1992) toxicological profile were considered for inclusion in the updated profile. The initial literature search, which was performed in April 2017 and October 2021, was restricted to studies added to databases since January 1990. An updated literature search was performed after the Toxicological Profile for Vinyl Acetate Draft for Public Comment was released in August 2023 to identify any additional studies added to databases between September 2021 and December 2023.

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

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

The search strategy used the chemical names, Chemical Abstracts Service (CAS) numbers, synonyms, Medical Subject Headings (MeSH) headings, and keywords for vinyl acetate. 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 acetate were identified by searching international and U.S. agency websites and documents.

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

Table B-2. Database Query Strings

Database search date	Query string
PubMed	
12/2023	((108-05-4[rn] OR "vinyl acetate"[supplementary concept]) AND (2021/09/01:3000[mhda])) OR ((("1-Acetoxyethylene"[tw] OR "Acetate de vinyle"[tw] OR "Acetic acid vinyl ester"[tw] OR "Acetic acid, ethenyl ester"[tw] OR "Acetic acid, ethylene ether"[tw] OR "Acetoxyethene"[tw] OR "Ethanoic acid, ethenyl ester"[tw] OR "Ethenyl acetate"[tw] OR "Ethenyl ethanoate"[tw] OR "Octan winylu"[tw] OR "Vinile (acetato di)"[tw] OR "Vinyl A monomer"[tw] OR "Vinyl acetate"[tw] OR "Vinyl acetate H.Q."[tw] OR "Vinyl acetate monomer"[tw] OR "Vinyl ethanoate"[tw] OR "Vinylacetaat"[tw] OR "Vinylacetat"[tw] OR "Vinylacetate"[tw] OR "Vinyle (acetate de)"[tw] OR "Vinylester kyseliny octove"[tw] OR "Zeset T"[tw]) AND (2021/09/01:3000[edat] OR 2021/09/01:3000[crdat])) NOT medline[sb])
10/2021	((108-05-4[rn] OR L9MK238N77[rn] OR "vinyl acetate"[supplementary concept] OR "vinyl acetate"[nm]) AND (1990/01/01 : 3000[dp] OR 1990/01/01 : 3000[mhda])) OR ((("1-Acetoxyethylene"[tw] OR "Acetate de vinyle"[tw] OR "Acetic acid vinyl ester"[tw] OR "Acetic acid, ethenyl ester"[tw] OR "Acetic acid, ethylene ether"[tw] OR "Acetoxyethene"[tw] OR "Ethanoic acid, ethenyl ester"[tw] OR "Ethenyl acetate"[tw] OR "Ethenyl ethanoate"[tw] OR "Octan winylu"[tw] OR "Vinile (acetato di)"[tw] OR "Vinyl A monomer"[tw] OR "Vinyl acetate"[tw] OR "Vinyl acetate H.Q."[tw] OR "Vinyl acetate monomer"[tw] OR "Vinyl ethanoate"[tw] OR "Vinylacetaat"[tw] OR "Vinylacetat"[tw] OR "Vinylacetate"[tw] OR "Vinyle (acetate de)"[tw] OR "Vinylester kyseliny octove"[tw] OR "Zeset T"[tw]) AND (1990/01/01 : 3000[dp] OR 1990/01/01 : 3000[crdat] OR 1990/01/01 : 3000[edat])) NOT medline[sb])

Table B-2. Database Query Strings

Database search date	Query string
NTRL	
12/2023	Limited to date published 2020 to 2023 Searched in title or keyword "1-Acetoxyethylene" OR "Acetate de vinyle" OR "Acetic acid vinyl ester" OR "Acetic acid, ethenyl ester" OR "Acetic acid, ethylene ether" OR "Acetoxyethene" OR "Ethanoic acid, ethenyl ester" OR "Ethenyl acetate" OR "Ethenyl ethanoate" OR "Octan winylu" OR "Vinile (acetato di)" OR "Vinyl A monomer" OR "Vinyl acetate" OR "Vinyl acetate H.Q." OR "Vinyl acetate monomer" OR "Vinyl ethanoate" OR "Vinylacetaat" OR "Vinylacetat" OR "Vinylacetate" OR "Vinyle (acetate de)" OR "Vinylester kyseliny octove" OR "Zeset T"
10/2021	"1-Acetoxyethylene" OR "Acetate de vinyle" OR "Acetic acid vinyl ester" OR "Acetic acid, ethenyl ester" OR "Acetic acid, ethylene ether" OR "Acetoxyethene" OR "Ethanoic acid, ethenyl ester" OR "Ethenyl acetate" OR "Ethenyl ethanoate" OR "Octan winylu" OR "Vinile (acetato di)" OR "Vinyl A monomer" OR "Vinyl acetate" OR "Vinyl acetate H.Q." OR "Vinyl acetate monomer" OR "Vinyl ethanoate" OR "Vinylacetaat" OR "Vinylacetat" OR "Vinylacetate" OR "Vinyle (acetate de)" OR "Vinylester kyseliny octove" OR "Zeset T"
Toxcenter	
12/2023	FILE 'TOXCENTER' ENTERED AT 16:48:25 ON 11 DEC 2023 CHARGED TO COST=ET027.02.08.LB.01 L1 4404 SEA FILE=TOXCENTER 108-05-4 L2 1957 SEA FILE=TOXCENTER L1 NOT PATENT/DT L3 205 SEA FILE=TOXCENTER L2 AND ED>=20210901 L38 200 DUP REM L3 (5 DUPLICATES REMOVED)
10/2021	FILE 'TOXCENTER' ENTERED AT 11:35:18 ON 01 OCT 2021 CHARGED TO COST=EH038.10.01.04 L1 3988 SEA 108-05-4 L2 3903 SEA L1 NOT TSCATS/FS L3 1652 SEA L2 NOT PATENT/DT L4 284 SEA L3 AND ED>=20170401 ACT TOXQUERY/Q --------- L5 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) L6 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT) L7 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50) L8 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT L9 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?) L10 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?) L11 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?) L12 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE)) L13 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?) L14 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?)

Table B-2. Database Query Strings

Database search date	Query string
	L15 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?)
	L16 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?)
	L17 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?)
	L18 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?)
	L19 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?)
	L20 QUE (ENDOCRIN? AND DISRUPT?)
	L21 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?)
	L22 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)
	L23 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)
	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 128 SEA L4 AND L37
	L39 11 SEA L38 AND MEDLINE/FS
	L40 2 SEA L38 AND BIOSIS/FS
	L41 115 SEA L38 AND CAPLUS/FS
	L42 0 SEA L38 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS)

Table B-2. Database Query Strings

Database search date	Query string
	L43 127 DUP REM L39 L40 L41 (1 DUPLICATE REMOVED) L*** DEL 11 S L38 AND MEDLINE/FS L*** DEL 11 S L38 AND MEDLINE/FS L44 11 SEA L43 L*** DEL 2 S L38 AND BIOSIS/FS L*** DEL 2 S L38 AND BIOSIS/FS L45 2 SEA L43 L*** DEL 115 S L38 AND CAPLUS/FS L*** DEL 115 S L38 AND CAPLUS/FS L46 114 SEA L43 L47 116 SEA (L44 OR L45 OR L46) NOT MEDLINE/FS SAVE TEMP L47 VINYLACETATE/A D SCAN L47 FILE HOME FILE TOXCENTER
04/2017	(FILE 'HOME' ENTERED AT 12:26:28 ON 07 APR 2017) FILE 'TOXCENTER' ENTERED AT 12:26:47 ON 07 APR 2017 CHARGED TO COST=EH011.13.01.01 L1 2765 SEA 108-05-4 L2 2680 SEA L1 NOT TSCATS/FS L3 1221 SEA L2 NOT PATENT/DT L4 2125 SEA L1 AND PY>=1990 L5 795 SEA L3 AND PY>=1990 ACTIVATE TOXQUERY/Q --------- L6 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) L7 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT) L8 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50) L9 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT L10 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?) L11 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?) L12 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?) L13 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE)) L14 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?) L15 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?) L16 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?) L17 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?) L18 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?)

Table B-2. Database Query Strings

Database search date	Query string
	L19 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?)
	L20 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?)
	L21 QUE (ENDOCRIN? AND DISRUPT?)
	L22 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?)
	L23 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)
	L24 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)
	L25 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?)
	L26 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)
	L27 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?)
	L28 QUE (NEPHROTOX? OR HEPATOTOX?)
	L29 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?)
	L30 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?)
	L31 QUE 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 OR L30
	L32 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?)
	L33 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE)
	L34 QUE L31 OR L32 OR L33
	L35 QUE (NONHUMAN MAMMALS)/ORGN
	L36 QUE L34 OR L35
	L37 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?)
	L38 QUE L36 OR L37

	L39 382 SEA L5 AND L38
	L40 43 SEA L39 AND MEDLINE/FS
	L41 48 SEA L39 AND BIOSIS/FS
	L42 274 SEA L39 AND CAPLUS/FS
	L43 17 SEA L39 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS)
	L44 323 DUP REM L40 L41 L43 L42 (59 DUPLICATES REMOVED)
	L*** DEL 43 S L39 AND MEDLINE/FS
	L*** DEL 43 S L39 AND MEDLINE/FS
	L45 43 SEA L44
	L*** DEL 48 S L39 AND BIOSIS/FS
	L*** DEL 48 S L39 AND BIOSIS/FS

Table B-2. Database Query Strings

Database search date	Query string
	L46 30 SEA L44 L*** DEL 274 S L39 AND CAPLUS/FS L*** DEL 274 S L39 AND CAPLUS/FS L47 235 SEA L44 L*** DEL 17 S L39 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS) L*** DEL 17 S L39 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS) L48 15 SEA L44 L49 280 SEA (L45 OR L46 OR L47 OR L48) NOT MEDLINE/FS
Toxline	
04/2017	("1-acetoxyethylene" OR "acetate de vinyle" OR "acetic acid vinyl ester" OR "acetic acid ethenyl ester" OR "acetic acid ethylene ether" OR "acetoxyethene" OR "ethanoic acid ethenyl ester" OR "ethenyl acetate" OR "ethenyl ethanoate" OR "octan winylu" OR "vinile (acetato di) " OR "vinyl a monomer" OR "vinyl acetate" OR "vinyl acetate h q " OR "vinyl acetate monomer" OR "vinyl ethanoate" OR "vinylacetaat" OR "vinylacetat" OR "vinylacetate" OR "vinyle (acetate de) " OR "vinylester kyseliny octove" OR "zeset t" OR 108-05-4 [rn]) AND 1990:2017 [yr] AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org]

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS via ChemView	
12/2023; 10/2021	Compounds searched: 108-05-4
NTP	
12/2023	Limited 2020-present 108-05-4 "Vinyl acetate" "Vinylacetate" "Acetic acid, ethenyl ester" "1-Acetoxyethylene" "Acetic acid vinyl ester" "Acetic acid, ethylene ether" "Acetoxyethene" "Ethanoic acid, ethenyl ester" "Ethenyl acetate" "Vinyl A monomer" "Vinyl ethanoate"
10/2021	"108-05-4" "Vinyl acetate" "Vinylacetate" "Acetic acid, ethenyl ester" "1-Acetoxyethylene" "Acetic acid vinyl ester" "Acetic acid, ethylene ether" "Acetoxyethene" "Ethanoic acid, ethenyl ester" "Ethenyl acetate" "Vinyl A monomer" "Vinyl ethanoate"
Regulations.gov	
12/2023	"108-05-4" "Vinyl acetate" "Vinylacetate" No date limit; Docket and EPA notices

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
NIH RePORTER	
09/11/2024	Fiscal Year: Active Projects Text Search: "1-Acetoxyethylene" OR "Acetate de vinyle" OR "Acetic acid vinyl ester" OR "Acetic acid, ethenyl ester" OR "Acetic acid, ethylene ether" OR "Acetoxyethene" OR "Ethanoic acid, ethenyl ester" OR "Ethenyl acetate" OR "Ethenyl ethanoate" OR "Octan winylu" OR "Vinile (acetato di)" OR "Vinyl A monomer" OR "Vinyl acetate" OR "Vinyl acetate H.Q." OR "Vinyl acetate monomer" OR "Vinyl ethanoate" OR "Vinylacetaat" OR "Vinylacetat" OR "Vinylacetate" OR "Vinyle (acetate de)" OR "Vinylester kyseliny octove" OR "Zeset T" (advanced) Limit to: Project Title, Project Terms, Project Abstracts
06/2022	Text Search: "1-Acetoxyethylene" OR "Acetate de vinyle" OR "Acetic acid vinyl ester" OR "Acetic acid, ethenyl ester" OR "Acetic acid, ethylene ether" OR "Acetoxyethene" OR "Ethanoic acid, ethenyl ester" OR "Ethenyl acetate" OR "Ethenyl ethanoate" OR "Octan winylu" OR "Vinile (acetato di)" OR "Vinyl A monomer" OR "Vinyl acetate" OR "Vinyl acetate H.Q." OR "Vinyl acetate monomer" OR "Vinyl ethanoate" OR "Vinylacetaat" OR "Vinylacetat" OR "Vinylacetate" OR "Vinyle (acetate de)" OR "Vinylester kyseliny octove" OR "Zeset T" (advanced) Limit to: Project Title, Project Terms, Project Abstracts
Other	Includes additional reference identified throughout the assessment process, which may include studies found by tree searching; recommended by intraagency, interagency, peer, or public reviewers; or published more recently than the date of literature search(es). Additional references include those for specific regulations or guidelines and publications found by targeted searches for specific information (e.g., searches for reviews of general [not chemical-specific] mechanisms of toxicity).

The 2021 pre-public comment search results were:

- Number of records identified from PubMed, NTRL, TOXCENTER, and Toxline (after duplicate removal): 1,491
- Number of records identified from other strategies: 76
- Total number of records to undergo literature screening: 1,567

The 2023 post-public comment search results were:

- Number of records identified from PubMed, NTRL, and TOXCENTER (after duplicate removal): 456
- Number of records identified from other strategies: 36
- Total number of records to undergo literature screening: 492

B.1.2 Literature Screening

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

- Title and abstract screen
- Full text screen

Pre-Public Comment Title and Abstract Screen. Within the reference library, titles and abstracts were screened manually for relevance. Studies that were considered (see Table B-1 for inclusion criteria) were

moved to the second step of the literature screening process. Studies were excluded when the title and abstract clearly indicated that the study was not relevant to the toxicological profile.

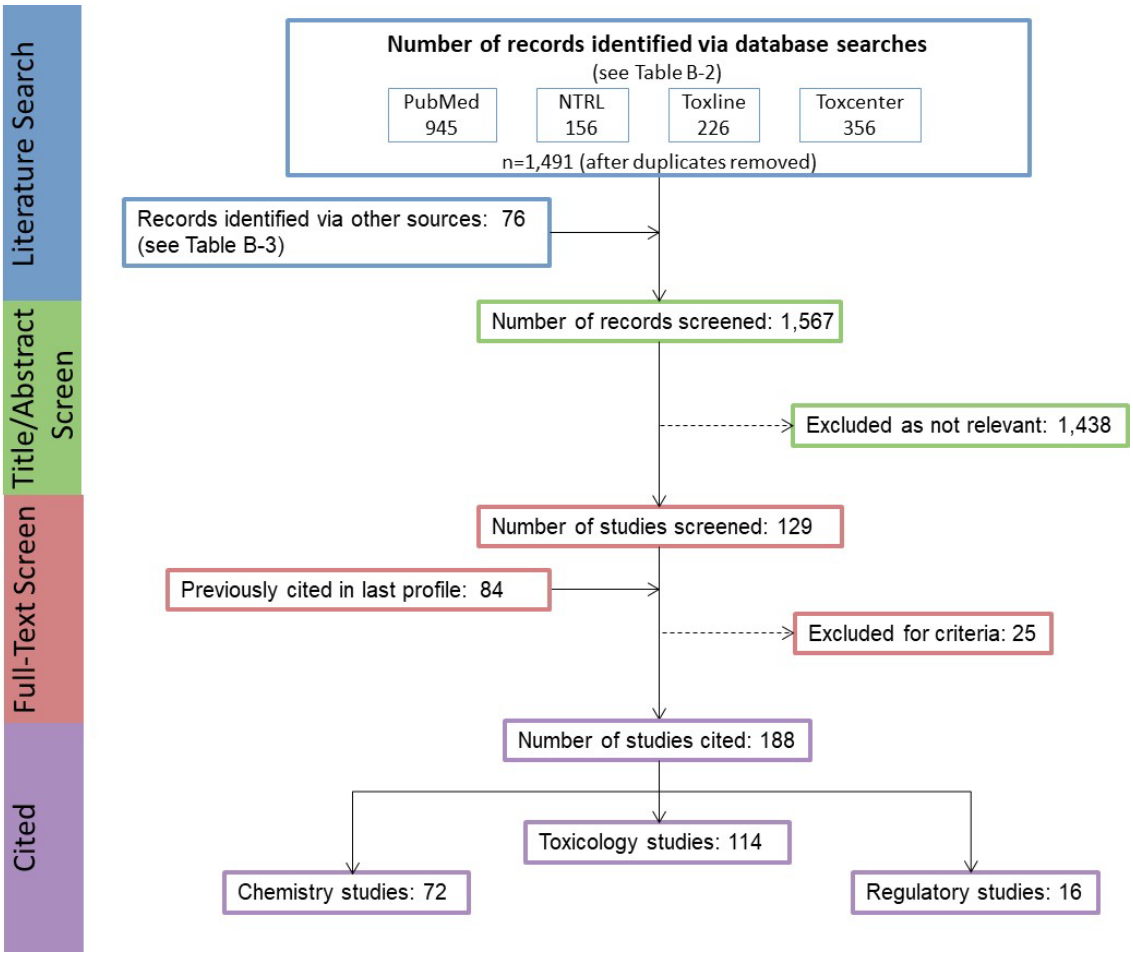
- Number of titles and abstracts screened: 1,567
- Number of studies considered relevant and moved to the next step: 129

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

- Number of studies undergoing full text review: 129
- Number of studies cited in the previous toxicological profile: 84
- Total number of studies cited in the profile: 188

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

Figure B-1. October 2021 Literature Search Results and Screen for Vinyl Acetate



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

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

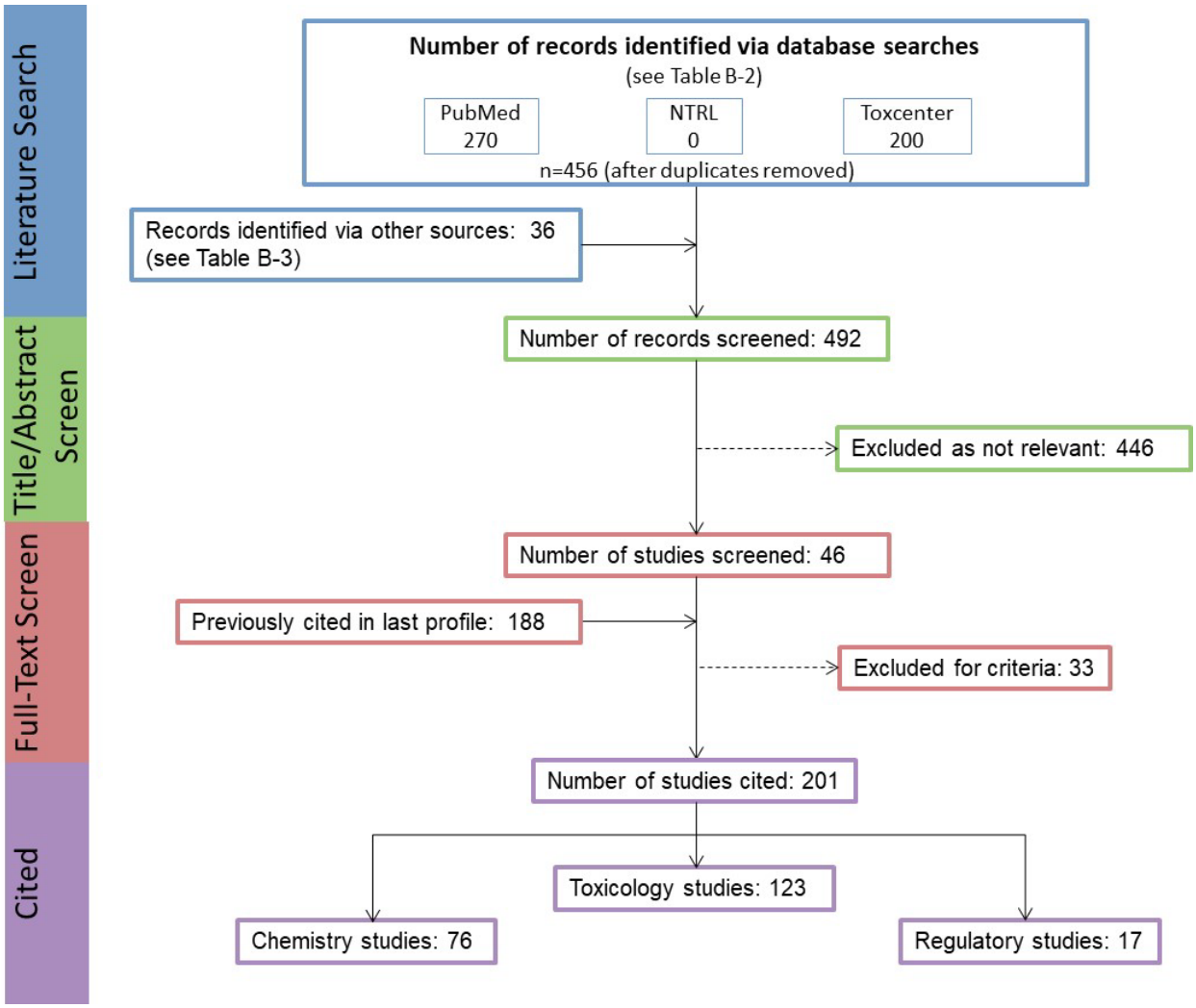
- Number of titles and abstracts screened: 492
- Number of studies considered relevant and moved to the next step: 46

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

- Number of studies undergoing full text review: 46
- Number of studies cited in the pre-public draft of the toxicological profile: 188
- Total number of studies cited in the profile: 201

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

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



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

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

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 acetate, 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 acetate:

- 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 acetate. The inclusion criteria used to identify relevant studies examining the health effects of vinyl acetate are presented in Table C-1.

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

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

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

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

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

C.2 LITERATURE SEARCH AND SCREEN FOR HEALTH EFFECTS STUDIES

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

C.2.1 Literature Search

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

A total of 1,567 and 492 records relevant to all sections of the toxicological profile were identified in the initial and update literature search, respectively.

C.2.2 Literature Screening

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

Title and Abstract Screen. In the Title and Abstract Screen step, 35 documents (inclusive of both literature searches) were considered to meet the health effects inclusion criteria in Table C-1 and were moved to the next step in the process.

Full Text Screen. In the second step in the literature screening process for the systematic review, a full text review of 35 health effect documents (documents identified in the update literature search and documents cited in older versions of the profile) was performed. From those 35 documents (61 studies), 16 documents (26 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 acetate and overviews of the results of the inhalation, oral, and dermal exposure studies are presented in presented in Sections 2.2–2.19 of the profile and in the Levels Significant Exposures tables in Section 2.1 of the profile (Tables 2-2, 2-3, and 2-4, respectively).

C.4 IDENTIFY POTENTIAL HEALTH EFFECT OUTCOMES OF CONCERN

Overviews of the potential health effect outcomes for vinyl acetate identified in human and animal studies are presented in Tables C-3 and C-4, respectively. Human data include a limited number of human controlled inhalation exposure and occupational studies with potential for exposure via multiple routes. These limited human studies indicate that the respiratory system may be susceptible to vinyl acetate toxicity. Animal studies examined a comprehensive set of endpoints following inhalation or oral exposure, but dermal studies were limited to acute lethality, skin and eye irritation, and skin sensitization. Respiratory effects were considered sensitive outcomes following inhalation exposure and developmental effects were considered sensitive outcomes following inhalation and oral exposure (i.e., effects were observed at low concentrations or doses). Decreased body weight effects were also noted in some

drinking water studies; however, assessment of compound-related effects on body weight is difficult due to concomitant decreases in water and/or food intake. No additional nonneoplastic effects were noted at concentrations or doses below high levels associated with increased mortality. Studies examining identified sensitive outcomes (respiratory effects following inhalation exposure; developmental effects following inhalation or oral exposure) were carried through to Steps 4–8 of the systematic review. There were 26 studies (published in 16 documents) examining these potential outcomes carried through to Steps 4–8 of the systematic review.

APPENDIX C

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

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

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

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

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

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

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

C.5 ASSESS THE RISK OF BIAS FOR INDIVIDUAL STUDIES

C.5.1 Risk of Bias Assessment

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

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

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

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

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

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

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

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

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

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

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

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

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

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

The results of the risk of bias assessment for human controlled exposure studies, human observational studies, 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 Acetate —Human Controlled Exposure Studies

Reference	Risk of bias criteria and ratings: Selection bias — Was administered dose or exposure level adequately randomized	Performance Bias — Does 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?	Detection bias — **Is there confidence in the outcome assessment?***	Selective reporting bias — Are all measured outcomes reported?	Risk of bias tier
Outcome: Respiratory Effects (inhalation only)							
Inhalation acute exposure							
Hinderliter et al. 2005	– –	–	++	++	–	++	Second
Union Carbide 1973	– –	–	++	++	–	++	Second
Outcome: Developmental Effects							
None identified							

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

*Key question used to assign risk of bias tier

Table C-9. Summary of Risk of Bias Assessment for Vinyl Acetate —Human Observational Studies

Reference	Risk of bias criteria and ratings: Selection bias — Were the comparison groups appropriate?	Selection bias — **Does 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 exposure characterization?***	Detection bias — **Is there confidence in the outcome assessment?***	Selective reporting bias — Were all measured outcomes reported?	Risk of bias tier
Outcome: Respiratory Effects (inhalation only)							
Inhalation acute exposure							
Deese and Joyner 1969	– –	–	++	++	–	++	Second
Inhalation chronic exposure							
Deese and Joyner 1969	++	–	++	++	+	++	Second
Khoshakhlagh et al. 2023	++	–	++	++	–	++	Second
Outcome: Developmental Effects							
None identified							

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

*Key question used to assign risk of bias tier

Table C-10. Summary of Risk of Bias Assessment for Vinyl Acetate —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: Respiratory Effects (inhalation only)										
Inhalation acute exposure										
Bogdanffy et al. 1997 (1 day, rat)	++	+	++	+	++	++	**++**	++	NA	First
Bogdanffy et al. 1997 (5 days, rat)	++	+	++	+	++	++	**++**	++	NA	First
Krieger et al. 2020 (1 day, rat)	++	+	++	+	++	++	**++**	++	NA	First
Krieger et al. 2020 (5 days, rat)	++	+	++	+	++	++	**++**	++	NA	First
Union Carbide 1973 (rat)	–	+	+	+	–	–	**–**	–	NA	Third
Union Carbide 1973 (mouse)	–	+	+	+	–	–	**–**	–	NA	Third
Union Carbide 1973 (rabbit)	–	+	+	+	–	–	**–**	–	NA	Third
Union Carbide 1973 (guinea pig)	–	+	+	+	–	–	**–**	–	NA	Third
Inhalation intermediate exposure										
Bogdanffy et al. 1997 (4 weeks, rat)	++	+	++	+	++	++	**++**	++	NA	First
Gage 1970 (15 days, rat)	–	–	–	+	+	–	**–**	+	NA	Third
Hazleton 1979c (4 weeks, rat)	++	+	+	+	++	++	**–**	++	NA	Second
Hazleton 1979b (4 weeks, mouse)	++	+	+	+	++	++	**–**	++	NA	Second
Hazleton 1980c (3 months, rat)	++	+	++	+	++	++	**++**	++	NA	First
Hazleton 1980b (3 months, mouse)	++	+	++	+	++	++	**++**	++	NA	First

Table C-10. Summary of Risk of Bias Assessment for Vinyl Acetate —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
Krieger et al. 2020 (20 days, rat)	++	+	++	+	++	++	++	++	NA	First
Krieger et al. 2020 (65 days, rat)	++	+	++	+	++	++	++	++	NA	First
Inhalation chronic exposure										
Bogdanffy et al. 1994a; Hazleton 1988 (rat)	++	+	++	+	++	++	++	++	NA	First
Bogdanffy et al. 1994a; Hazleton 1988 (mouse)	++	+	++	+	++	++	++	++	NA	First
Outcome: Developmental Effects										
Inhalation acute exposure										
Hurtt et al. 1995; Hazleton 1980d	++	+	++	+	++	++	+	++	NA	First
Oral acute exposure										
Hurtt et al. 1995	++	+	++	+	++	++	++	++	NA	First

Table C-10. Summary of Risk of Bias Assessment for Vinyl Acetate —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?		
Oral intermediate exposure											
Mebus et al. 1995	++	+	+	+	++	++	–	++	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 acetate 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 acetate and a particular outcome was given an initial confidence rating based on the key features of the individual studies examining that outcome. The presence of these key features of study design was determined for individual studies using four "yes or no" questions, which were customized for epidemiology, human controlled exposure, or experimental animal study designs. Separate questionnaires were completed for each outcome assessed in a study. The key features for observational epidemiology (cohort, population, and case-control) studies, human controlled exposure, and experimental animal studies are presented in Tables C-11, C-12, and C-13, respectively. The initial confidence in the study was determined based on the number of key features present in the study design:

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

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

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

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

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

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

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

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

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

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

The presence or absence of the key features and the initial confidence levels for studies examining respiratory (inhalation only) and developmental effects in human controlled exposure studies, human observational studies, and animal experimental studies are presented in Tables C-14, C-15 and C-16, respectively.

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-14. Presence of Key Features of Study Design for Vinyl Acetate—Human-Controlled Exposure Studies

Reference	Key features				Initial study confidence
	Comparison group	Sufficient number subjects	Appropriate methods to assessed outcomes	Appropriate Statistical analysis	
Outcome: Respiratory Effects (inhalation only)					
Inhalation acute exposure					
Hinderliter et al. 2005	Yes	No	Yes	No	Low
Union Carbide 1973	No	Yes	No	No	Very Low
Outcome: Developmental					
None identified					

Table C-15. Presence of Key Features of Study Design for Vinyl Acetate—Observational Epidemiology Studies

Reference	Key features				Initial study confidence
	Controlled exposure	Exposure prior to outcome	Outcomes assessed on an individual level	Comparison group	
Outcome: Respiratory Effects (inhalation only)					
Inhalation acute exposure					
Deese and Joyner 1969	No	Yes	Yes	No	Low
Inhalation chronic exposure					
Deese and Joyner 1969	No	Yes	Yes	Yes	Moderate
Khoshakhlagh et al. 2023	No	No	Yes	Yes	Low
Outcome: Developmental					
None identified					

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

Reference	Key feature: Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	Initial study confidence
Outcome: Respiratory Effects (inhalation only)					
Inhalation acute exposure					
Bogdanffy et al. 1997 (rat, 1 day)	Yes	Yes	Yes	Yes	High
Bogdanffy et al. 1997 (rat, 5 days)	Yes	Yes	Yes	Yes	High
Krieger et al. 2020 (1 day, rat)	Yes	Yes	Yes	Yes	High
Krieger et al. 2020 (5 days, rat)	Yes	Yes	Yes	Yes	High
Union Carbide 1973 (rat)	No	Yes	No	No	Very Low
Union Carbide 1973 (mouse)	No	Yes	No	No	Very Low
Union Carbide 1973 (rabbit)	No	Yes	No	No	Very Low
Union Carbide 1973 (guinea pig)	No	Yes	No	No	Very Low
Inhalation intermediate exposure					
Bogdanffy et al. 1997 (4 weeks)	Yes	Yes	Yes	Yes	High
Gage 1970 (rat, 15 days)	No	Yes	Yes	No	Low
Hazleton 1979c (rat, 4 weeks)	Yes	Yes	No	Yes	Moderate
Hazleton 1979b (mouse, 4 weeks)	Yes	Yes	No	Yes	Moderate
Hazleton 1980c (rat, 3 months)	Yes	Yes	Yes	Yes	High
Hazleton 1980b (mouse, 3 months)	Yes	Yes	Yes	Yes	High
Krieger et al. 2020 (20 days, rat)	Yes	Yes	Yes	Yes	High
Krieger et al. 2020 (65 days, rat)	Yes	Yes	Yes	Yes	High
Inhalation chronic exposure					
Bogdanffy et al. 1994a; Hazleton 1988 (rat)	Yes	Yes	Yes	Yes	High
Bogdanffy et al. 1994a; Hazleton 1988 (mouse)	Yes	Yes	Yes	Yes	High
Outcome: Developmental					
Inhalation acute exposure					
Hurtt et al. 1995; Hazleton 1980d	Yes	Yes	Yes	Yes	High
Oral acute exposure					
Hurtt et al. 1995	Yes	Yes	Yes	Yes	High
Oral intermediate exposure					
Mebus et al. 1995	Yes	Yes	Yes	Yes	High

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

	Initial study confidence	Initial confidence rating
Outcome: Respiratory Effects (inhalation only)		
Inhalation acute exposure		
Human studies		
Deese and Joyner 1969	Low	Low
Hinderliter et al. 2005	Low	
Union Carbide 1973	Very Low	
Animal studies		
Bogdanffy et al. 1997 (rat, 1 day)	High	High
Bogdanffy et al. 1997 (rat, 5 days)	High	
Krieger et al. 2020 (1 day, rat)	High	
Krieger et al. 2020 (5 days, rat)	High	
Union Carbide 1973 (rat)	Very Low	
Union Carbide 1973 (mouse)	Very Low	
Union Carbide 1973 (rabbit)	Very Low	
Union Carbide 1973 (guinea pig)	Very Low	
Inhalation intermediate exposure		
Animal studies		
Bogdanffy et al. 1997 (4 weeks)	High	High
Gage 1970 (rat, 15 days)	Low	
Hazleton 1979c (rat, 4 weeks)	Moderate	
Hazleton 1979b (mouse, 4 weeks)	Moderate	
Hazleton 1980c (rat, 3 months)	High	
Hazleton 1980b (mouse, 3 months)	High	
Krieger et al. 2020 (20 days, rat)	High	
Krieger et al. 2020 (65 days, rat)	High	
Inhalation chronic exposure		
Human studies		
Deese and Joyner 1969	Moderate	Moderate
Khoshakhlagh et al. 2023	Low	
Animal studies		
Bogdanffy et al. 1994a; Hazleton 1988 (rat)	High	High
Bogdanffy et al. 1994a; Hazleton 1988 (mouse)	High	
Outcome: Developmental effects		
Inhalation acute exposure		
Animal studies		
Hurtt et al. 1995; Hazleton 1980d	High	High
Oral acute exposure		
Animal studies		
Hurtt et al. 1995	High	High

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

	Initial study confidence	Initial confidence rating
Oral intermediate exposure		
Animal studies		
Mebus et al. 1995	High	High

C.6.2 Adjustment of the Confidence Rating

The initial confidence rating was then downgraded or upgraded depending on whether there were substantial issues that would decrease or increase confidence in the body of evidence. The nine properties of the body of evidence that were considered are listed below. The summaries of the assessment of the confidence in the body of evidence for respiratory 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 acetate exposure is presented in Table C-19.

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

	Initial confidence	Adjustments to the initial confidence rating	Final confidence
Outcome: Respiratory effects (inhalation only)			
Human studies	Moderate	-1 for risk of bias, -1 for imprecision, -1 for unexplained inconsistency	Very low
Animal studies	High	+1 consistency in findings, +1 dose-response	High
Outcome: Developmental effects			
Animal studies	High	-1 for unexplained inconsistency, -1 for indirectness	Low

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

	Confidence in body of evidence	
Outcome	Human studies	Animal studies
Respiratory effects (inhalation only)	Very low	High
Developmental effects	No data	Low

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, respectively). Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for risk of bias:
    - No downgrade if most studies are in the risk of bias first tier
    - Downgrade one confidence level if most studies are in the risk of bias second tier
    - Downgrade two confidence levels if most studies are in the risk of bias third tier

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

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

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

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

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

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

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

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

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

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

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

In the seventh step of the systematic review of the health effects data for vinyl acetate, 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 acetate is presented in Table C-20.

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

Outcome	Confidence in body of evidence	Direction of health effect	Level of evidence for health effect
Human studies			
Respiratory effects (inhalation)	Very Low	Health effect	Inadequate
Animal studies			
Respiratory effects (inhalation)	High	Health effect	High
Developmental effects	Low	Health effect	Low

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:

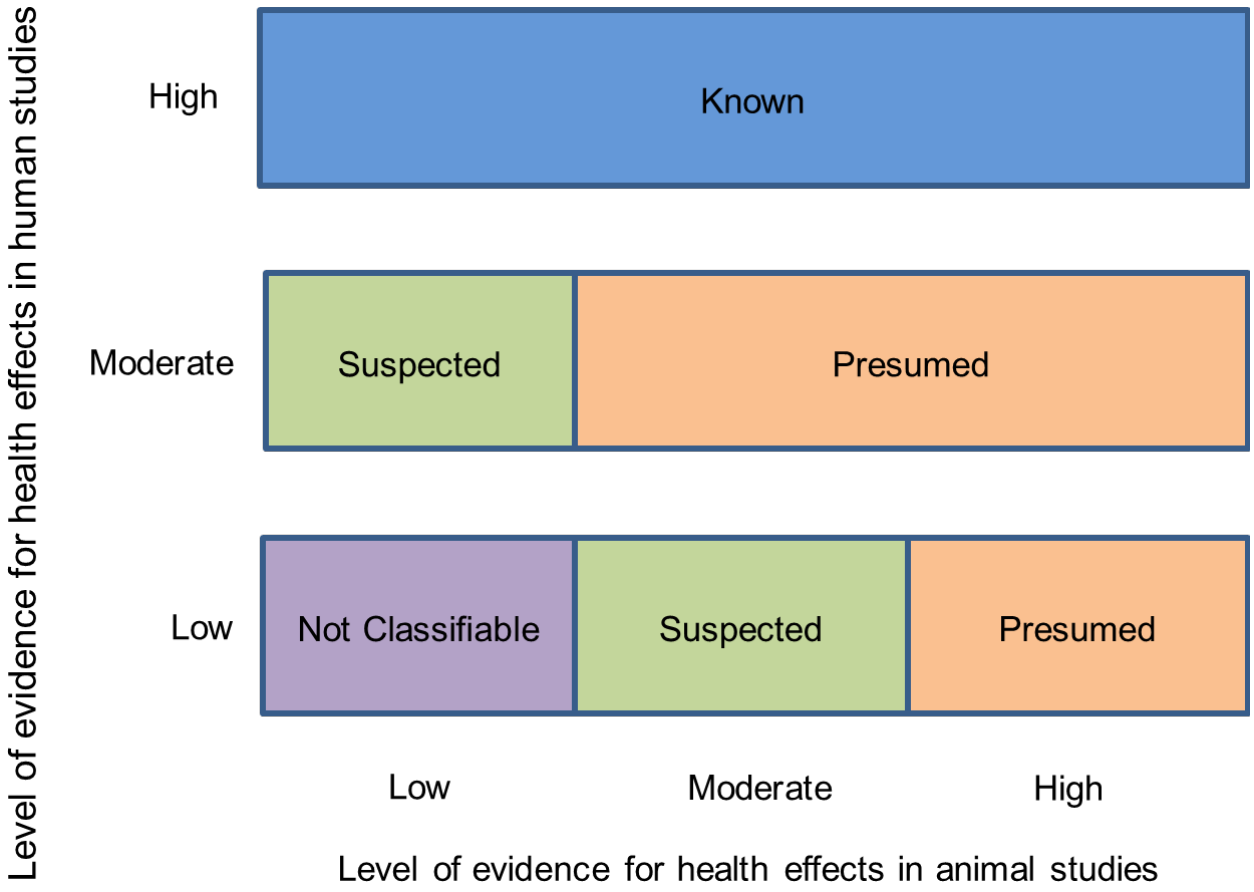
- **Known** to be a hazard to humans
- **Presumed** to be a hazard to humans
- **Suspected** to be a hazard to humans
- **Not classifiable** as to the hazard to humans

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 acetate are listed below and summarized in Table C-21.

Table C-21. Hazard Identification Conclusions for Vinyl Acetate

Outcome	Hazard identification
Respiratory effects (inhalation only)	Presumed health effect
Developmental effects	Not classifiable

Presumed Health Effects

- Respiratory effects (inhalation only)
  - Inadequate evidence of respiratory effects from controlled exposure to vinyl acetate with a very small number of individuals evaluating very limited endpoints (Deese and Joyner 1969; Hinderliter et al. 2005; Union Carbide 1973) and two occupational studies of workers exposed to vinyl acetate (Deese and Joyner 1969; Khoshakhlagh et al. 2023).
  - High level of evidence of respiratory tract damage in rats and mice following acute-, intermediate-, and chronic-duration exposure (Bogdanffy et al. 1997; 1994a; Gage 1970; Hazleton 1980b, 1988; Krieger et al. 2020).

Not Classifiable Effects

- Developmental effects
  - No human data were identified.
  - Low level of evidence for impaired growth and development in rats following developmental exposure to vinyl acetate via inhalation or oral exposure. Decreased fetal weight and length as well as delayed ossification were observed in rat fetuses following maternal inhalation exposure during gestation; these effects may have been secondary to decreased maternal weight (Hazleton 1980d; Hurtt et al. 1995). Decreased F1 weanling weights were also observed in rats in a 2-generation drinking-water study; these effects may have been secondary to decreases in both maternal water intake and body weight gain during lactation (Mebus et al. 1995). However, no effects were noted in F2 pup weights, despite F1 dam body weight effects (Mebus et al. 1995). In an oral gestation-only study, neither maternal nor fetal effects were noted (Hurtt et al. 1995).

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 C-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 C-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									

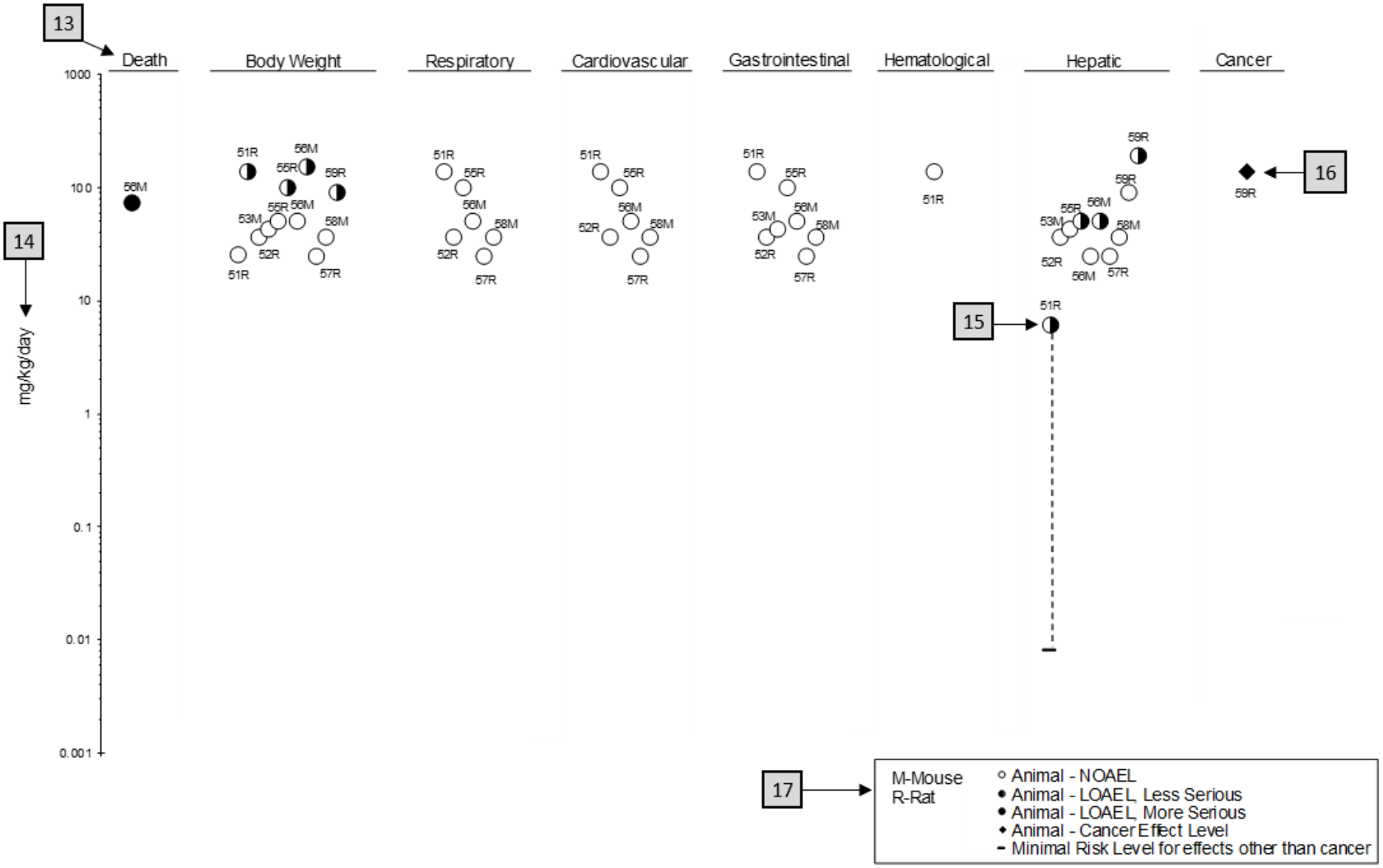
[a]The number corresponds to entries in Figure 2-x.

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

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

APPENDIX D

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



APPENDIX E. QUICK REFERENCE FOR HEALTH CARE PROVIDERS

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

Primary Chapters/Sections of Interest

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

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

Pediatrics:

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

ATSDR Information Center

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

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

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

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

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

Other Agencies and Organizations

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

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

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

Clinical Resources (Publicly Available Information)

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

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

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

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

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

APPENDIX F. GLOSSARY

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

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

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

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

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

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

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

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

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

Carcinogen—A chemical capable of inducing cancer.

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

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

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

Ceiling Value—A concentration that must not be exceeded.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

APPENDIX G. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

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

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

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

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

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