CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

Vinyl acetate is a man-made compound that is used in the production of polymers and copolymers, including polyvinyl acetate, polyvinyl alcohol, polyvinyl acetals, ethylene-vinyl acetate (EVA) copolymer, and polyvinyl chloride-acetate copolymer. It is used in adhesives, paint and powder coatings, plastics and resins, rubber foam, packaging, sporting equipment (e.g., ski boots, bicycle seats), auto-related films, and intermediates in construction and building materials. Vinyl acetate also is approved for use as a food additive (masticatory substance, solvent/vehicle) and as a component in polymerized food packaging (e.g., EVA copolymers).

Vinyl acetate has been detected at low levels in ambient air and water, with the most frequent detections in outdoor air. It has also been detected at low levels in air and soil near hazardous waste sites. Volatilization to the atmosphere is an important transport process if it is released to surface water and soils, due to the high vapor pressure of vinyl acetate. Based on the low soil adsorption coefficient and high water solubility, vinyl acetate is expected to be highly mobile in soils and is likely to partition to groundwater when released to subsurface soils. The low octanol/water partition coefficient for vinyl acetate suggests that it is unlikely to bioconcentrate/biomagnify in terrestrial or aquatic organisms/food chains. This apparent lack of vinyl acetate bioconcentration indicates that consumption of meat or fish is not an important exposure pathway for this compound. In the atmosphere, vinyl acetate is rapidly broken down by photochemical oxidation with an atmospheric lifetime on the order of hours to days. In soil, surface water, and groundwater, the compound undergoes hydrolysis and biotransformation, with half-lives on the order of hours to days. The main products of these transformation processes are acetic acid, acetaldehyde, and acetate.

General population exposure to vinyl acetate is expected to be low. Potential sources of exposure include inhalation of contaminated ambient air and cigarette smoke, dermal contact with products containing the compound (e.g., glues and paints), ingestion of food items containing the compound, and dermal and inhalation exposure during domestic water use (e.g., showering or washing activities) if the water contains vinyl acetate. Vapor intrusion of vinyl acetate into structures from contaminated soil and groundwater may result in indoor air levels of vinyl acetate in buildings and residences. Since vinyl acetate has been detected at hazardous waste sites, populations living near contaminated sites may have increased exposure via ambient air, groundwater contamination, and/or vapor intrusion, compared to the

general population. Occupational exposure to vinyl acetate occurs via inhalation of contaminated workplace air. Workers may also be exposed by dermal contact with vinyl acetate vapor or liquids and products containing the compound.

1.2 SUMMARY OF HEALTH EFFECTS

Information on the noncancer toxicity of vinyl acetate comes primarily from studies in laboratory animals; however, a limited number of human controlled exposure and occupational studies contribute to the identification of primary toxicity targets. The majority of animal studies evaluate inhalation or oral exposure, with only a few evaluating dermal exposure.

As illustrated in Figures 1-1 and 1-2, sensitive noncarcinogenic effects in laboratory animals following vinyl acetate exposure include respiratory effects (inhalation) and developmental effects (inhalation, oral). 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. Therefore, the systematic review was limited to respiratory and developmental effects, resulting in the following hazard identification conclusions:

- Respiratory system effects are a presumed health effect for humans following inhalation exposure.
- The data are inadequate to conclude whether developmental effects will occur in humans.

Respiratory Effects. The primary target of vinyl acetate toxicity following inhalation exposure in humans and animals is the respiratory system, presumably due to chronic irritation at the portal of entry. Limited human data report irritation of the nose and throat following controlled and occupational exposure in small groups. Some individuals reported mild irritation after acute exposure to concentrations ranging from 4 to 34 ppm, with exposures of 72 ppm associated with persistent irritation (Deese and Joyner 1969; Union Carbide 1973). Limited data suggest that repeated occupational exposure to vinyl acetate is generally without adverse respiratory effect at levels <10 ppm (Deese and Joyner 1969). However, subjective respiratory complaints and mild reductions in pulmonary function were reported in one study at an average concentration of 3.61 ppm (range of 0.02–11.71 ppm) (Khoshakhlagh et al. 2023). In laboratory rats and mice, damage to the respiratory system is consistently reported following inhalation exposure at acute- and intermediate-duration exposures ≥598.5 ppm (Bogdanffy et al. 1997; Hazleton

Figure 1-1. Health Effects Found in Animals Following Inhalation Exposure to Vinyl Acetate

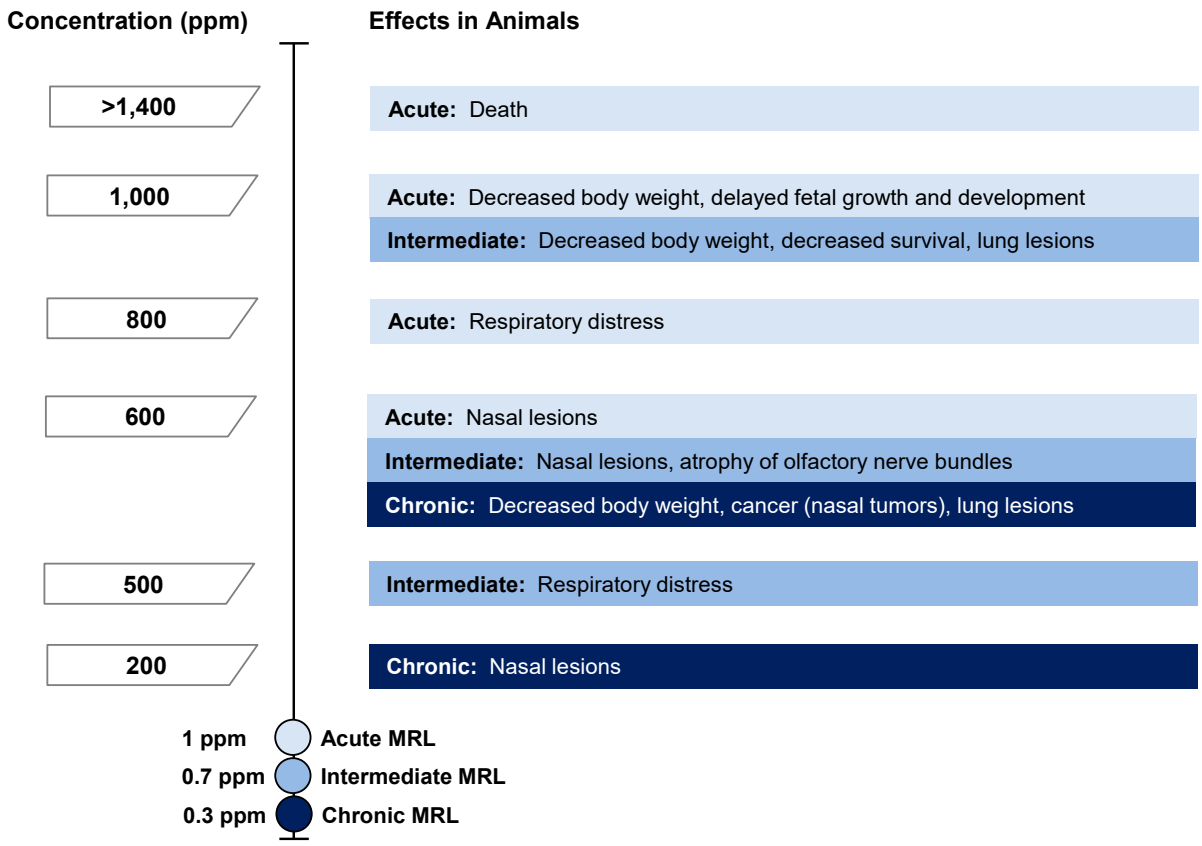
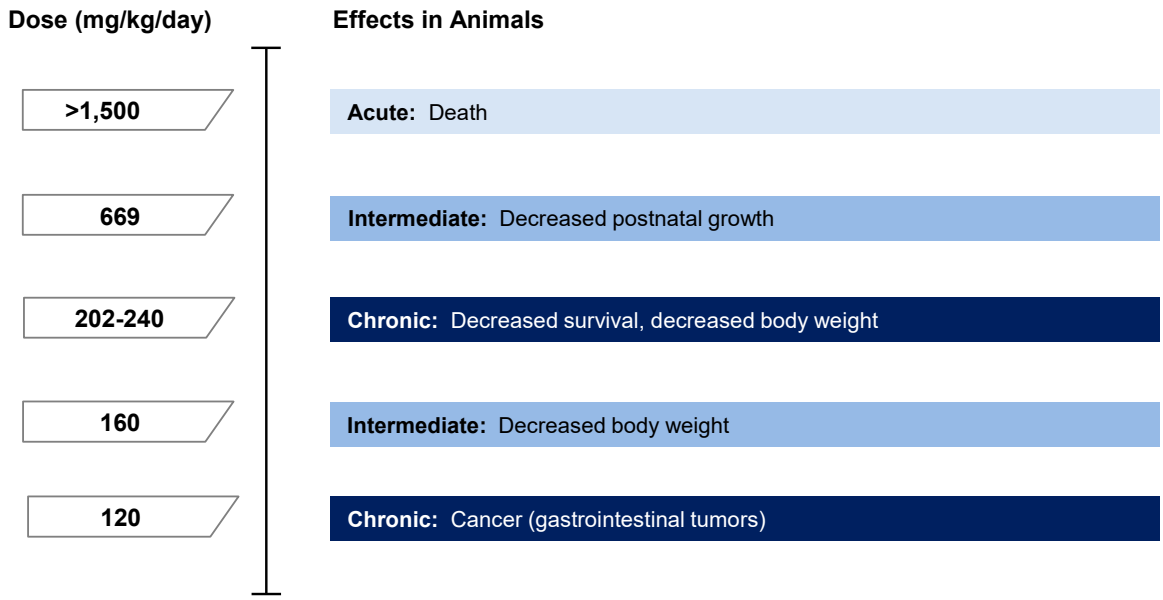


Figure 1-2. Health Effects Found in Animals Following Oral Exposure to Vinyl Acetate



1980b, 1980c; Krieger et al. 2020) and chronic-duration exposures ≥200.5 ppm (Bogdanffy et al. 1994a; Hazleton 1988). While lesions were found throughout the respiratory tract, findings indicated that the extrathoracic region is more susceptible to the irritant effects of inhaled vinyl acetate than the lower respiratory tract. The olfactory epithelium of the nasal cavity in rats appears to be particularly susceptible to vinyl acetate toxicity, with degenerative, necrotic, and/or hyperplastic lesions following exposure for acute-, intermediate-, or chronic-duration exposure (Bogdanffy et al. 1994a, 1997; Krieger et al. 2020). These effects are attributed to intracellular acidification resulting from metabolism of vinyl acetate to acetic acid (Bogdanffy 2002).

Developmental Effects. No studies were located regarding developmental effects in humans following exposure to vinyl acetate. No exposure-related embryolethality or teratogenicity were observed in rat offspring following maternal exposure to inhalation concentrations up to 1,005 ppm (Hazleton 1980d; Hurtt et al. 1995) or drinking water concentrations up to 477 mg/kg/day during gestation (Hurtt et al. 1995) or drinking water concentrations up to 697 mg/kg/day in a 2-generation study (Mebus et al. 1995). In the inhalation study, fetal effects at 1,005 ppm included decreased weight and length as well as delayed ossification; these effects may have been secondary to decreased maternal weight. No changes in fetal growth or development were observed following oral exposure during gestation. However, F1 pup weight at weaning was decreased in the 2-generation drinking-water study. As with the inhalation study, this may be secondary to decreased F0 maternal water intake (which may impair milk production) as well as decreased F0 maternal body weight gain during lactation (Mebus et al. 1995). F2 pup weights were not decreased, despite decreases in F1 maternal water intake and body weights.

Cancer. No adequate studies evaluating carcinogenic potential of vinyl acetate in humans have been found. Studies in animals indicate that vinyl acetate causes route-specific tumors at the portal of entry, with exposure-related neoplastic lesions in the upper respiratory system in rats following chronic-duration inhalation exposure (Bogdanffy et al. 1994a; Hazleton 1988) and in the oral cavity and upper gastrointestinal tract of rats and mice following chronic-duration drinking-water exposure (Belpoggi et al. 2002; Maltoni et al. 1997; Minardi et al. 2002). Observed portal-of-entry effects are attributed to rapid hydrolysis of vinyl acetate following contact with mucosal surfaces (Albertini 2013; Bogdanffy 2002; Bogdanffy and Valentine 2003; Bogdanffy et al. 1999, 2001, 2004; Slikker et al. 2004). Hydrolysis products include acetaldehyde, a known genotoxicant, and acetic acid, which lowers cellular pH, resulting in cellular damage and subsequent proliferation. Evidence for neoplastic effects at sites distant from the site of administration is limited but includes uterine carcinoma in rats following exposure to vinyl acetate in drinking water for 104 weeks following *in utero* exposure (Belpoggi et al. 2002).

The International Agency for Research on Cancer (IARC) has determined that vinyl acetate is possibly carcinogenic to humans (Group 2B) based on inadequate evidence in humans and limited evidence in experimental animals (IARC 1995). The U.S. Environmental Protection Agency (EPA) (IRIS 1990) and the Department of Health and Human Services (HHS) (NTP 2021) have not evaluated the potential for vinyl acetate to cause cancer in humans.

1.3 MINIMAL RISK LEVELS (MRLs)

The inhalation database was considered adequate for deriving acute-, intermediate-, and chronic-duration MRLs. As presented in Figure 1-3, the available inhalation data for vinyl acetate suggest that the respiratory system is the most sensitive target of toxicity in laboratory animals following inhalation exposure. Additional effects noted at higher exposure levels included neurological, developmental, body weight, and cancer effects. No other effects were noted below high concentrations associated with increased mortality.

The oral database was considered inadequate for deriving acute-, intermediate-, or chronic-duration MRLs. No exposure-related effects were observed in acute-duration oral exposure studies in animals below the lowest identified median lethal dose (Figure 1-4). Following intermediate- and chronic-duration oral exposure, decreased body weights were observed in drinking water studies; however, some of the observed body weight decreases may be attributable to observed decreases in drinking water intake (due to unpalatability of test substance) and/or decreased food consumption. Decreased body weights were also observed in F1 rats at weaning from a 2-generation study. Similar to adult findings, F1 body weight effects are of unclear biological relevance because they may be secondary to decreased maternal water intake (which may impair milk production) rather than direct toxic action of vinyl acetate. No additional non-neoplastic targets were identified following intermediate- or chronic-duration oral exposure (Figure 1-4).

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

Figure 1-3. Summary of Sensitive Targets of Vinyl Acetate – Inhalation

Available data indicate that the respiratory system is the most sensitive target of vinyl acetate inhalation exposure.

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

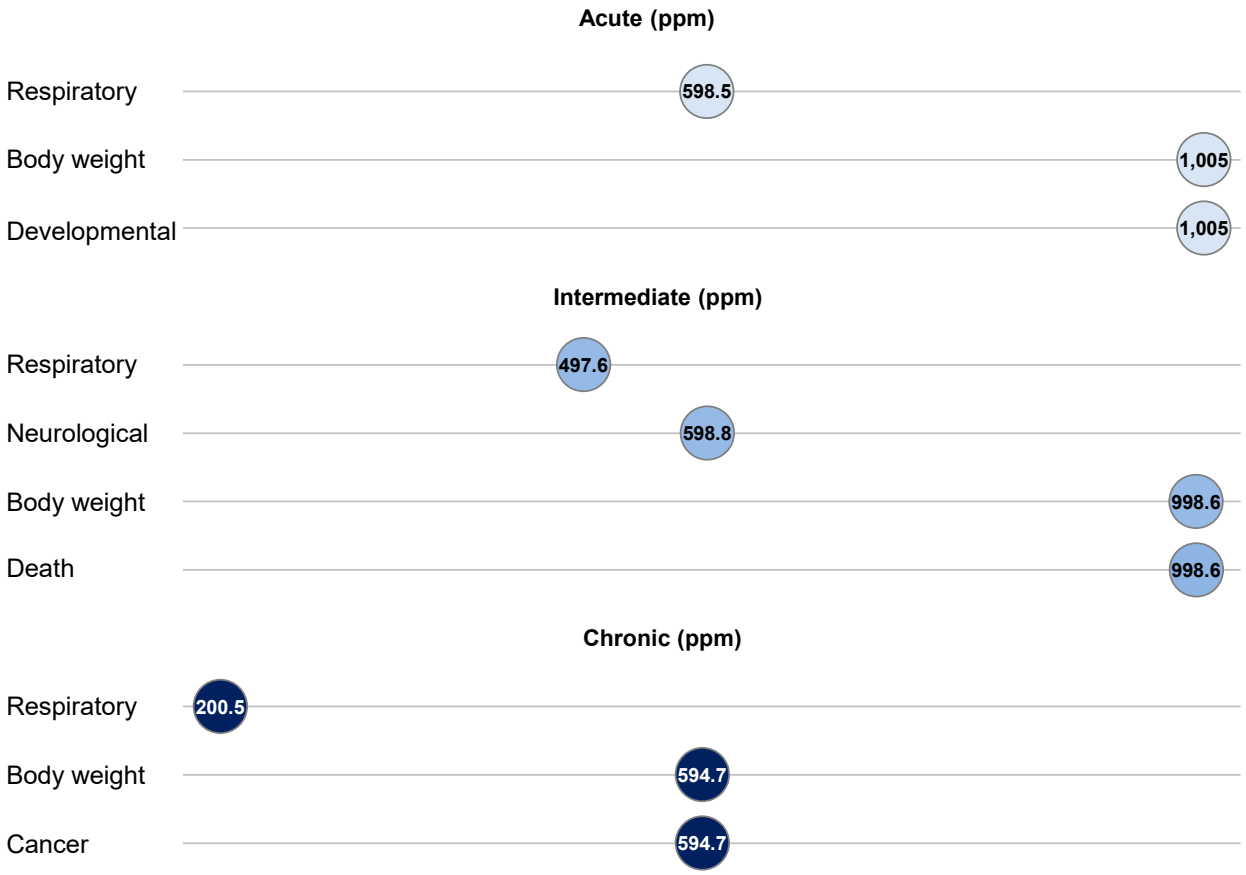


Figure 1-4. Summary of Sensitive Targets of Vinyl Acetate – Oral

Available data indicate that the body weight effects, the developing organism, and cancer are the most sensitive targets of vinyl acetate oral exposure.

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

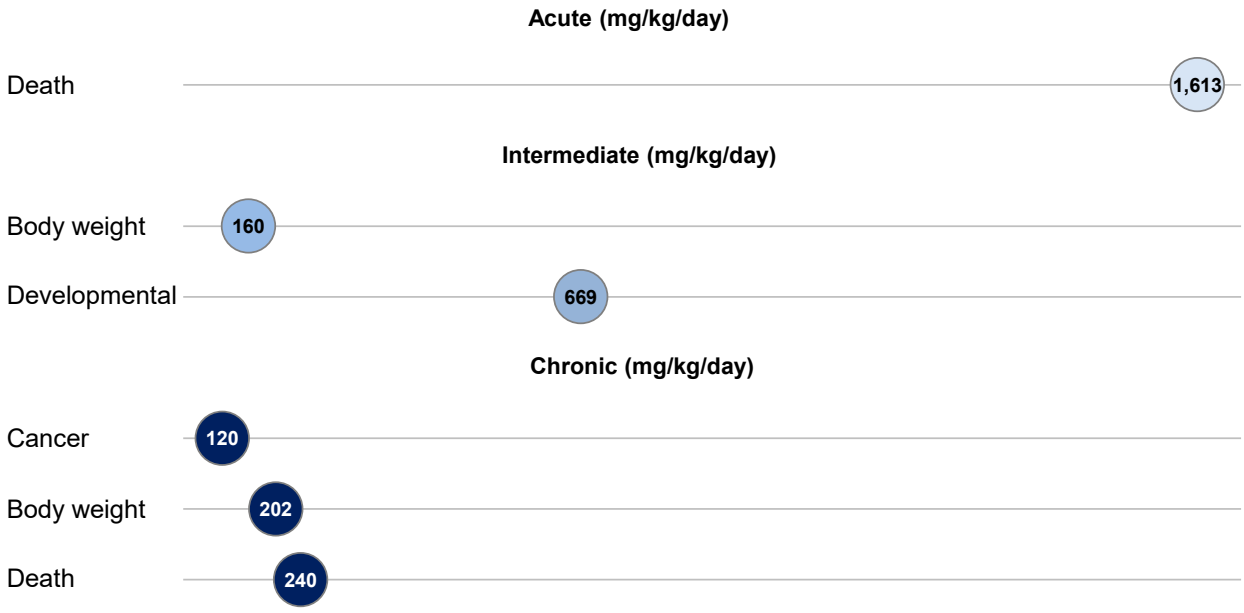


Table 1-1. Minimal Risk Levels (MRLs) for Vinyl Acetate[a]

Exposure route	Exposure duration	MRL	Critical effect	POD type	POD value[b]	Uncertainty/ modifying factor	Reference
Inhalation	Acute	**1 ppm** (3.5 mg/m^3)	Nasal lesions	$NOAEL_{HEC}$	29.1 ppm	UF: 30	Bogdanffy et al. 1997
	Intermediate	**0.7 ppm** (2.5 mg/m^3)	Nasal lesions	$NOAEL_{HEC}$	21.6 ppm	UF: 30	Bogdanffy et al. 1997
	Chronic	**0.3 ppm** (1.1 mg/m^3)	Nasal lesions	$NOAEL_{HEC}$	8.52 ppm	UF: 30	Bogdanffy et al. 1994a; Hazleton 1988
Oral	Acute	None	–	–	–	–	–
	Intermediate	None	–	–	–	–	–
	Chronic	None	–	–	–	–	–

[a]See Appendix A for additional information.
[b]HEC values were calculated using a PBPK model (Bogdanffy et al. 1999; Hinderliter et al. 2005) with model parameters from 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. Parameters in this model account for adjustments to a continuous (24 hours/day) exposure scenario. See Appendix A for additional details and calculations.

HEC = human equivalent concentration; NOAEL = no-observed-adverse-effect level; PBPK = physiologically based pharmacokinetic; POD = point of departure; TWA = time-weighted average; UF = uncertainty factor