CHAPTER 3. TOXICOKINETICS, SUSCEPTIBLE POPULATIONS, BIOMARKERS, CHEMICAL INTERACTIONS

3.1 TOXICOKINETICS

Toxicokinetic data are available from *in vivo* animal studies and *in vitro* studies regarding the absorption, distribution, metabolism, and excretion of vinyl acetate. Available data are summarized below.

- Vinyl acetate is rapidly and effectively absorbed via the inhalation and oral route. Absorption data following dermal exposure are not available. However, vinyl acetate is expected to be absorbed to some degree based on lethality reported in a single rabbit study following exposure to a highly concentrated dermal dose.

- Vinyl acetate is rapidly and widely distributed, with the highest concentration in the Harderian gland, salivary glands, lacrimal glands, gastrointestinal mucosa, and respiratory tract.

- Vinyl acetate is rapidly hydrolyzed by carboxylesterases to form acetaldehyde and acetic acid. Under physiological conditions, acetic acid is highly ionized into acetate, which is incorporated into the "2 carbon pool" of normal body metabolism and eventually forms carbon dioxide (CO_2) as the major breakdown product.

- Vinyl acetate is eliminated rapidly from the body, primarily through expired air as CO_2.

- Available *in vivo* and *in vitro* data have been utilized to develop PBPK models to simulate the kinetics of vinyl acetate uptake and metabolism in the nasal cavity in rats and humans.

3.1.1 Absorption

No studies were located regarding the absorption of vinyl acetate in humans after exposure via any route.

Studies in rats indicate that vinyl acetate is rapidly and effectively absorbed via the inhalation route. Following administration of radiolabeled vinyl acetate ([vinyl-1,2-^{14}C]-VA, or ^{14}C-VA) in the air at a concentration of 1,000 ppm for 6 hours, almost half of the radioactivity was eliminated via expired air within 6 hours after exposure (Hazleton 1979a). The exact dose of vinyl acetate administered by inhalation, however, could not be determined because some of the radioactivity was exhaled during the 6-hour exposure period. A follow-up study using rats exposed to 750 ppm ^{14}C-VA for 6 hours supported these results and showed that the major portion of the radioactivity was eliminated in expired air primarily as CO_2 during the first 24 hours (Hazleton 1980a).

Animal studies indicate that vinyl acetate is also quickly and effectively absorbed via the oral route. Following gavage administration of 1 mL of a 5,000-ppm aqueous solution of ^{14}C-VA, high

concentrations of the radiolabel were found to be distributed throughout the body, and the majority was eliminated in expired air primarily as CO_2 during the first 6 hours after dosing (Hazleton 1979a). Similarly, 65% of the radioactivity of six 1-mL doses of a 10,000-ppm solution orally administered by gavage to rats in a follow-up study was eliminated during both the 6-hour dosing period and 96-hour collection period (Hazleton 1980a). In mice, 1 mL of a 5,000 ppm ^{14}C-VA aqueous solution was quickly absorbed as shown by the wide distribution of radiolabel in tissues throughout the body 1 hour after oral administration (Hazleton 1980a).

Dermal penetration of vinyl acetate in rabbits was indirectly demonstrated through the observation of mortality in animals that were dermally treated with 2.5 mL/kg (Smyth and Carpenter 1948). No further details regarding dermal absorption in laboratory animals are available.

3.1.2 Distribution

No studies were located regarding the distribution of vinyl acetate in humans following exposure via any route or animals following dermal exposure.

Studies in male and female rats show that radioactivity is immediately and widely distributed throughout the body after inhalation exposure to 1,000 ppm ^{14}C-VA (Hazleton 1979a). The salivary glands, lacrimal glands, Harderian glands, gastrointestinal mucosa, nasoturbinates, kidneys, and certain portions of the larynges had the highest concentrations of the radiolabel. The brain, spinal cord, liver, fat, and bone marrow also had readily detectable levels of radioactivity. Low levels in the heart, blood, testes, and skeletal muscle were also observed. Whole-body autoradiographs obtained at 1 and 6 hours after exposure showed a general decrease in the radioactivity with increased time. Seventy-two hours after exposure, radioactivity was still found in the brain, spinal cord, Harderian glands, maxillary sinuses, adrenal glands, and kidneys. Approximately 19% of the total radioactivity recovered was found in the carcass 96 hours after exposure.

In a follow-up study, 16 rats were exposed to air containing 750 ppm ^{14}C-VA for 6 hours (Hazleton 1980a). The tissue distribution of radioactivity is given in Table 3-1. As can be seen in Table 3-1, the highest concentrations were observed in the Harderian gland, followed by the ileum, submaxillary salivary gland, and the contents of the gastrointestinal tract. Radioactivity was also found at significant levels in the liver, kidney, lung, brain, stomach, colon, and ovaries. Differences between the sexes in the distribution of radioactivity was seen in the gonads; females had higher concentrations in the ovaries than

did males in the testes. Although the total radioactivity decreased with time, no major differences in the distribution pattern were found at 1, 6, and 72 hours after exposure.

Table 3-1. Distribution of Radioactivity in Rats Immediately After Inhalation of 750 ppm [^{14}C]-Vinyl Acetate for 6 Hours

Tissue	Concentration of radioactivity (µg equivalents/g)
Adrenals	119
Blood	72
Bone	79
Brain	153
Colon	257
Fat	29
Gastrointestinal contents	291
Gonads	117
Harderian gland	2,045
Heart	82
Ileum	393
Kidney	204
Liver	204
Lungs	270
Residual carcass	72
Submaxillary salivary gland	341
Skeletal muscle	61
Stomach	210

Source: Hazleton 1980a

In animals, the distribution of radioactivity following oral exposure to ^{14}C-VA has been studied using male and female rats and mice (Hazleton 1979a, 1980a). Similar distribution patterns were observed in rats administered either 6 hourly 1-mL doses of an aqueous solution containing 10,000 ppm vinyl acetate (equivalent to 237 mg/kg) by gavage (Hazleton 1980a) or one dose containing 1 mL of a 5,000-ppm vinyl acetate solution (equivalent to 23.4 mg/kg) (Hazleton 1979a). One hour following administration of either dose, the radioactivity was found to be widely distributed with the highest concentrations found in the Harderian gland and salivary glands. High levels of radioactivity were also found in the liver, kidney, heart, and gastrointestinal tract. As with inhalation exposure, the level of radioactivity decreased with time, and there were no major differences in the distribution pattern at 6 and 72 hours after oral exposure. A mean of 7.1% of the administered radioactivity was present in the carcass 96 hours after exposure. As with inhalation exposure, a sex difference in the distribution of radioactivity was seen in the gonads;

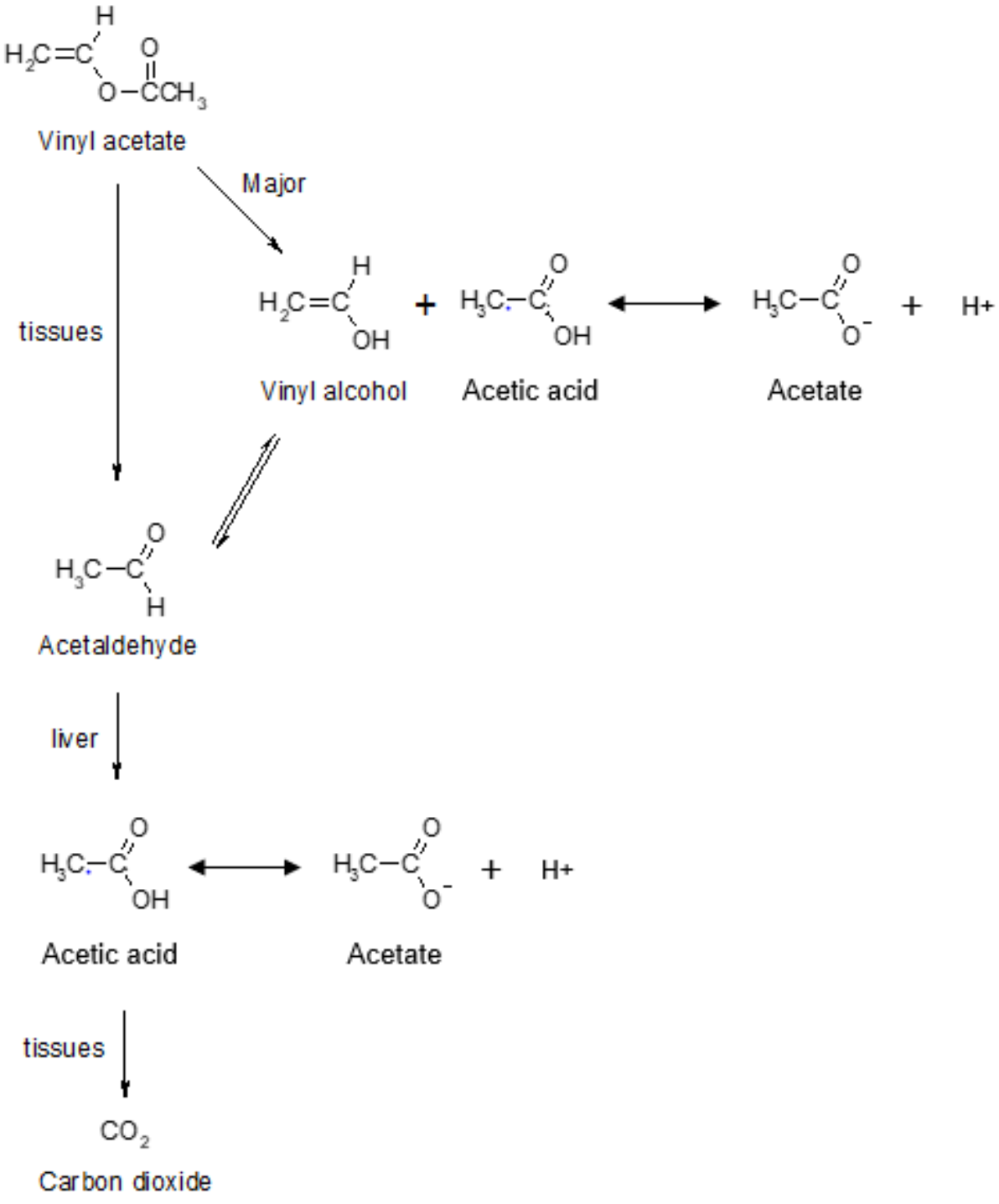
females had higher concentration in the ovaries than did males in the testes. A similar distribution pattern was seen in mice of both sexes administered a single oral dose of 5,000 ppm of ^{14}C-VA as an aqueous solution (Hazleton 1980a). In this study, the highest concentrations of radioactivity were found in Harderian glands, salivary and lingual glands, gastrointestinal mucosa, liver, and brown fat. Low levels were found in blood, muscle, fat, and testes. As with the rats, the distribution pattern was unchanged 6 and 72 hours after dosing, although the levels were reduced. Relative tissue concentrations also tended to be higher in animals exposed via inhalation compared with oral exposure. This was particularly true in the lung and brain.

3.1.3 Metabolism

The metabolism of vinyl acetate has been studied in humans (Bogdanffy et al. 1998; Hinderliter et al. 2005), animals (Hazleton 1979a, 1980a; Holub and Tarkowski 1982; Morris et al. 2002; Simon et al. 1985a), and *in vitro* studies (Bogdanffy and Taylor 1993; Bogdanffy et al. 1998, 1999; Boyland and Chasseaud 1967; Fedtke and Wiegand 1990; Morris et al. 2002). Metabolism of vinyl acetate, particularly at the portal of entry, has also been thoroughly reviewed (Andersen and Sarangapani 1999; Andersen et al. 2002; Bogdanffy et al. 2001; Plowchalk et al. 1997; Slikker et al. 2004). Collectively, these studies show that vinyl acetate quickly undergoes hydrolysis in the body through several intermediate steps to form the principal end products, CO_2, and water. The metabolic pattern was not influenced by the route of vinyl acetate exposure but did show nonlinear kinetic patterns at high concentrations, indicating that the metabolic processes are saturable. A summary of the proposed metabolic pathways for vinyl acetate is discussed below and presented in Figure 3-1.

The primary metabolic pathway for vinyl acetate is rapid hydrolysis into acetic acid and the unstable intermediate vinyl alcohol via a high-affinity carboxylesterase pathway (Andersen et al. 2002; Bogdanffy et al. 1999, 2001; Plowchalk et al. 1997; Slikker et al. 2004). Vinyl alcohol is rapidly converted to acetaldehyde, and acetic acid is extensively ionized into acetate under physiological conditions. *In vivo* and *in vitro* experiments have shown that the carboxylesterases in epithelial cells in the respiratory tract of rats and humans and the oral mucosa of rats and mice are capable of metabolizing vinyl acetate, although hydrolysis activity is approximately 100-fold lower in oral mucosal cells compared with nasal mucosal cells (Bogdanffy and Taylor 1993; Bogdanffy et al. 1998, 1999; Hinderliter et al. 2005; Morris et al. 2002). These findings indicate that metabolism of vinyl acetate is expected to occur at the portal of entry, although blood and liver cells are also capable of hydrolyzing vinyl acetate into acetaldehyde and acetate via esterases (Fedtke and Wiegand 1990; Hazleton 1979a, 1980a; Simon et al. 1985a). In the liver,

Figure 3-1. Proposed Primary Metabolic Pathway for Vinyl Acetate



acetaldehyde can be further metabolized into acetate. This in turn is incorporated into the "2 carbon pool" of normal body metabolism and eventually forms CO_2 as the major breakdown product. Therefore, the metabolism of vinyl acetate results in two acetate molecules that enter the "2 carbon pool." This has been confirmed in excretion studies that have documented $^{14}CO_2$ in exhaled air as the major metabolite and source of radioactivity recovered following either inhalation or oral exposure to ^{14}C-VA (Hazleton 1979a, 1980a). Following inhalation exposure, zero-order kinetics were observed at higher concentrations (800–1,400 ppm) and first-order kinetics at lower concentrations (Simon et al. 1985a). This indicates that the metabolic pathways of vinyl acetate are saturable at high levels.

In vitro studies show that the half-lives for conversion of vinyl acetate to acetaldehyde in rat plasma to be 57, 58, and 57 seconds at concentrations of 25, 50, or 100 ppm, respectively. Using rat whole blood, the half-lives of vinyl acetate were found to be 112, 121, and 141 seconds at the same conditions, respectively. In rat liver homogenates, the half-lives were 50, 97, and 167 seconds, again at the same concentrations, respectively. Similar half-lives were seen in mouse plasma, whole blood, and liver homogenates. Furthermore, even with diluted preparations of plasma, whole blood, and liver homogenates, the hydrolysis of vinyl acetate is very rapid (Hazleton 1979a). A later *in vitro* study using human blood and plasma found that the hydrolysis of vinyl acetate proceeded at a similar rate as reported for the rat and mouse (Hazleton 1980a). However, different results were reported by Fedtke and Wiegand (1990) using 200 µM vinyl acetate added to rat and human blood. They reported that the half-life of vinyl acetate elimination in human whole blood was 4.1 minutes as compared to <1 minute in rat whole blood (Fedtke and Wiegand 1990). The majority of the hydrolysis was found to occur in the red blood cells rather than the plasma of human blood. The half-life in plasma was 62 minutes as compared to 5.5 minutes in red blood cells. However, in rat plasma, the half-life of vinyl acetate elimination was 1.2 minutes as compared to 5.6 minutes in rat red blood cells. While these results differ from those reported above with regard to the location of the hydrolytic enzymes in the blood across species, they do confirm that hydrolysis is the predominant route of metabolism for vinyl acetate in both human and rat blood.

Further *in vitro* metabolic studies show that vinyl acetate added to preparations of rat liver supernatant did conjugate (although not to a large degree) with glutathione (Boyland and Chasseaud 1967). The reaction is mediated by glutathione S-transferase and further metabolism produces mercapturic acid derivatives that are eliminated in the urine (Boyland and Chasseaud 1967, 1970). Rats exposed for 5 hours/day for 6 months to vinyl acetate in the air (10, 100, or 500 mg/m^3) showed a significant depletion of free nonprotein thiols in the liver, but not in a dose-dependent pattern (Holub and Tarkowski 1982).

According to the study authors, the thiol depletion indicates that conjugation with glutathione plays an important role in the detoxification of this chemical. Similar results were seen in rats, guinea pigs, and mice given single intraperitoneal doses of vinyl acetate (Holub and Tarkowski 1982). However, Bogdanffy et al. (1999) concluded that the lack of observed glutathione depletion following exposure indicates that glutathione conjugation is not a major metabolic pathway for vinyl acetate.

Based on analogy to vinyl chloride and vinyl carbamate, it is possible that vinyl acetate could be metabolized into its corresponding epoxide form by cytochrome P450 (CYP450) enzymes; however, evidence of epoxide formation has not been identified following *in vivo* exposure to vinyl acetate (Laib and Bolt 1986; Simon et al. 1985a). Furthermore, inhibition of CYP2E1 using diallyl sulfide did not affect the pharmacological uptake of vinyl acetate by rat nasal explants, but inhibition of carboxylesterases with BNPP decreased uptake by approximately 60% (Bogdanffy et al. 1999). Taken together, these studies do not indicate that metabolism by CYP450 is a major metabolic pathway for vinyl acetate.

3.1.4 Excretion

No studies were located regarding the excretion of vinyl acetate in humans following exposure via any route.

Studies in animals indicate that vinyl acetate is rapidly eliminated following inhalation exposure (Hazleton 1979a, 1980a). In one of these studies, rats were exposed to 750 ppm ^{14}C-VA for 6 hours (Hazleton 1980a). Ninety-six hours following administration, the mean proportions of the recovered radioactivity found in the urine, feces, and expired air were 4.8, 3.6, and 74.6%, respectively. Most of the radioactivity was eliminated in the form of CO_2 during the first 24 hours after exposure. Also, a substantial percentage (16.4%) of the total recovered radioactivity was present in the carcasses at 96 hours. Similar results were obtained in an earlier study conducted by Hazleton (1979a). In this study, rats were exposed to 1,000 ppm vinyl-1,2-^{14}C-VA for 6 hours. Ninety-six hours following administration, the mean proportions of the recovered radioactivity in the urine, feces, and expired air were 7.1, 3.9, and 70.3%, respectively. As with the above study, much of the radioactivity was eliminated within 24 hours of exposure.

The excretion of vinyl acetate following oral exposure has been studied in male and female rats (Hazleton 1979a, 1980a). The excretion of radioactivity in rats following oral administration of 1 mL of a

5,000 ppm [vinyl-1,2-^{14}C]-VA solution (equivalent to 23.4 mg/kg) by gavage was rapid (as in inhalation exposure) (Hazleton 1979a). Ninety-six hours after administration, 3.1, 1.1, and 86.3% of the mean radioactivity was excreted in the urine, feces, and expired air, respectively. After 96 hours, an additional 7% was recovered in the carcasses, accounting for a total of 96% of the administered radioactivity. Most of the radioactivity was eliminated during the first 6 hours after exposure. In a later study, rats were given 6 hourly doses of a 10,000-ppm aqueous solution of [vinyl-1,2-^{14}C]-VA by gavage (Hazleton 1980a). During the 6 hours of exposure and the 96-hour collection period, 1.8, 1.4, and 61.2% of the mean radioactivity was excreted in the urine, feces, and expired air, respectively. After 96 hours, an additional 5% was recovered from the carcasses, accounting for a total of 70% of the administered radioactivity. The authors attributed the unaccounted 30% to loss in expired air that escaped from the metabolic cages housing the animals. The studies show that following oral exposure, vinyl acetate is eliminated rapidly from the body, primarily through expired air as CO_2.

3.1.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

Models are simplified representations of a system with the intent of reproducing or simulating its structure, function, and behavior. PBPK models are more firmly grounded in principles of biology and biochemistry. They use mathematical descriptions of the processes determining uptake and disposition of chemical substances as a function of their physicochemical, biochemical, and physiological characteristics (Andersen and Krishnan 1994; Clewell 1995; Mumtaz et al. 2012a; Sweeney and Gearhart 2020). PBPK models have been developed for both organic and inorganic pollutants (Ruiz et al. 2011) and are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Mumtaz et al. 2012b; Ruiz et al. 2011; Sweeney and Gearhart 2020; Tan et al. 2020). PBPK models can also be used to more accurately extrapolate from animal to human, high dose to low dose, route to route, and various exposure scenarios and to study pollutant mixtures (El-Masri et al. 2004). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic endpoints (Clewell 1995).

Research on PBPK models for vinyl acetate have focused on simulating characteristics of the anatomy and physiology of the rodent and human that are thought to contribute to interspecies differences in dose-response relationships for nasal lesions (Andersen and Sarangapani 1999; Andersen et al. 2002). Important features of vinyl acetate-induced nasal lesions and vinyl acetate kinetics that are relevant to

interspecies extrapolation include: (1) regional gradients of nasal lesions, with more severe lesions occurring in the anterior regions (Bogdanffy et al. 1994a); (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).

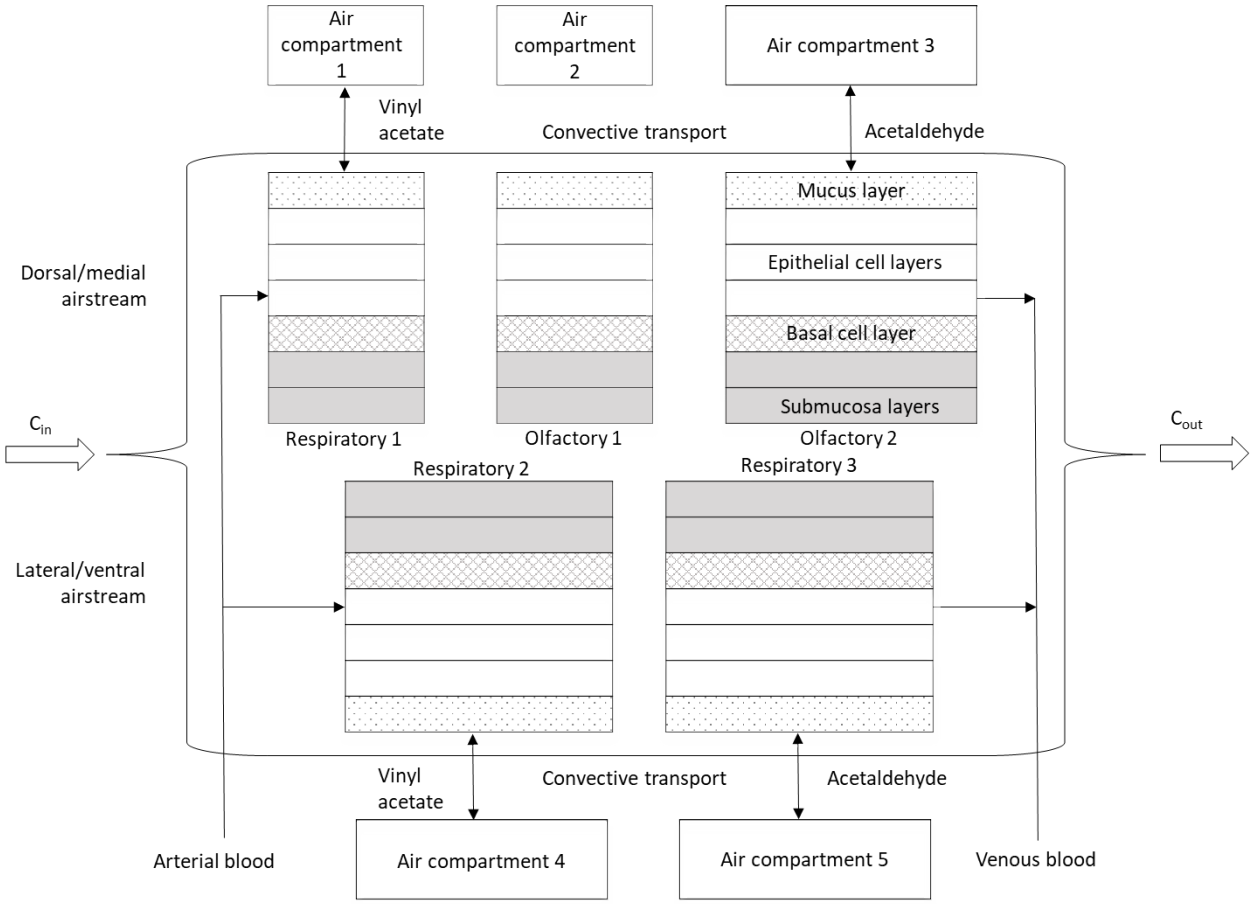
Several models have been developed to simulate the kinetics of vinyl acetate uptake and metabolism in the nasal cavity (Andersen and Sarangapani 1999; Bogdanffy et al. 1999; Plowchalk et al. 1997; Morris et al. 1993). Two models are described in detail in the following discussion because they provide a means to simulate the nasal cavities of rats (Bogdanffy et al. 1999; Plowchalk et al. 1997) and humans (Bogdanffy et al. 1999); and have been evaluated with experimental observations other than those used in model calibration (Bogdanffy et al. 1999; Hinderliter et al. 2005). The models have been applied to predicting nasal tissue dosimetry and interspecies extrapolation of dosimetry in rats to humans (Andersen et al. 2002; Bogdanffy et al. 1999). These models have several features that are important for predicting vinyl acetate dosimetry in the nasal cavity: (1) convective delivery of vinyl acetate to the mucus surface layer of olfactory and respiratory tissues; (2) diffusion of vinyl acetate into progressively deeper layers of olfactory and respiratory tissues; (3) saturable metabolism of vinyl acetate to acetic acid and acetaldehyde; (4) systemic absorption of vinyl acetate and metabolites from submucosal layers; and (5) acidification of olfactory and respiratory tissues resulting from release of protons in the formation of acetic acid.

Bogdanffy et al. (1999; Plowchalk et al. 1997) Model

Description. Bogdanffy et al. (1999) modified the Plowchalk et al. (1997) model to create models of the kinetics of vinyl acetate uptake and metabolism in the nasal cavity of rats and humans. Two major changes were made from the Plowchalk et al. (1997) rat model. The number of compartments was increased from three to five by including an additional dorsal/medial olfactory tissue compartment, and an additional lateral/ventral respiratory tissue compartment (Figure 3-2). Flow-limited exchange of vinyl acetate and its metabolites at the air-mucus layer interface was replaced with diffusion limited exchange.

The Bogdanffy et al. (1999) model divides the nasal tissues into compartments representing: (1) dorsal medial respiratory tissue; (2) dorsal/medial olfactory tissue; and (3) lateral/ventral respiratory tissue. The rat model includes two dorsal medial olfactory tissue compartments; the human model includes a single dorsal medial olfactory tissue compartment. Each tissue compartment is represented by layered

Figure 3-2. PBPK Model of the Rat Nasal Cavity Used to Compute Vinyl Acetate Extraction and Acetaldehyde Exhalation Under Steady-State Conditions*



*The generated structure of the human model is identical to that of the rat, with the exception of having only one olfactory tissue compartment.

Source: Bogdanffy et al. (1999), by permission of Oxford University Press

subcompartments that provide a diffusion pathway for vinyl acetate and its metabolites between the surface mucus layer and deeper epithelial, basal cell, and submucosal layers. Inhaled vinyl acetate deposits in the surface mucus layer of each tissue compartment and then diffuses to deeper subcompartments where it is cleared by metabolism and absorption to blood. The model simulates two air flow patterns in the nasal cavity. A dorsal/medial flow contacts the dorsal olfactory and respiratory compartments and a lateral/ventral flow that contacts the lateral ventral respiratory tissue. Vinyl acetate and its volatile metabolites are assumed to be homogeneously distributed in the air flows and move through the nasal cavity by convection. Exchanges between chemicals in air and the mucus surface layer is assumed to occur by diffusion, governed by the air-mucus concertation gradient, the mucus surface area, a mass transfer coefficient (cm/hour) and a tissue:air partition coefficient. Exchange between tissue subcompartments is governed by diffusion coefficients (cm^2/hour) and the concentration gradient between subcompartments. Metabolism is simulated as Michaelis-Menten processes (V_{max}, K_M), with parameter values assigned to carboxylesterase, acetyl-CoA synthetase, and aldehyde dehydrogenase for each tissue subcompartment. Absorption of vinyl acetate and metabolites from the submucosa is assumed to be flow-limited and governed by the mass of each chemical in the submucosa and blood flow rate to the submucosa. The partition coefficients that govern exchange between air and the mucus surface layer are 29 for vinyl acetate, 140 for acetaldehyde, and 80,000 for acetic acid. These values promote release of acetaldehyde to air and trapping of acetic acid in tissues. The model includes parameters to simulate the change in intracellular pH (free hydrogen ion concentration, H^+) in olfactory and respiratory tissues. This is achieved by simulating the production of H^+ in the conversion of vinyl acetate to acetic acid and removal of intracellular H^+ from facilitated H^+/Na^+ exchange. The rate of formation of H^+ is governed by the rate of formation of acetic acid from vinyl acetate which results in 3 moles of H^+ per mole of vinyl acetate consumed. Rate of H^+/Na^+ exchange is simulated from a Hill equation for the saturable exchange (V_{max}, K_M, Hill coefficient).

Parameter Estimates and Calibration. Distribution of metabolism enzymes to tissue subcompartments was based on studies of the histochemical localization of the enzymes in nasal tissue (Plowchalk et al. 1997). A high affinity carboxylesterase activity (K_M 4.7 µg/mL) was attributed to the mucus surface layer. Lower affinity carboxylesterase activities (K_M 40–50 µg/mL) were attributed to the respiratory and olfactory epithelium, and submucosa. Acetyl-CoA synthetase activities were attributed to the respiratory and olfactory epithelium, and submucosa. Aldehyde dehydrogenase activity was limited to the respiratory and olfactory epithelia. Parameters for carboxylesterase and aldehyde dehydrogenase were obtained from studies of whole tissues and were scaled (V_{max}) to tissue compartment surface areas (Bogdanffy et al. 1998). Parameters for acetyl-CoA synthetase were based on studies of rat liver and

were assumed to be the same for nasal tissues. Values for humans were scaled based on surface area of the nasal tissues (Knowles et al. 1974). Tissue:air partition coefficients for vinyl acetate acetaldehyde were obtained from gas uptake studies (Plowchalk et al. 1997), and the partition coefficient from acetic acid was from Hine and Mookerjee (1975). Diffusion coefficients for vinyl acetate, acetaldehyde, and acetic acid were estimated by Morris et al. (1993). Parameters for the Hill equation used to simulate H^+/Na^+ exchange were based on studies of H^+/Na^+ exchange in human leukocytes (Frelin et al. 1988).

Evaluation. The rat model was evaluated against observations made in rats exposed nose-only to vinyl acetate (Bogdanffy et al. 1999). Air containing vinyl acetate (75–1,500 ppm) was drawn through the nasal cavity of rats and air exiting through the nasopharynx was collected from a nasopharyngeal cannula. This configuration allowed measurements of first-pass extraction and metabolism of vinyl chloride within the nasal cavity. Values for the metabolism parameters for carboxylesterase were calibrated to fit observations from rats exposed at an air flow rate of 100 mL/minute and then the model was evaluated against observations made at 50 and 200 mL/minute. The calibrated model predicted the observed concentration-dependent extraction of vinyl acetate from the inhaled air at all three air flow rates. The model also predicted the concentrations of acetaldehyde in nasopharyngeal air observed at 50 and 100 mL/minute, but overpredicted concentrations at 200 mL/minute.

The Bogdanffy et al. (1999) human model was evaluated against data from an experimental study conducted in humans (Hinderliter et al. 2005). Five adult subjects inhaled, nose-only, vinyl acetate (labeled with ^{13}C at the 1 and 2 positions) from an exposure bag. A nasopharyngeal probe was inserted to allow collection of air exiting the nasal cavity at the nasopharynx. Subjects inhaled vinyl acetate at concentrations of 1, 5, or 10 ppm for periods of 3–5 minutes, at rest or during light exercise. Agreement between observations and model predictions was assessed from the Pearson's correlation coefficient (r) for the observed and predicted nasopharyngeal concentrations of vinyl acetate and acetaldehyde. Without adjustment of model parameter values from those reported in Bogdanffy et al. (1999), the correlation coefficient was 0.9 for vinyl acetate and 0.6 for aldehyde. The experimental design could not control for increases in breathing frequency that accompanied exposures (e.g., doubling with exposure to 10 ppm). When exposures were simulated at inspired air flows of 0.5 or 2 times the default value (7.5 L/minute), the observed mean nasopharyngeal concentrations of vinyl acetate and acetaldehyde fell within the ranges predicted for the range of air flows. Nasopharyngeal concentrations of vinyl acetate were uniformly lower than the inspired concentrations, indicating extraction of vinyl acetate, and increased in proportion to the inspired concentration, suggesting the extraction was not saturated at the exposures studied.

Applications to Dosimetry. Bogdanffy et al. (1999) applied the model to simulating doses of vinyl acetate, acetaldehyde, acetic acid, and intracellular free hydrogen ion to the olfactory epithelium of the rat and human exposed to the same concentrations of vinyl acetate. In both humans and rats, the internal external concentration-epithelium dose relationship was predicted to be nonlinear at exposure concentrations >200 ppm. At exposure concentrations of 200 or 600 ppm, steady-state olfactory tissue concentrations of vinyl acetate, acetaldehyde, and acetic acid were predicted to be higher in humans compared to rats.

3.1.6 Animal-to-Human Extrapolations

The toxicokinetics of inhaled vinyl acetate in humans are similar to those that have been observed in rats and mice, although some differences may occur due to differences in carboxylesterase distribution and/or activity. As described in section 3.1.5, steady-state olfactory tissue concentrations of vinyl acetate, acetaldehyde, and acetic acid were predicted to be higher in humans compared to rats given the same external exposure levels (Bogdanffy et al. 1999). In nasal tissue explants, carboxylesterase activity is about 3 times higher in rat respiratory tissues than human tissues, but roughly equivalent in rat and human olfactory tissues (Bogdanffy et al. 1998). However, K_m values were similar between species and nasal tissue regions (0.04–0.05 mg/mL) (Bogdanffy et al. 1998).

Additional species-specific properties of the respiratory system also impact animal-to-human extrapolations. In addition to differences in physiology (e.g., carboxylesterase distribution and/or activity), there are differences in upper airway morphology between rodents and humans resulting in a higher ratio of the nasal passage surface area to ventilation volume in rodents, compared to humans (EPA 1994). PBPK models evaluating nasal effects of vinyl acetate exposure account for these differences in morphology in dosimetric calculations (Bogdanffy et al. 1997). However, PBPK models do 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). Additionally, the available PBPK models were developed for adult rodents and humas. In order to extrapolate across life stages, all parameters (e.g., ventilation rate) would have to be reevaluated and assigned values that represent specific pre-adult ages (e.g., infants, children).

While no oral toxicokinetic data are available in humans, data in laboratory animals indicate that toxicokinetics are similar between routes and species. Oral tissue carboxylesterase activities were similar between rats and mice (0.5–0.9 mM) (Morris et al. 2002).

3.2 CHILDREN AND OTHER POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Children may be more or less susceptible than adults to health effects from exposure to hazardous substances and the relationship may change with developmental age.

This section also discusses unusually susceptible populations. A susceptible population may exhibit different or enhanced responses to certain chemicals than most persons exposed to the same level of these chemicals in the environment. Factors involved with increased susceptibility may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters can reduce detoxification or excretion or compromise organ function.

Populations at greater exposure risk to unusually high exposure levels to vinyl acetate are discussed in Section 5.7, Populations with Potentially High Exposures.

Available literature does not specifically identify any populations with confirmed unusual or increased susceptibility to the health effects of vinyl acetate. However, based on reported irritative properties of vinyl acetate, certain groups may be more susceptible to health effects of vinyl acetate exposure. For example, individuals with pre-existing health problems in the upper respiratory tract, eyes, and possibly the skin may be unusually susceptible to the irritative effects associated with exposure to vinyl acetate. Preplacement medical examinations to identify such conditions have been recommended for people who may be occupationally exposed to vinyl acetate (NIOSH 1978). Smokers may also represent another potentially susceptible subpopulation because vinyl acetate is a respiratory irritant. In addition, vinyl acetate has been shown to have an effect on mucociliary clearance similar to that of nicotine, so the combined effects of vinyl acetate and nicotine in smokers could result in enhanced impairment of respiratory function (Battista 1976).

Certain genetic variants in the human population may confer increased susceptibility to the toxic effects of vinyl acetate since toxic effects are presumably mediated via metabolites (acetaldehyde and acetic acid; see Section 2.21 for more details). Since hydrolysis of vinyl acetate is carboxylesterase-dependent, identified genetic variants of carboxylesterase that alter enzymatic function could potentially increase susceptibility to toxic effects (Fukami et al. 2008; Yamada et al. 2010; Zhu et al. 2008); however, data regarding human carboxylesterase and vinyl acetate metabolism are limited to a single study reporting a small range of activity in nasal epithelial cells from eight male and one female Caucasian donors (Bogdanffy et al. 1998). Individuals with certain aldehyde dehydrogenase (ALDH2) polymorphisms that reduce the rate of acetaldehyde metabolism may also have increased susceptibility to toxic effects. However, a PBPK model incorporating ALDH2 polymorphisms predicted that the impact of polymorphisms would be negligible in human olfactory tissue (Teeguarden et al. 2008).

It is unclear if the developing fetus or neonate are uniquely susceptible to toxic effects of vinyl acetate, as all available studies report developmental effects at exposure levels associated with parental toxicity (Hazleton 1980d; Hurtt et al. 1995; Mebus et al. 1995).

3.3 BIOMARKERS OF EXPOSURE AND EFFECT

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 2006). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. Biomarkers of exposure to vinyl acetate are discussed in Section 3.3.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that (depending on magnitude) can be recognized as an established or potential health impairment or disease (NAS/NRC 2006). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effect caused by vinyl acetate are discussed in Section 3.3.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.2, Children and Other Populations that are Unusually Susceptible.

3.3.1 Biomarkers of Exposure

Metabolic studies demonstrate that vinyl acetate is effectively hydrolyzed by esterases in the blood to vinyl alcohol and acetate. The vinyl alcohol is subsequently converted to acetaldehyde (Hazleton 1979a, 1980a; Simon et al. 1985a). Acetaldehyde is subsequently metabolized to acetate in the liver. Acetate enters normal metabolic pathways and is broken down to CO_2, which is eliminated in expired air. Because the metabolism of vinyl acetate occurs rapidly (*in vivo* tests indicate that most is eliminated within 24 hours after exposure), it would be difficult to measure the presence of vinyl acetate or acetaldehyde for reasonable periods following exposure to vinyl acetate. Likewise, other metabolites would not be useful because these are incorporated into normal metabolic pathways, making it difficult to determine which metabolites were due to vinyl acetate exposure and which were present as a result of normal metabolic processes. No other biomarkers (specific or otherwise) have been identified to indicate exposure to vinyl acetate.

3.3.2 Biomarkers of Effect

Numerous positive genotoxic endpoints in human lymphocytes (e.g., micronuclei, chromosomal aberrations, sister chromatid exchange, and DNA cross-links) have been associated with exposure to vinyl acetate. However, because these results are from *in vitro* tests and because many other commonly encountered chemicals and factors (e.g., smoking) may also cause these same abnormalities, these changes cannot be considered specific biomarkers of effects caused by vinyl acetate. Intracellular acidification in nasal tissue has been proposed as the most sensitive measure of vinyl acetate toxicity (Bogdanffy and Valentine 2003; Bogdanffy et al. 1999, 2001, 2004). Again, this effect cannot be considered a specific biomarker of effects caused by vinyl acetate because intracellular acidification is a proposed mechanism for several other known nasal toxicants, including numerous aldehydes and esters (Bogdanffy et al. 1990).

3.4 INTERACTIONS WITH OTHER CHEMICALS

There are no chemicals known that influence the toxicity of vinyl acetate in the body.