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

3.1 TOXICOKINETICS

No studies were located regarding 1,2-dichloropropane toxicokinetics in humans. Data from animal studies are summarized below.

- 1,2-Dichloropropane is rapidly and extensively absorbed following inhalation and oral exposure. The rate and extent of dermal absorption is unknown.
- 1,2-Dichloropropane appears to be widely distributed throughout the body following inhalation and oral exposure. For both exposure routes, the highest levels were found in the liver, kidney, and blood; high levels were also observed in the lung following inhalation exposure. The distribution following dermal exposure is unknown.
- The predominant pathway for 1,2-dichloropropane metabolism consists of oxidation of the C-position of the parent compound followed by glutathione conjugation resulting in formation of mercapturic acids (N-acetyl-S-(2-hydroxypropyl)-L-cysteine, N-acetyl-S-(2-oxopropyl)-L-cysteine, and N-acetyl-S-(l-carboxyethyl)-L-cysteine). 1,2-Dichloropropane may also conjugate with lactate, forming carbon dioxide and acetyl Co-A.
- The primary routes of excretion following oral, inhalation, or intraperitoneal exposure are urine and expired air, with small amounts excreted in feces following oral exposure.

3.1.1 Absorption

No studies were located regarding the rate and extent of absorption of 1,2-dichloropropane following inhalation exposure in humans. Available data from rats indicate that 1,2-dichloropropane is rapidly and extensively absorbed following inhalation exposure (Take et al. 2014; Timchalk et al. 1989, 1991). During a 3-hour exposure to 80 or 500 ppm, blood concentrations in rats rapidly increased within the first 60 minutes, with concentrations in blood being dictated by the blood-to-gas partition coefficient (Take et al. 2014). During the first 24 hours after a 6-hour exposure of rats to ^{14}C-1,2-dichloropropane (5, 50, or 100 ppm), 71–88% of the recovered dose was found in the excreta, with 55–65% of the recovered dose found in the urine, and 16–23% of the recovered dose found in expired air as $^{14}CO_2$ (Timchalk et al. 1989, 1991). These data suggest that 1,2-dichloropropane was absorbed through the lungs. The data indicate that 1,2-dichloropropane was rapidly absorbed according to a zero-order input, but that absorption was not linear with respect to the concentration of 1,2-dichloropropane. The authors assumed that 60% of the inspired concentration of ^{14}C-1,2-dichloropropane was absorbed, but the basis for this assumption was not reported (Timchalk et al. 1989). Gargas et al. (1989) reported blood:air partition coefficients for humans

and rats of 8.75±0.50 and 18.7±0.5, respectively, indicating that 1,2-dichloropropane is readily absorbed from the lungs.

No studies were located regarding the rate and extent of absorption of 1,2-dichloropropane following oral exposure in humans. Take et al. (2017) reported peak blood concentrations of 1,2-dichloropropane in rats 1–3 hours after oral exposure. Other studies in rats by Hutson et al. (1971) and Timchalk et al. (1989, 1991), which found that an average of 74–95% of the ^{14}C-labeled 1,2-dichloropropane dose was excreted in the urine or in expired air within 24 hours of dosing, suggest that 1,2-dichloropropane is readily and extensively absorbed from the gastrointestinal tract. This is supported by the fact that only 0.5% of the administered dose remained in the gut 4 days after administration (Hutson et al. 1971).

No studies were located regarding the rate and extent of absorption of 1,2-dichloropropane following dermal exposure in humans or animals. It can be inferred that 1,2-dichloropropane is absorbed by the skin based on studies reporting lethality in rabbits following dermal exposure (see Section 2.1). Systemic toxicity (acute renal failure, impaired liver function, acute hepatocellular necrosis, rhabdomyolysis, and severe disseminated intravascular coagulation) in a human case report following prolonged dermal exposure (~5 hours) to a commercial fixative containing 30–40% 1,2-dichloropropane and 33–38% toluene (Fiaccadori et al. 2003) may also be attributable to dermal absorption of 1,2-dichloropropane and/or toluene. A human skin permeability constant of 0.01 cm/hour and a permeability coefficient of 0.206 cm/hour were calculated by EPA (1992). Additionally, Fiserova-Bergerova et al. (1990) estimated that 1,2-dichloropropane had a significant dermal absorption potential based on a dermal penetration rate (flux) predicted from physical properties.

3.1.2 Distribution

No studies were located regarding the distribution of 1,2-dichloropropane following inhalation exposure in humans. After rats were exposed for 6 hours to 5, 50, or 100 ppm ^{14}C-labeled 1,2-dichloropropane, the radioactivity was well distributed among the major tissues, with the highest concentration in the liver, kidneys, lungs, and blood (Timchalk et al. 1989, 1991). Similarly, rats exposed to 80 or 500 ppm for 3 hours showed widespread distribution; however, the highest concentration was observed in abdominal fat (Take et al. 2014).

No studies were located regarding the distribution of 1,2-dichloropropane following oral exposure in humans. Following oral administration of 100 mg/kg ^{14}C-labeled 1,2-dichloropropane, Timchalk et al.

(1989, 1991) observed that radioactivity was well distributed among the major tissues at 48 hours in rats. The distribution of radioactivity in the tissues of rats was similar following inhalation and oral exposure to 1,2-dichloropropane in the Timchalk et al. (1989, 1991) study, with the exception of the lungs (low radioactivity after oral exposure). Take et al. (2017) evaluated distribution of ^{14}C-labeled 1,2-dichloropropane in blood, abdominal fat, lungs, liver, and kidneys following oral exposure to 62 or 125 mg/kg in rats and reported a higher concentration in abdominal fat compared to blood and other tissues at both doses. Twenty-four hours after exposure, 1,2- dichloropropane was only detectible in blood and abdominal fat of rats given 62 mg/kg, and was detected in the blood, liver, kidneys, lungs, and abdominal fat of rats given 125 mg/kg. These findings suggest that low levels of 1,2- dichloropropane can remain in tissues for prolonged periods after exposure. In support, 1.5 and 3.5% of the ^{14}C dose were found in the skin and carcass, respectively, in rats 96-hours after exposure to 4.8 mg/kg ^{14}C-labeled 1,2-dichloropropane (Hutson et al. 1971).

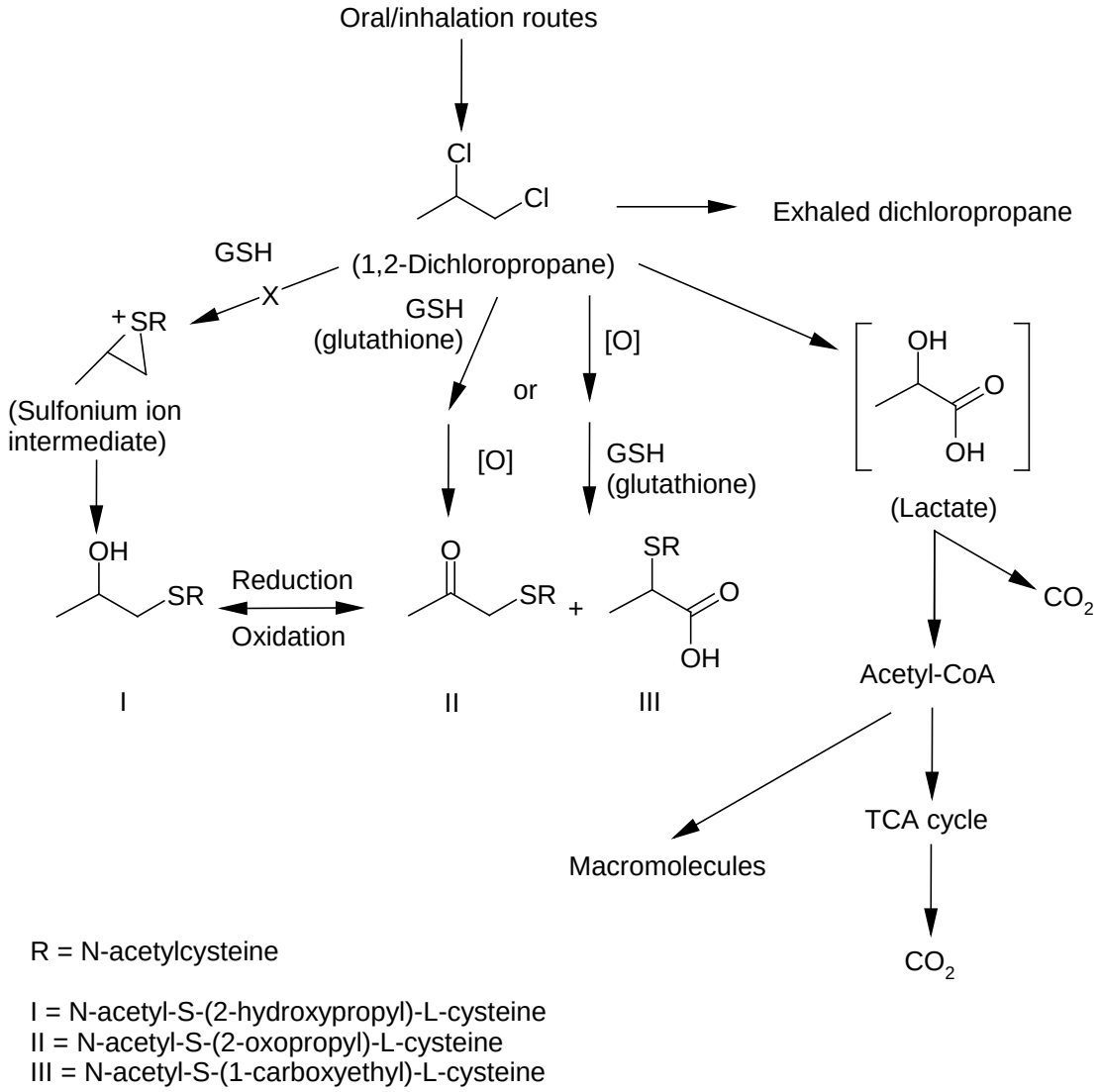
No studies were located regarding the distribution of 1,2-dichloropropane following dermal exposure in humans or animals.

3.1.3 Metabolism

No studies were located regarding the metabolism of 1,2-dichloropropane in humans. The proposed metabolic pathways for 1,2-dichloropropane, based on data from rat studies, are shown in Figure 3-1. The primary pathway consists of oxidation of the C-position of the parent compound by CYP2E1 followed by glutathione conjugation by glutathione S-transferase (GST) T1-1 (Bartels and Timchalk 1990; Gi et al. 2015a; Gonzalez and Gelboin 1994; Guengerich et al. 1991; Sato et al. 2014; Yanagiba et al. 2016). The major urinary metabolites in rats resulting from this metabolic pathway include three mercapturic acids: N-acetyl-S-(2-hydroxypropyl)-L-cysteine, N-acetyl-S-(2-oxopropyl)-L-cysteine, and N-acetyl-S-(l-carboxyethyl)-L-cysteine (Bartels and Timchalk 1990; Jones and Gibson 1980; Timchalk et al. 1989, 1991; Trevisan et al. 1988). These metabolites accounted for approximately 84% of the urinary metabolites excreted following exposure (Timchalk et al. 1989, 1991). Additional minor metabolites identified in urine include N-acetyl-S-(2,3-dihydroxypropl)cysteine, β-chlorolactaldehyde, and β-chlorolactate (Jones and Gibson 1980). 1,2-Dichloropropane may also conjugate with lactate, forming carbon dioxide and acetyl Co-A. Acetyl Co-A may then enter the tricarboxylic acid cycle and generate more carbon dioxide or may be utilized in various biosynthetic pathways (Timchalk et al. 1989, 1991). Hutson et al. (1971) administered 4.8 mg/kg ^{14}C-labeled 1,2-dichloropropane orally to rats, and 42.4% of

the given dose was measured in the expired air after 96 hours. Of the 42.4%, 19.3% was expired as ^{14}C-labeled carbon dioxide, indicating that extensive metabolism of 1,2-dichloropropane had occurred.

Figure 3-1. Proposed Metabolic Scheme for 1,2-Dichloropropane in the Rat (R = N-Acetylcysteine)



3.1.4 Excretion

Data on excretion of 1,2-dichloropropane are limited to a biomarker study that reports a correlation between occupational 1,2-dichloropropane air levels and unmetabolized 1,2-dichloropropane levels in end-of-shift urine samples from exposed workers (Kawai et al. 2015). This indicates that urine is a route

of excretion in humans following inhalation exposure. No additional studies were located regarding the rate or route of excretion of 1,2-dichloropropane following exposure in humans.

In animals, the primary routes of excretion following oral, inhalation, or intraperitoneal exposure are urine and expired air, with small amounts excreted in feces following oral exposure (Hutson et al. 1971; Jones and Gibson 1980; Timchalk et al. 1989, 1991; Trevisan et al. 1988). Toyoda et al. (2016) showed that glutathione-conjugated metabolites of 1,2-dichloropropane are also excreted into the bile via the bile canalicular membrane transporter ABCC2 following exposure to high oral doses (500 mg/kg). With inhalation exposure, the relative contribution of excretion via expired air increased with increased exposure levels (Timchalk et al. 1989, 1991). For example, in rats exposed to 5, 50, or 100 ppm of ^{14}C-labeled 1,2-dichloropropane vapors for 6 hours, the principal routes of elimination were the urine and expired air; 55–65% of the recovered dose was excreted in the urine, expired carbon dioxide accounted for 16–23% of the recovered dose, and 1.7, 2.1–3.4, and 6–7% of the recovered dose was expired as organic volatiles in the 5, 50, and 100 ppm groups, respectively (Timchalk et al. 1989, 1991). The majority of the administered dose was excreted within the first 24 hours after exposure. Similarly, 80–90% of the administered dose was excreted in the urine, feces, and expired air within 24 hours in rats that were administered one dose of 4.0 mg/kg ^{14}C-labeled 1,2-dichloropropane by gavage (Hutson et al. 1971). After 24 hours, males had excreted 48.5% of the dose in the urine and 5.0% of the dose in the feces. Females had excreted 51.9% of the dose in the urine and 3.8% of the dose in the feces in the same time period. Therefore, the percentage of radioactivity in expired air after 24 hours ranged from 24.3 to 36.5% of the dose in both sexes. In a separate experiment, 42.4% of the administered ^{14}C dose of 4.8 mg/kg ^{14}C-labeled 1,2-dichloropropane was detected in the expired air after 96 hours (Hutson et al. 1971). Similar results were observed in rats administered 1 or 100 mg/kg of ^{14}C-labeled 1,2-dichloropropane (Timchalk et al. 1989, 1991). Elimination patterns were similar with single and repeat oral exposures, suggesting that accumulation of 1,2-dichloropropane in the body is not expected.

Elimination half-life ($t_{1/2}$) values and area under the curve values over the first 1,440 minutes ($AUC_{0–1,440}$) were estimated in rats for blood and select organs following inhalation or oral exposure (Take et al. 2014, 2017). Values are presented in Tables 3-1 and 3-2, respectively. These values support that at low levels, accumulation of 1,2-dichloropropane in the body is not expected; however, concentration in body fat is predicted if the metabolic capacity is exceeded following high-level inhalation or oral exposures.

Table 3-1. Elimination Half-Lives ($t_{1/2}$) and $AUC_{0–1,440}$ in Rats for 1,2-Dichloropropane Following a 3-Hour Inhalation Exposure

Tissue	Exposure level (ppm)	Elimination $t_{1/2}$ (minutes)	$AUC_{0–1,440}$ (µg/mL in blood, µg/g in tissue)
Blood	80	182	251
	500	168	3,272
Lung	80	39	122
	500	61	2,352
Liver	80	57	425
	500	125	7,113
Kidney	80	59	317
	500	127	4,951
Abdominal fat	80	154	9,553
	500	186	139,711

$AUC_{0–1,440}$ = area under the curve values over the first 1,440 minutes

Source: Take et al. 2014

Table 3-2. Elimination Half-Lives ($t_{1/2}$) and $AUC_{0\text{-}1,440}$ in Rats for 1,2-Dichloropropane Following a Single Gavage Exposure

Tissue	Dose (mg/kg)	Elimination $t_{1/2}$ (minutes)	$AUC_{0\text{-}1440}$ (µg/mL in blood, µg/g in tissue)
Blood	62	193	359
	125	315	992
Lung	62	144	2,038
	125	187	6,436
Liver	62	144	1,034
	125	193	3,125
Kidney	62	114	527
	125	165	1,867
Abdominal fat	62	257	17,771
	125	330	49,731

$AUC_{0–1,440}$ = area under the curve values over the first 1,440 minutes

Source: Take et al. 2017

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

PBPK models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK

models are also called biologically based tissue dosimetry models. PBPK models 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 (Clewell and Andersen 1985). 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.

No chemical specific PBPK models have been developed. However, Timchalk et al. (1989, 1991) described the time course of 1,2-dichloropropane in the blood as a one-compartment open pharmacokinetic model, with zero-order input and first-order elimination. In rats exposed to 50 or 100 ppm 1,2-dichloropropane vapors for 6 hours, the peak blood concentrations were 17–19- and 68–84-fold higher, respectively, than the peak blood concentration of the 5-ppm group. This dose-dependent nonlinearity of blood clearance suggests that metabolism and/or elimination of 1,2-dichloropropane becomes saturated with increasing concentrations (Timchalk et al. 1989).

3.1.6 Animal-to-Human Extrapolations

No studies were identified that could evaluate potential differences in the toxicity or toxicokinetics of 1,2-dichloropropane between humans and animals. In the absence of adequate human toxicokinetic studies, animal data are assumed relevant to humans. In addition, most primary toxicity targets identified in animal studies (respiratory, hepatic, hematological, neurological) have been reported in case studies of humans following exposure to high levels of 1,2-dichloropropane. Some species differences were observed between different laboratory species; however, the targets of toxicity appear to be similar. Available mechanistic data are inadequate to evaluate potential species differences.

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 1,2-dichloropropane are discussed in Section 5.7, Populations with Potentially High Exposures.

No populations with unusual or increased susceptibility to the health effects of 1,2-dichloropropane were identified based on the available literature. It is unclear if the developing fetus or neonate are uniquely susceptible to toxic effects of 1,2-dichloropropane, as all available studies report developmental effects at doses associated with parental toxicity (Kirk et al. 1990, 1995). Based on glutathione conjugation during metabolism of 1,2-dichloropropane (see Section 3.1.3), differences in glutathione metabolism due to life-stage and/or genotype may alter susceptibility. For example, individuals with GSTM1- and GSTT1-positive genotypes have full reduced glutathione conjugating capability, which may result in more efficient production of toxic derivatives (Fiaccadori et al. 2003). In addition, differential expression of GST isoforms has been reported during developmental stages, compared to adults, which may alter the glutathione conjugating rate and capability (Raijmakers et al. 2001). Similar differences in hepatic cytochrome P450 expression have been reported throughout development (Hines 2007). These potential differences in age-related metabolism may infer differential susceptibility in the developing fetus, neonate, or child.

Due to the potential role of glutathione depletion in the toxicity of 1,2-dichloropropane (see Sections 2.7, 2.9, and 2.10), individuals with inherited glucose-6-phosphate dehydrogenase (G6PDH) deficiency may be more susceptible to toxicity. The biological implications of genetic G6PDH deficiency, an x-linked inherited disorder most commonly found in individuals of African, Asian, Mediterranean, or Middle Eastern descent, are well established and extensively reviewed (e.g., Cappellini and Fiorelli 2008; Frank 2005; Harcke et al. 2019). G6PDH deficiency decreases the ability to reduce oxidized glutathione due to reduced capacity to produce nicotinamide adenine dinucleotide phosphate (NADPH) via the pentose phosphate pathway. This results in increased glutathione depletion following both intrinsic and extrinsic sources of oxidative stress in individuals with genetic G6PDH deficiency, compared to the general population. Since NADPH in erythrocytes is only formed via the pentose phosphate pathway (due to lack of mitochondria), individuals with genetic G6PDH deficiency are particularly vulnerable to chemical-induced hemolytic anemia. No studies specifically evaluating susceptibility to 1,2-dichloropropane toxicity in individuals with G6PDH deficiency were identified; however, individuals with genetic G6PDH

variants are known to have increased susceptibility to naphthalene- and 2,4,6-trinitrotoluene-induced hemolytic anemia (Harcke et al. 2019; Santucci and Shah 2000). Based on the known impairments associated with genetic G6PDH deficiency, evidence of glutathione depletion following exposure to 1,2-dichloropropane, and supporting data from chemicals with the same proposed mechanism of action, individuals with genetic G6PDH deficiency may be more susceptible to 1,2-dichloropropane toxicity, particularly hemolytic anemia.

3.3 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as biomarkers of exposure, biomarkers of effect, and biomarkers of susceptibility (NAS/NRC 1989).

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 1989). 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 1,2-dichloropropane are discussed in Section 3.3.1. The National Report on Human Exposure to Environmental Chemicals provides an ongoing assessment of the exposure of a generalizable sample of the U.S. population to environmental chemicals using biomonitoring (see http://www.cdc.gov/exposurereport/). If available, biomonitoring data for 1,2-dichloropropane from this report are discussed in Section 5.6, General Population Exposure.

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 1989). 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 1,2-dichloropropane 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

Unmetabolized parent compound levels in the urine have been proposed as a reliable biomarker of exposure for organic solvents, including 1,2-dichloropropane (Ghittori et al. 1987; Kawai et al. 2015). Kawai et al. (2015) showed significant correlation of 1,2-dichloropropane levels in workplace air with 1,2-dichloropropane levels in end-of-shift urine samples in print shop workers. Ghittori et al. (1987) calculated that a urinary concentration of 1,2-dichloropropane of 268 µg/L is equivalent to an air exposure concentration of 300 µg/L. Detection of metabolites in the urine could also be considered as a biomarker of exposure; however, Kawai et al. (2015) indicated that tests for unmetabolized 1,2-dichloropropane are more straightforward.

Unmetabolized 1,2-dichloropropane in whole blood was used in the National Health and Nutritional Examination Survey (NHANES) as a biomarker to generate data on general U.S. population exposures between 2002 and 2012 (CDC 2019). In all years evaluated, blood levels were below the level of detection using this analytical method (0.008 µg/L; see details in Section 5.6). While background levels in the general population appear to be below the level of detection of this analytical method, Kirman et al. (2012) and Aylward et al. (2010) indicate that the whole blood analytical method used to collect NHANES data is sensitive enough to detect recent toxicologically relevant exposures.

Glutathione conjugated metabolites in the serum have also been proposed as biomarkers of exposure based on studies in rats (Toyoda et al. 2016).

3.3.2 Biomarkers of Effect

There are no specific biomarkers used to characterize the effects from 1,2-dichloropropane exposure, as biomarkers of effects for 1,2-dichloropropane are likely to be common to the general class of chlorinated solvents, rather than specific for 1,2-dichloropropane.

3.4 INTERACTIONS WITH OTHER CHEMICALS

Based on epidemiological studies in Japanese printers, there may be an interaction between 1,2-dichloropropane and other chlorinated solvents (e.g., dichloromethane) with regard to the development of cholangiocarcinoma (CCA) (Kubo et al. 2014a, 2014b; Kumagai et al. 2013, 2014, 2016; Sobue et al. 2015; Yamada et al. 2014, 2015a, 2015b). However, available data are inadequate to determine the existence and/or nature of the potential interaction (e.g., one chemical may induce CCA on its own, regardless of co-exposure with additional chlorinated solvents).

In animals, the joint toxicity of 1,2-dichloropropane was assessed with a variety of different compounds; however, these studies lack adequate study design and/or reporting to independently evaluate results. Pozzani et al. (1959) determined that 1,2-dichloropropane has an additive toxic effect when given orally or by inhalation to rats with 1,1,2-trichloroethane, and when given with both ethylene dichloride and perchloroethylene (LD_{50} assessed). Drew et al. (1978) reported that inhalation of 1,2-dichloropropane in combination with trichloropropane by rats did not result in a greater-than-additive toxic effect with regards to hepatic serum enzyme changes (elevated ALT, AST, and ornithine carbamyl transferase levels). Sidorenko et al. (1976, 1979) determined that inhalation of 1,2-dichloropropane has an additive effect in rats and mice when given in combination with 1,2,3-trichloropropane and perchloroethylene with regard to toxic effects on lung, liver, and nervous system.

Several studies have evaluated potential adverse effects of inhalation, oral, or dermal exposure to mixtures of dichloropropanes and dichloropropenes (e.g., soil fumigant D-D); however, studies were not designed to evaluate potential interactions between the chemical components (Linnett et al. 1988; Nater and Gooskens 1976; Parker et al. 1982; Shell Oil Co. 1982, 1983).