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

3.1 TOXICOKINETICS

Toxicokinetics of 1,2-dibromoethane has been studied in animal models and in *in vitro* models of animal and human tissues. These studies have revealed the following:

- Ingested 1,2-dibromoethane is rapidly absorbed (within 30 minutes in rats).
- Absorbed 1,2-dibromoethane and its metabolites are widely distributed. Based on studies with ^{14}C-labeled 1,2-dibromoethane, the highest concentrations of ^{14}C are found in kidney, liver, and spleen.
- Metabolism is the dominant mechanism of elimination of absorbed 1,2-dibromoethane. Major pathways of metabolism include oxidation mediated by CYP450 and conjugation with GSH mediated by GST.
- The two primary products of CYP450 and GST, 2-bromoacetaldehye and S-(2-bromoethyl)-glutathione, respectively, are both reactive and contribute to 1,2-dibromoethane toxicity.
- S-(2-Bromoethyl)glutathione forms adducts with protein and DNA, which is thought to contribute to genotoxicity and carcinogenicity of 1,2-dibromoethane.
- Absorbed 1,2-dibromoethane is rapidly eliminated (>99% in 1 day in rats).
- Metabolites of 1,2-dibromoethane (e.g., mercapturic acids) are excreted in urine.

3.1.1 Absorption

No studies were located in humans regarding the inhalation absorption of 1,2-dibromoethane. The available animal toxicity data indicate that absorption of 1,2-dibromoethane occurs in rats, mice, rabbits, guinea pigs, and monkeys exposed via inhalation for acute, intermediate, and chronic durations (Rowe et al. 1952; Stott and McKenna 1984). Based on the findings in animal studies, 1,2-dibromoethane is expected to be absorbed in humans exposed via the inhalation route.

No studies were located in humans regarding the oral absorption of 1,2-dibromoethane. However, there is evidence to suggest that oral absorption occurs in humans. Death and poisoning resulting from suicide attempts (Olmstead 1960; Saraswat et al. 1986) and from consumption of contaminated fruits, grains, and drinking water (EPA 1983) indicate that absorption occurred.

Uptake of 1,2-dibromoethane readily occurs in rats following oral dosing (Botti et al. 1982; Hissink et al. 2000; Nachtomi 1981; Plotnick et al. 1979; Van Bladeren et al. 1980). In rats, peak blood concentrations of 1,2-dibromoethane occurred within 30 minutes following gavage dosing (the earliest time of sampling of blood), suggesting that absorption was nearly complete within 30 minutes.

No studies were located regarding the dermal absorption of 1,2-dibromoethane in humans. However, two occupational case reports suggest that dermal absorption of 1,2-dibromoethane (versus inhaled) was the major route of exposure to 1,2-dibromoethane that resulted in death (Letz et al. 1984). Dermal absorption does occur in animals but has not been quantified. Absorption of 1,2-dibromoethane was demonstrated in guinea pigs whose blood levels were monitored during dermal exposure to 1 mL of 1,2-dibromoethane (Jakobson et al. 1982). Following dermal application, the blood level of 1,2-dibromoethane increased rapidly, reaching a maximum level of approximately 2.1 µg/mL at 1 hour and 1.8 µg/mL at 6 hours.

3.1.2 Distribution

No studies were located in humans or animals regarding the distribution of 1,2-dibromoethane after inhalation exposure. Although occupational cases of inhalation exposure of humans have been reported (Letz et al. 1984), there were no data on 1,2-dibromoethane levels in tissues.

No studies were located in humans regarding the distribution of 1,2-dibromoethane after oral exposure. In humans intentionally ingesting 1,2-dibromoethane, kidney lesions and centrilobular necrosis of the liver were found (Olmstead 1960; Saraswat et al. 1986). This is indirect evidence of distribution of 1,2-dibromoethane to these tissues.

The tissue distribution of 1,2-dibromoethane has been studied in rats following exposure by the oral route. The kidneys, liver, and spleen appear to retain the highest amounts of the administered dose (Plotnick et al. 1979) as illustrated in Table 3-1. Rats received an oral dose of 15 mg/kg/day of labeled 1,2-dibromo-ethane in corn oil. Twenty-four hours later, 3% of radioactivity was detected in fat, brain, kidney, liver, spleen, testes, blood, and plasma, 72.38% was detected in the urine, and 1.65% was detected in the feces (Plotnick et al. 1979). By 48 hours after administration, 73% of the radiolabeled dose was accounted for in the urine, 1.1% in the liver, and 2.4% in the feces. Total recovery was 77.8% of the administered radioactivity. 1,2-Dibromoethane in the expired air was not measured. In rats, 1,2-dibromoethane and its

metabolites can bind covalently to serum albumin (Kaphalia and Ansari 1992). As shown in Table 3-1, blood also has a high concentration of radiolabeled 1,2-dibromoethane.

Table 3-1. Distribution of ^{14}C in Selected Tissues and Body Fluids of Male Rats 24 and 48 Hours After a Single Oral Dose of 15 mg/kg [U-^{14}C]-1,2-Dibromoethane

	Tissue concentration[a]		Percentage of dose[b]	
Tissue	24 Hours	48 Hours	24 Hours	48 Hours
Liver	4.78±0.24	2.87±0.33	1.79±0.07	1.10±0.21
Kidneys	3.32±0.42	1.06±0.16	0.21±0.02	0.08±0.01
Spleen	1.00±0.03	0.66±0.03	0.02±<0.01	0.01±<0.01
Blood[c]	0.90±0.05	0.64±0.07	0.59±0.03	0.43±0.04
Testes	0.49±0.05	0.19±0.02	0.04±<0.01	0.01±<0.01
Brain	0.41±0.04	0.17±0.02	0.02±<0.01	0.01±<0.01
Fat[d]	0.35±0.04	0.44±0.06	0.15±0.02	0.20±0.03
Plasma	0.46±0.04	0.22±0.02	No data	No data
Urine	No data	No data	72.38±0.98[e]	73.54±2.80[f]
Feces	No data	No data	1.65±0.28[e]	2.42±0.54[f]
Total recovery	No data	No data	76.85	77.8

[a]Values represent mean concentration in µg/g or µg/mL (expressed as parent compound) plus or minus the standard error of the mean of duplicate determinations on six animals.
[b]Values represent the mean percentage of the administered radioactivity plus or minus the standard error of the mean of duplicate determinations on six animals.
[c]Assumed 9% of body weight.
[d]Assumed 6% of body weight.
[e]n=12 (includes 24-hour samples obtained from rats killed 48 hours after compound administration).
[f]Cumulative 48-hour excretion.

Source: Plotnick et al. 1979

The retention of 1,2-dibromoethane in tissues and body fluids can be altered by concurrent exposure to modifiers of enzyme activity, such as disulfiram (Plotnick et al. 1979). The concentration of radiolabeled 1,2-dibromoethane in the liver, kidneys, spleen, testes, and brain increased significantly in rats fed disulfiram in the diet for 12 days before an oral dose of 15 mg ^{14}C-1,2-dibromoethane/kg compared with rats not fed disulfiram. Disulfiram, an inhibitor of cytochrome P-450 metabolism (via action on acetaldehyde dehydrogenase), was found to increase the uptake of ^{14}C into liver nuclei. These observations correlate well with the results of chronic studies (Wong et al. 1982) that demonstrated enhanced tumorigenic effects in the liver and testes following combined 1,2-dibromoethane and disulfiram exposure.

No studies were available in humans or animals regarding the distribution of 1,2-dibromoethane following dermal exposure. However, toxic effects observed in humans and animals after dermal exposure indicate that the compound is widely distributed throughout the body.

Tissue distribution of 1,2-dibromoethane following intraperitoneal administration was studied in mice (Edwards et al. 1970) and guinea pigs (Plotnick and Conner 1976). The kidney and liver retained the highest amounts of the administered 1,2-dibromoethane dose across all of the observation periods (see Tables 3-2 and 3-3). Autoradiographic studies of mice injected intraperitoneally with ^{14}C-1,2-dibromoethane (40 mg/kg) revealed radioactivity primarily in the intestines, kidneys, liver, blood, fat, and spleen. Only 1% of the administered dose (per gram of wet tissue) was detected in the kidney and in the stomach tissue, 6.2% was detected in whole blood, and 2.6% was detected in plasma 24 hours posttreatment (Edwards et al. 1970).

Following a single intraperitoneal injection of 30 mg/kg ^{14}C-1,2-dibromoethane in corn oil to guinea pigs, the majority of the dose was accounted for in the urine (65.9%), liver (2.16%), and feces (3%) by the end of the 72-hour period. Approximately 10–12% of the administered dose was excreted via the lungs (Plotnick and Conner 1976). Plotnick and Conner (1976) investigated tissue distribution of 1,2-dibromoethane in guinea pigs because they found similarities in metabolism and biotransformation pathways between guinea pigs and humans. The authors reported that target organs for tissue distribution in guinea pigs were the same as those in rats, although the percentage of dose recovered was higher in guinea pig tissues.

Table 3-2. Distribution of 1,2-Dibromoethane in Mice

	Percentage of dose[a]		
Organ	1 Hour	3 Hours	24 Hours
Small intestine	34.0	5.8	0.39
Kidney	13.0	12.0	1.0
Liver	12.0	6.6	0.42
Lung	0.9	1.0	0.14
Spleen	4.1	4.7	0.61
Plasma	12.0	12.0	2.6

[a]Intraperitoneal injection of 40 mg/kg body weight.

Source: Edwards et al. 1970

Table 3-3. Percentage of Administered ^{14}C in Selected Tissues and Body Fluids of Male Guinea Pigs at Various Time Intervals Following Intraperitoneal Administration of 30 mg/kg of ^{14}C-1,2-Dibromoethane[a]

Organ	4 Hours	8 Hours	12 Hours	24 Hours	48 Hours	48 Hours
Liver	16.29±2.42	13.65±0.39	10.50±2.13	4.72±0.21	2.12±0.07	2.16±0.21
Kidneys	6.00±0.42	5.69±0.43	3.31±0.17	1.64±0.45	0.31±0.01	0.24±0.02
Stomach[b]	1.14±0.44	0.52±0.20	0.62±0.08	0.18±0.02	0.18±0.02	0.18±0.04
Lungs	0.35±0.06	0.38±0.09	0.37±0.01	0.24±0.01	0.12±0.01	0.10±0.01
Pancreas	0.31±0.10	0.36±0.06	0.33±0.02	0.20±0.03	0.07±0.01	0.06±0.01
Testes	0.16±0.04	0.17±0.01	0.12±0.01	0.12±0.01	0.07±0.01	0.06±0.01
Heart	0.13±0.02	0.16±0.02	0.12±0.01	0.10±0.01	0.04±0.01	0.03±0.01
Brain	0.12±0.02	0.16±0.02	0.14±0.01	0.13±0.01	0.07±0.01	0.05±0.00
Adrenals	0.08±0.02	0.10±0.04	0.04±0.01	0.03±0.01	0.01±0.01	0.02±0.01
Spleen	0.07±0.01	0.06±0.01	0.07±0.01	0.08±0.02	0.03±0.00	0.02±0.01
Urine[c]	14.9±1.0	26.3±10.1	43.2±8.1	46.0±4.8	54.3±3.4	65.9±4.6

[a]Values represent the mean plus or minus the standard error of the mean of duplicate determinations on three animals at each time interval.
[b]Including stomach contents.
[c]Cumulative excretion.

Source: Plotnick and Conner 1976

These results are similar to those after oral administration and suggest that 1,2-dibromoethane is rapidly absorbed and distributed but retained to only a limited extent mainly in the kidneys and liver, regardless of the route of exposure and the species tested.

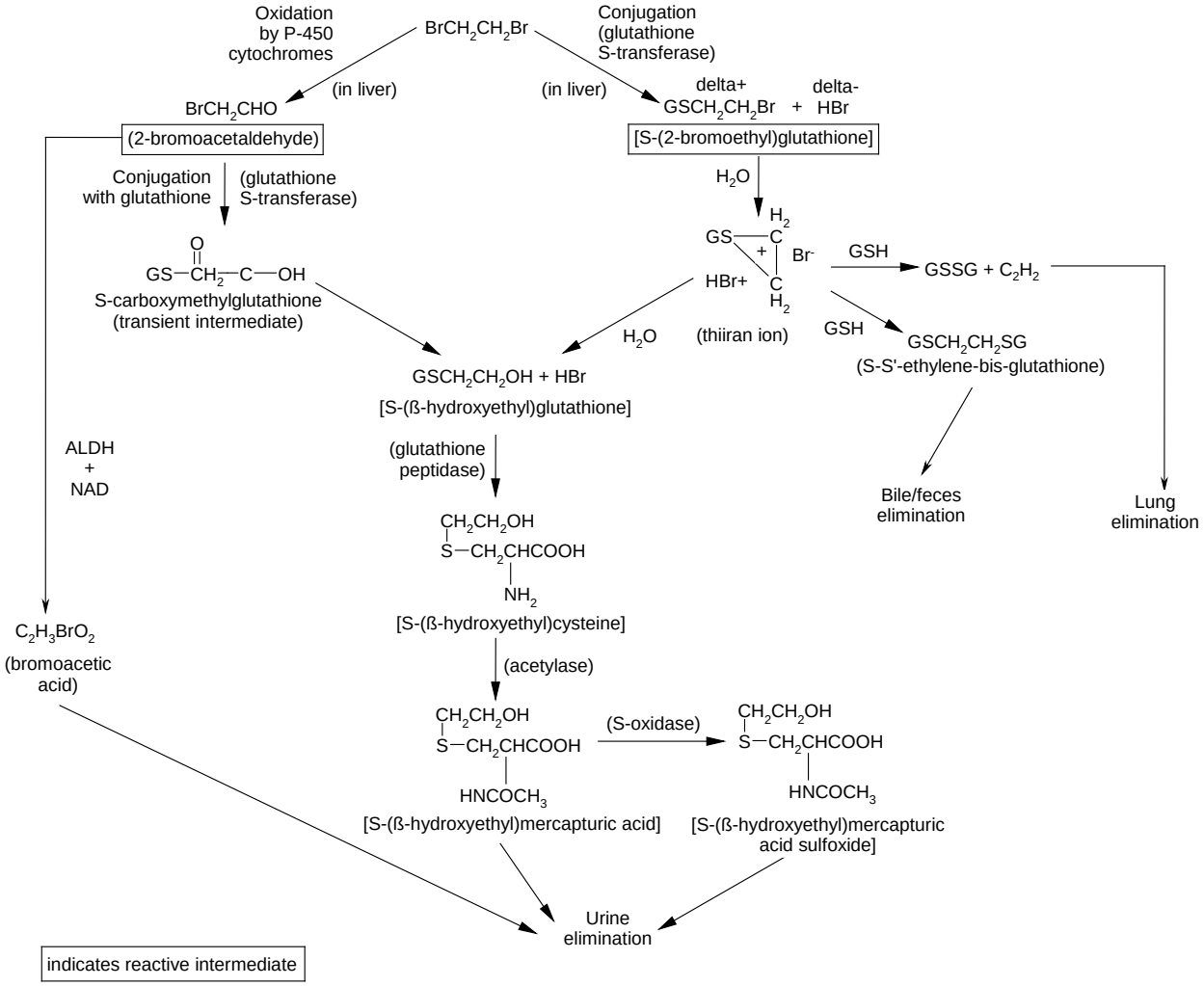
3.1.3 Metabolism

No human studies were located that provided information on metabolism of 1,2-dibromoethane from inhalation or oral exposures. However, 1,2-dibromoethane is metabolized by enzyme systems known to be present in humans. 1,2-Dibromoethane is metabolized to active forms capable of inducing toxic effects by either of two systems: the microsomal monooxygenase system (cytochrome P-450 oxidation, CYP450) or the cytosolic activation system (glutathione conjugation). Figure 3-1 provides an overview of the metabolism of 1,2-dibromoethane by the two systems. The pathway of biotransformation for 1,2-dibromoethane appears to be the controlling factor for its biological activity. Two reactive intermediates, 2-bromoacetaldehyde and S-(2-bromoethyl) glutathione, are formed. The 2-bromoacetaldehyde is responsible for tissue damage caused by covalent binding to cellular macromolecules. S-(2-Bromoethyl)glutathione is responsible for genotoxicity of 1,2-dibromoethane and, perhaps its carcinogenic effect observed in laboratory animals. These two systems and their relative importance are discussed in detail below.

Results of animal studies show that 1,2-dibromoethane is metabolized in various tissues through oxidation by CYP450 to form 2-bromoacetaldehyde (Guengerich et al. 1991; Tamura et al. 1986; Van Duuren et al. 1985; Wormhoudt et al. 1996a, 1996b). Although various isoforms of CYP450 can utilize 1,2-dibromoethane as a substrate, the dominant contributor to metabolism of 1,2-dibromoethane appears to be CYP2E1 (Wormhoudt et al. 1996a, 1996b). The metabolic product of CYP450, 2-bromo-acetaldehyde, can produce histopathological changes such as liver damage, by binding to cellular proteins (Hill et al. 1978; Kaphalia and Ansari 1992). 2-Bromoacetaldehyde can also be metabolized by aldehyde dehydrogenase in the presence of nicotinamide adenine dinucleotide to bromoacetic acid, which is excreted in the urine. In addition, 2-bromoacetaldehyde can also be conjugated with glutathione. The conjugated metabolite is reduced to S-carboxymethylglutathione. This compound can form S-carboxy-methylcysteine, which may be metabolized to thioglycolic acid and excreted in the urine or can be metabolized to S-(β-hydroxyethyl) cysteine. The latter is excreted in the urine following action by N-acetyl transferase in the presence of acetyl CoA enzyme and subsequent sulfoxidation to form mercapturic acids (Nachtomi et al. 1966; Van Bladeren 1983). Mercapturic acids are the primary urinary metabolites of 1,2-dibromoethane. Tomasi et al. (1983) demonstrated that 1,2-dibromoethane can form a

free radical intermediate under hypoxic conditions, suggesting a new metabolic pathway for 1,2-dibromoethane.

Figure 3-1. Proposed Metabolic Pathways for 1,2-Dibromoethane



ALDH = aldehydehydrogenase; GSH = glutathione; NAD = nicotinamide adeinine dinucleotide

Source: Lawrence and Michaels 1984

As shown in Figure 3-1, 1,2-dibromoethane can be conjugated with glutathione through the action of GSTs to form S-(2-bromoethyl) glutathione (Peterson et al. 1988). Although various isoforms of GST can utilize 1,2-dibromoethane as a substrate, the alpha and theta isoforms (GSTA2 and GST T1) appear to be major contributors (Cmarik et al. 1990; Ploemen et al. 1997; Sherratt et al. 1998). The GSH conjugate, S-(2-bromoethyl) glutathione, can react to form ethylene and glutathione disulfide through further action of glutathione transferases. These are considered to be detoxification pathways. Ethylene can be exhaled, and the glutathione disulfide is eliminated in the feces via the bile.

S-(2-Bromoethyl)glutathione is considered to be the genotoxic, and probably the carcinogenic, intermediate of 1,2-dibromoethane metabolism (Cho and Guengerich 2013; DeLeve 1997; Thomas et al. 2001; Van Bladeren et al. 1981); for additional information, see the discussion on mechanisms in Section 2.20 (Genotoxicity). It has also been implicated as a contributor to mitochondrial toxicity by alkylating mitochondrial DNA (Thomas et al. 2001). S-(2-Bromoethyl)glutathione is a highly reactive alkylating agent that can bind to DNA either through direct nucleophilic substitution (Van Bladeren 1983) or substitution through the ethylene-S-glutathionyl-episulfonium ion to form S-[2-(N7-guanyl)ethyl] glutathione (Cho and Guengerich 2013; Koga et al. 1986; Ozawa and Guengerich 1983; Peterson et al. 1988). S-(2-Bromoethyl) glutathione is the main genotoxic metabolite that binds to DNA to form the complex S-[2-(N7-guanyl)ethyl]mercapturic acid (Bolt et al. 1986; Guengerich et al. 1995; Koga et al. 1986). The ethylene-S-glutathionyl-episulfonium ion can also react with water and be detoxified to form S-(β-hydroxyethyl)glutathione, or react with glutathione to form S,S'-ethylene-bis-(glutathione). The latter is excreted in the feces via the bile. S-(β-hydroxyethyl)glutathione can form S-(β-hydroxyethyl)-glutathione-S-oxide by sulfoxidation or react with peptidases to form S-(β-hydroxyethyl)cysteine. The former is excreted in the feces via the bile. The latter forms S-(β-hydroxyethyl)mercapturic acid by the action of N-acetyl transferase and is excreted in the urine (EPA 1985; Nachtomi 1970; Van Bladeren 1983).

In animals, 1,2-dibromoethane is rapidly metabolized after oral administration and is ultimately converted into mercapturic acid derivatives that appear in urine (Kirby et al. 1980; Nachtomi 1970; Nachtomi et al. 1965). The principal mercapturic acid derivative, N-acetyl-S-(2-hydroxyethyl-)L-cysteine, and other related metabolites are derived from the metabolism of GSH conjugates formed with 1,2-dibromoethane or its CYP450 metabolites (Figure 3-1). An *in vivo* study (Van Duuren et al. 1985) provides evidence that CYP450 of 1,2-dibromoethane in rodents can produce adducts that bind preferentially to protein. In a study using tetradeutero-1,2-dibromoethane, only about 20% of the mercapturic acid excreted was formed via direct glutathione conjugation for 1,2-dibromoethane (Van Bladeren 1983). The reactive metabolites formed by these the CYP450 and GST pathways may bind to protein (2-bromoacetaldehyde) or DNA (S-[2-bromoethyllglutathione) producing either cytotoxicity or genotoxicity, respectively. Adducts formed via cytosolic glutathione conjugation, identified as S-[2-(N7-guanyl)ethyl]glutathione by Ozawa and Guengerich (1983), have been associated with genotoxic, and perhaps carcinogenic, effects (Van Bladeren et al. 1982; White et al. 1983). Edwards et al. (1970) also identified metabolites after oral administration.

3.1.4 Excretion

No studies were located-in humans or animals regarding the excretion of 1,2-dibromoethane after inhalation exposure.

No studies were available in humans regarding the excretion of 1,2-dibromoethane after oral exposure. Oral administration of 1,2-dibromoethane to rats primarily results in mercapturic acid derivatives excreted in the urine (approximately 74% of the administered dose) (Plotnick et al. 1979) as shown in Table 3-1. Unmetabolized 1,2-dibromoethane or its metabolites (e.g., ethylene) may be excreted via the lungs; fecal excretion of metabolites accounts for approximately 3% of the administered dose (Plotnick et al. 1979). In rats, absorbed 1,2-dibromoethane is rapidly eliminated from blood, primarily by metabolism, although excretion in exhaled air may also be a contributing elimination pathway. Biphasic elimination of 1,2-dibromoethane from blood was observed following an oral dose of 50 mg/kg, with half-times estimated to be approximately 25 and 121 minutes. The terminal half-time of 121 minute predicts elimination of approximately >99% of absorbed 1,2-dibromoethane in 24 hours. Systemic clearance, as measured by blood 1,2-dibromoethane kinetics, was considerably slower following a 150 mg/kg oral dose (55 mL/minute/kg) compared to a 50 mg/kg dose (125 mL/minute/kg). Dose-dependence of systemic clearance has been attributed to a capacity limitation of metabolism. Kinetics of blood 1,2-dibromoethane observed following an intravenous dose were similar to kinetics observed following an oral dose (Hissink et al. 2000). Following an intravenous injection of 1,2-dibromoethane, elimination from blood exhibited biphasic kinetics, with half-times estimated to be approximately 15 and 85 minutes following a dose of 10 mg/kg and 38 and 77 minutes following a dose of 50 mg/kg (Hissink et al. 2000). Systemic clearance was slower (28 mL/minute/kg) following a 50 mg/kg intravenous dose compared to a 10 mg/kg dose (75 mL/minute/kg; Hissink et al. 2000).

Based on the rapid and extensive metabolism and systemic clearance seen in animals, the fate of 1,2-dibromoethane in humans would be expected to be similar. The lack of persistence of metabolites in the tissues indicate that 1,2-dibromoethane is readily removed from the body. Low-level exposure would not be expected to result in accumulation of 1,2-dibromoethane or its metabolites in human tissue. However, theoretically, acute high-level exposure may saturate metabolic pathways and consequently allow 1,2-dibromoethane to accumulate in the tissues for a longer period of time (Hissink et al. 2000).

Plotnick and Conner (1976) reported that 10–12% of a dose is excreted via the lungs 72 hours after intraperitoneal injection of 30 mg/kg ^{14}C-1,2-dibromoethane to guinea pigs. The majority of the dose was accounted for in the urine (65.9%), liver (2.16%), and feces (3%).

Intraperitoneal administration of 37.6, 75, or 113 mg 1,2-dibromoethane/kg/day (0.2, 0.4, or 0.6 mmol/kg) to rats resulted in metabolic biotransformation into mercapturic acid, which was strongly indicative of saturable metabolism (Goyal et al. 1989). Administration of L-2-oxothiazolidine-4-carboxylic acid (OTCA) (4±5 mmol/kg) enhanced glutathione availability and increased excretion of urinary mercapturic acid at the higher doses. These results suggest that OTCA increases the capacity for detoxification via the glutathione pathway.

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.

Hissink et al. (2000) Model for Rats and Humans

Model Structure. Hissink et al. (2000) reported a PBPK model of 1,2-dibromoethane in rats and humans. The model includes compartments representing blood, lung, stomach and intestines, fat, kidneys, liver, skeletal muscle, testes, and lumped compartments representing other rapidly or slowly perfused tissues. Absorption of ingested 1,2-dibromoethane is simulated as a series of first-order transfers through and out of the gastrointestinal tract, which are governed by rate coefficients (hour^{-1}). These include transfer coefficients for stomach lumen to small intestine lumen, small intestine lumen to liver, stomach lumen to stomach tissue, and small intestine lumen to small intestine tissue. Absorption of inhaled 1,2-dibromo-ethane is simulated as flow-limited transfer from inhaled air to blood governed by a ventilation rate (L/hour), a blood:air partition coefficient, and cardiac output (L/hour). Transfers of 1,2-dibromoethane between blood and each tissue compartment are simulated as flow-limited transfers governed by

tissue:blood partition coefficients and tissue blood flows (L/hour). Elimination of absorbed 1,2-dibromoethane is attributed entirely to metabolism, which is assumed to occur in all tissues, except fat, and rapidly and slowly perfused tissues. Two metabolism pathways are included in the model: (1) capacity limited oxidation mediated by CYP450, assumed to be entirely P450E1, governed by a V_{max} (µmol/hour/kg) and K_m (µM); and (2) conjugation with GSH mediated by GST, governed by a rate coefficient. The CYP450 pathway is assumed to active in kidney, liver, and lung of rats and in liver and lung of humans. The GST pathway is assumed to be active in kidney, liver, lung, stomach and small intestines, skeletal muscle, and testes of both rats and humans.

Parameter Values. Parameter values for the model and literature sources of the estimates are reported in Table 1 of Hissink et al. (2000). Metabolic parameters were derived from *in vitro* studies that estimated enzyme or pathway kinetics parameters in rat or human tissues (Ploemen et al. 1997). Some parameters were indicated as having been derived from *in vivo* data, with no further explanation (e.g., gastrointestinal absorption parameters). Absorption parameters were assigned different values for oral dosing at 50 and 150 mg/kg.

Model Evaluation. Hissink et al. (2000) compared model predictions of blood 1,2-dibromoethane kinetics in rats following a single gavage dose of 1,2-dibromoethane (50 or 150 mg/kg) or a single intravenous dose (10 or 50 mg/kg). Inclusion of extrahepatic metabolism improved agreement between observations and predictions for blood 1,2-dibromoethane concentrations following both the oral and intravenous dose. Hissink et al. (2000) explored the impact of including active extrahepatic metabolism in the performance of the model. In general, assigning all metabolism to the liver resulted in predictions of blood 1,2-dibromoethane that were higher than when extrahepatic metabolism was assumed to occur (see Figure 2 of Hissink et al. 2000). This effect resulted from greater metabolic clearance of 1,2-dibromoethane when extrahepatic metabolism was active. Including active extrahepatic metabolism improved agreement between predicted and observed blood 1,2-dibromoethane time profiles for both oral and intravenous dosing. However, the model has not been evaluated for predicting blood 1,2-dibromoethane kinetics in rats repeatedly dosed or exposed by inhalation and was not evaluated for making dosimetry predictions in humans; therefore, a figure depicting this model has not been included.

Model Applications. Hissink et al. (2000) applied the model to predicting blood concentration of 1,2-dibromoethane and cumulative metabolism through the CYP450 and GST pathways for 8-hour inhalation exposures to 40 ppm 1,2-dibromoethane in rats and humans (see Figure 3 of Hissink et al. 2000). The model predicted a rapid decline in blood 1,2-dibromoethane concentrations following

cessation of inhalation exposures. Higher cumulative metabolism through both the CYP450 and GST pathways was predicted in rats compared to humans. Inclusion of active extrahepatic metabolism in the model increased cumulative metabolism. The relative amounts of metabolites predicted to be formed from the CYP450 and GST pathways depended on assumptions regarding the relative activities of the two pathways. Alternative parameter values for the two pathways were explored based on expression ratios obtained from human liver samples (Ploeman et al. 1997). High P450E1/GST activity ratios resulted in greater contributions of CYP450 metabolism to overall elimination from metabolism. No reports describing risk assessment applications of the Hissink et al. (2000) model were located (e.g., dose-response assessment or dosimetry extrapolation).

3.1.6 Animal-to-Human Extrapolations

PBPK models for 1,2-dibromoethane in rats and human have been reported and used to make dosimetry comparisons between rats and humans exposed by the inhalation route (Hissink et al. 2000). However, the models have not been evaluated for accuracy of predictions of toxicokinetics in humans, or of toxicokinetics of inhalation dosing or repeated dosing in rats or humans. Therefore, use of these models for extrapolating internal dosimetry in rats to humans is not recommended without further verification of the model for these types of applications.

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 risk to unusually high exposure levels to 1,2-dibromoethane are discussed in Section 5.7, Populations with Potentially High Exposures.

No data are available on the toxicity of 1,2-dibromoethane in children, but it is assumed that effects will be similar to those seen in adults. Developmental studies in animals observed incomplete ossification of the skeleton following gestational exposure to inhaled 1,2-dibromoethane (see study details in Section 2.17). However, no information on developmental effects in humans was identified.

1,2-Dibromoethane produces damage to the respiratory tract, gastrointestinal system, liver, kidneys, or male reproductive system in humans and animals. Individuals with underlying diseases of the systems may be more sensitive to the toxicity of 1,2-dibromoethane.

As discussed in Section 2.20 (Genotoxicity), the major mechanism of genotoxicity of 1,2-dibromoethane is conjugation 1,2-dibromoethane with GSH to an active genotoxic metabolite. This reaction is catalyzed by GST, which exists as isozymes. Thus, polymorphisms in GST may alter toxicity of glutathione. For example, in a study in human fibroblasts from individuals with decreased GSH levels due to a hereditary deficiency, the number of sister chromatid exchanges was significantly lower than in fibroblast from individuals without this deficiency (DeLeve 1997).

3.3 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They are classified into 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-dibromoethane 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-dibromoethane 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-dibromoethane 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

Precluding the detection of 1,2-dibromoethane in blood or urine, there are no specific exposure biomarkers. In a 2007-2008 survey of 2,577 individuals, 1,2-dibromoethane in blood was below the limits of detection (<0.015 ng/mL) (CDC 2017). Urinary mercapturic acids have been considered as possible biomarkers of exposures of electrophilic chemicals, including 1,2-dibromoethane (Calafat et al. 1999; De Rooij et al. 1998; van Welie et al. 1992). Because various electrophilic chemicals share common pathway for conjugation with GSH, urinary mercapturic acids would not specific for 1,2-dibromoethane. For example, 2-hydroxyethyl mercapturic acid is a urinary metabolite for a variety of electrophilic hydrocarbons, including 1,2-dibromoethane, acrylonitrile, 2-brompropanol, 2-chloroethylnitroso ureas, ethene, ethylene oxide, and vinyl chloride (De Rooij et al. 1998). Data on urinary levels of 2-hydroxyethyl mercapturic acid (N-acetyl-S-(2-hydroxyethyl)-L-cysteine) in the U.S. non-institutionalized population are collected as part of the National Health and Nutrition Examination Survey (NHANES) (Calafat et al. 1999; CDC 2017). Based on data for the period 2011–2012, the 2-hydroxyethyl mercapturic acid geometric mean and 95th percentile in children (6–11 years of age) were 1.69 and 5.11 µg/g creatinine, respectively (CDC 2017). The 95th percentile for adults (≥20 years of age) was 6.87 µg/g creatinine; the geometric mean for adults was not reported. These levels reflect exposures to all chemicals that are metabolized to 2-hydroxyethyl mercapturic acid, including 1,2-dibromoethane.

3.3.2 Biomarkers of Effect

There are no adverse effects that are specific for or unique to 1,2-dibromoethane. However, some biochemical markers may indicate effects of 1,2-dibromoethane. Biochemical markers of effect are typically measured in tissues collected by methods that are non-invasive (e.g., urine, exhaled air) or minimally invasive (e.g., blood). Protein or DNA adducts could potentially provide biomarkers of effective (e.g., genotoxic) dose or long-term exposure because they are retained form longer periods of time (Van Welie et al. 1992). The DNA adduct, S-[2-(N7-guanyl)ethyl]mercapturic acid, would be of potential importance as a biomarker for 1,2-dibromoethane because it is thought to represent the dose of reactive metabolite formed from 1,2-dibromoethane, and has been implicated in 1,2-dibromoethane genotoxicity and carcinogenicity (Bolt et al. 1986; Guengerich et al. 1995; Koga et al. 1986). However, formation of S-[2-(N7-guanyl)ethyl]mercapturic acid is not unique to 1,2-dibromoethane; it is also formed in association with exposures to other electrophiles metabolized through the GST pathway (Guengerich 2005). Adducts with serum albumin may also be potential biomarkers of reactive metabolites produced from 1,2-dibromoethane, as 1,2-dibromoethane and its metabolites can bind covalently to serum albumin (Kaphalia and Ansari 1992).

3.4 INTERACTIONS WITH OTHER CHEMICALS

Exposure to chemicals that modify activity of GST have the potential to alter the toxicity of 1,2-dibromoethane. Agents that inhibit GST have been shown to increase hepatotoxicity of 1,2-dibromoethane. These chemicals include ethanol and its metabolite (i.e., acetaldehyde), the acetaldehyde inhibitor disulfiram (Wong et al. 1982), diethylmaleate (Botti et al. 1986), and carbon tetrachloride (Aragno et al. 1996; Chiarpotto et al. 1995a, 1995b; Danni et al. 1991). This effect is thought to occur as the result of increasing metabolism through the CYP450 pathway and increased formation of 2-bromacetaldehyde, a reactive product of CYP450 in liver and other tissues (Guengerich et al. 1991; Tamura et al. 1986; Van Duuren et al. 1985; Wormhoudt et al. 1996a, 1996b).

Chemicals that deplete cellular GSH have been shown decrease the formation of 1,2-dibromoethane-DNA adducts and genotoxicity of 1,2-dibromoethane. These chemicals include diethylmaleate and butathione sulfoxamine (Cho and Guengerich 2013; Cmarike et al. 1990). This effect is thought to occur as the result of decreasing metabolism through the GST and decreased formation of S-(2-bromoethyl)-glutathione, a reactive product of GST which can form DNA adducts (Cho and Guengerich 2013; DeLeve 1997; Thomas et al. 2001; Van Bladeren et al. 1981).

Consistent with the effect of depletion of GST, hereditary deficiency in GST has been associated with decreased genotoxicity of 1,2-dibromoethane in cultured human fibroblasts (DeLeve 1997). In the opposite direction, chemicals that induce GST increase metabolism of 1,2-dibromoethane through the GST pathway. These include coumarin, ethoxyquin, and phenobarbital (Sherratt et al. 1998). This suggests the possibility that chemical exposures that result in GST induction could also potentiate the genotoxicity of 1,2-dibromoethane.