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

3.1 TOXICOKINETICS

No studies were located regarding 1,2,3-trichloropropane toxicokinetics in humans, but there are limited data from studies in animals. These data are summarized below.

- Approximately 80% of an oral dose is absorbed through the gastrointestinal tract. No absorption data are available for inhalation or dermal routes, although absorption is presumed based on remote toxicity.
- Absorbed 1,2,3-trichloropropane is widely distributed throughout the body.
- 1,2,3-Trichloropropane is rapidly and extensively metabolized. It likely undergoes cytochrome P450-catalyzed dehalogenation reactions.
- 1,2,3-Trichloropropane and its metabolites are excreted via urine, feces, and exhaled breath. It is excreted within 2 days of a single exposure.

3.1.1 Absorption

No quantitative information was located regarding absorption of 1,2,3-trichloropropane following inhalation exposure; however, since liver and hematological toxicity has been reported in animals exposed by the inhalation route (Johannsen et al. 1988; Miller et al. 1986a), it can be concluded that absorption occurs to some extent. The results of studies performed in rats indicate that near complete absorption (>80%) from the gastrointestinal tract occurs within the first day following oral exposure (Mahmood et al. 1991; Sipes et al. 1982; Volp et al. 1984). As with inhalation exposure, dermal absorption can be implied based on the lethality study conducted by Smyth et al. (1962) in which the dermal application site was protected by an impervious membrane.

3.1.2 Distribution

Muscle, blood, liver, skin, and adipose tissue contained the largest amounts of 1,2,3-trichloropropane following oral exposure in rats (Sipes et al. 1982). Retention in all tissues was low, however, as elimination of 1,2,3-trichloropropane-derived radioactivity from tissues was nearly complete (>97%) within 8 days after oral exposure in rats (Sipes et al. 1982). Another study found that 6 hours after receiving a gavage dose of radiolabeled 1,2,3-trichloropropane, the highest concentrations of radioactivity were found in the gastrointestinal tract (in decreasing concentration: forestomach, glandular stomach,

small intestine, large intestine), adipose, kidney, and liver (Mahmood et al. 1991). After 60 hours, the highest concentrations were found in the liver, kidneys, and forestomach. In mice, the highest concentrations were found in the forestomach, liver, and kidney 60 hours post-dosing (Mahmood et al. 1991). The 1,2,3-trichloropropane remaining in the forestomach, liver, and kidney was non-extractable metabolites, suggesting that it was covalently bound to tissue macromolecules.

Distribution studies of intravenously injected 1,2,3-trichloropropane in rats have provided a quantitative description of the distribution kinetics from which predictions can be made regarding other routes of exposure (Sipes et al. 1982; Volp et al. 1984). Intravenously injected 1,2,3-trichloropropane rapidly distributes to many tissues. The major sites of accumulation are liver, kidney, small and large intestine, adipose tissue, muscle, and skin. Peak concentrations are achieved within l–2 hours after intravenous injection. Elimination of 1,2,3-trichloropropane from tissues in the rat is also rapid and a two-phase process (Volp et al. 1984). Elimination half-times for >90% of the 1,2,3-trichloropropane in tissues ranged from 20 minutes in kidney to 2 hours in adipose tissue (first phase). A small fraction of the 1,2,3-trichloropropane in these tissues (<10%) was eliminated more slowly, with half-times ranging from 23 to 45 hours (second phase). Elimination of total radioactivity from the tissues after intravenous injection of radiolabeled 1,2,3-trichloropropane (phase one half-times between 2 and 5 hours, phase two half-times between 87 and 182 hours) is slower than elimination of parent 1,2,3-trichloropropane. This suggests that metabolites of 1,2,3-trichloropropane are eliminated slower than the parent compound. Based on the results of studies in the rat, it can be concluded that 1,2,3-trichloropropane absorbed by any route is likely to be widely distributed in the body. Most of the 1,2,3-trichloropropane that enters tissues is eliminated within hours to days.

3.1.3 Metabolism

Gavage administered or intravenously injected 1,2,3-trichloropropane is extensively metabolized within hours in rats. Metabolic products in rats include carbon dioxide, which is expired, and numerous metabolites that are excreted in urine and enter the bile to be excreted in feces or absorbed in the intestines (Mahmood et al. 1991; Sipes et al. 1982; Volp et al. 1984). Many of the metabolites of 1,2,3-trichloropropane that are formed in the rat have not been identified; based on the metabolic pathways that have been identified for other halogenated alkanes, dehalogenation products, glutathione conjugates, and their subsequent metabolites, mercapturic acids, can be anticipated. Chloroalkanes such as 1,2,3-trichloropropane undergo dehalogenation reactions catalyzed by cytochrome P450 (Ivanetich et al. 1978; Salmon et al. 1981; Van Dyke et al. 1971). Depending on the reaction mechanism, highly

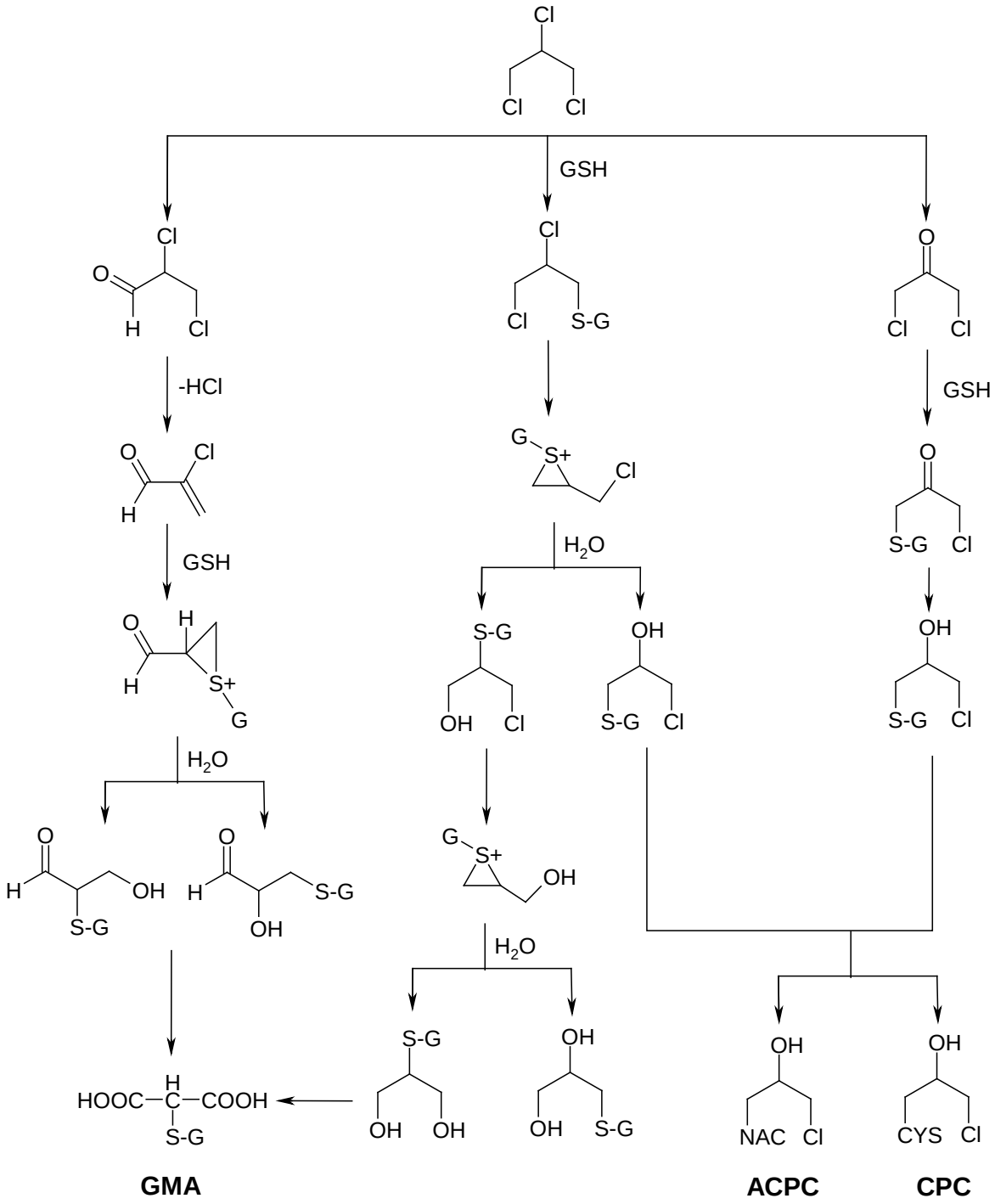
reactive intermediates (e.g., radicals) can be formed from these reactions, leading to protein and DNA adducts or lipid peroxidation. Conjugation with glutathione could result in formation of sulfur mustard-like compounds that are potential alkylating agents.

Mahmood et al. (1991) proposed three possible metabolic pathways for 1,2,3-trichloropropane, which involve cytochrome P450 metabolism or glutathione conjugation. The possible pathways are summarized below and illustrated in Figure 3-1:

1. Nucleophilic displacement of chlorine at the C1 or C2 position, possibly by glutathione transferase, to form a β-chlorothio ether. Displacement of the β-chlorine could result in the formation of a reactive episulfonium ion. The episulfonium ion could react with water to form glutathione conjugates at the C1 or C2 position.
    a. Cleavage of the glutathione conjugate at the C2 position could ultimately result in the formation of N-acetyl-S-(3-chloro-2-hydroxypropyl)-L-cysteine (ACPC) or S-(3-chloro-2-hydroxypropyl)-L-cysteine (CPC).
    b. The episulfonium ion could also react with water at the C1 position to form another episulfonium ion. The second episulfonium ion could react with water at the C3 position to form a 1,3-dihydroxypropyl glutathione conjugate, which could oxidize to form 2-(S-glutathionyl)malonic acid (GMA).
2. Oxidation of 1,2,3-trichloropropane at the C2 position, possibly by cytochrome P450, would result in the formation of 1,3-dichloroacetone. 1,3-Dichloroacetone could undergo chlorine displacement by glutathione and reduction of the keto group to form ACPC and CPC.
3. Oxidation of 1,2,3-trichloropropane at the C1 position, possibly by cytochrome P450, to form the α-chlorohydrin, 2,3-dichloropropanal. Loss of HCl from 2,3-dichlorpropanal would form chloroacrolein, which could react with glutathione to form an episulfonium ion. The episulfonium ion could react with water at the C3 position to form GMA after oxidation of the C2 and C3 atoms to carboxylic acids.

The results of an *in vitro* study (Weber and Sipes 1992) in rat hepatic microsomes suggest two similar possible metabolic pathways for 1,2,3-trichloropropane: (1) oxidation at the C2 position to form the unstable compound *gem*-chlorohydrin, which is dehalogenated to form 1,3-dichloroacetone, and (2) oxidation at the C1 position to form *gem*-chlorohydrin, which is dehalogenated to form 2,3-dichloropropanal, which is subsequently reduced to 2,3-dichloropropanol.

Figure 3-1. Possible Metabolic Pathways for the Formation of ACPC, CPC, and GMA from 1,2,3-Trichloropropane



ACPC = N-Acetyl-S-(3-chloro-2-hydroxypropyl)-L-cysteine; CPC = S-(3-chloro-2-hydroxypropyl)-L-cysteine; GMA = 2-(S-glutathionyl)malonic acid

Source: Mahmood et al. 1991

3.1.4 Excretion

Studies conducted with rats showed that 1,2,3-trichloropropane and its metabolites were excreted in urine, feces, and exhaled breath after oral exposure (Sipes et al. 1982). Excretion was nearly complete (95–96%) within 2 days. Most of the dose was excreted in the urine and feces (up to 56 and 25%, respectively), with the remainder in the breath. Mahmood et al. (1991) demonstrated that ≥90% of the radioactivity was excreted 60 hours following a gavage dose of radiolabeled 1,2,3-trichloropropane in rats and mice. Urine was the primary route of excretion, accounting for 50–57% of the dose in rats and 65% of the dose in mice. In the urine, the radiolabel was primarily found in the form of *N*-acetyl-*S*-(3-chloro-2-hydroxypropl)-L-cysteine. Excretion as carbon dioxide or in the feces accounted for 20 and 20% of the radiolabel, respectively, in rats and 20 and 15% of the label, respectively, in mice. Comparison of excretion data from rats and mice suggest that at a given dose, male mice appear to eliminate 1,2,3-trichloropropane faster and retain less radioactivity than male (or female) rats (Mahmood et al. 1991).

Studies of the excretion of intravenously injected 1,2,3-trichloropropane in rats have provided a quantitative description of the excretion kinetics from which predictions can be made about other routes of exposure (Sipes et al. 1982; Volp et al. 1984). Excretion of intravenously injected 1,2,3-trichloropropane and metabolites is nearly complete within 2 days. Unchanged 1,2,3-trichloropropane and its major metabolite, carbon dioxide, are expired in exhaled breath. Nonvolatile metabolites are excreted in the urine. Extensive biliary excretion of nonvolatile metabolites also occurs, resulting in fecal excretion as well as reabsorption of metabolites from the gastrointestinal tract. Based on the results of studies in rats, exhaled breath, urine, and feces are likely to be significant routes of excretion of absorbed 1,2,3-trichloropropane and its metabolites in humans.

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.

Volp et al. (1984) developed a PBPK model in male rats to investigate the time course of 1,2,3-trichloropropane is tissues. The flow-limited model consisted of seven compartments: blood, liver, kidney, fat, muscle, skin, and remaining distribution volume. The model, with some adjustments of pharmacokinetic parameters, predicted the concentration versus time curves for the selected tissues.

3.1.6 Animal-to-Human Extrapolations

The limited available toxicokinetic data do not allow for an assessment of potential species differences. Most of the toxicity studies were conducted in rats; two studies tested rats and mice, which allow for a comparison across species. In an 11-day inhalation study, Miller et al. (1986a) found similar targets of toxicity, but differences in sensitivity between rats and mice. In rats, exposure to 3 ppm resulted in thickening of the nasal olfactory epithelium. In mice, 3 ppm was a NOAEL for nasal effects; at 10 ppm, nasal olfactory inflammation was observed. Similar findings were observed in intermediate- and chronic-duration studies (NTP 1993). In rats, increases in liver weight were observed at ≥16 mg/kg (5 days/week) and hepatocellular necrosis and bile duct hyperplasia were observed at 125 ppm. In contrast, an increase in liver weight was not observed in mice at doses lower than 125 ppm and hepatocellular necrosis was observed at 250 ppm. Chronic-duration exposure resulted in differences in the types of effects (e.g., bile duct hyperplasia in rats and hepatocellular necrosis in mice) and sensitivity. Collectively, these studies suggest species differences in the toxicity of 1,2,3-trichloropropane. There are insufficient data to assess whether rats or mice would be a better model for human toxicity. In the absence of these data, it was assumed that the most sensitive species would be appropriate for MRL derivation.

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 1,2,3-trichloropropane are discussed in Section 5.7, Populations with Potentially High Exposures.

There are limited data on the susceptibility of children to the toxicity of 1,2,3-trichloropropane; in the absence of data to the contrary, it is assumed that it would be the same as in adults. The developmental toxicity of 1,2,3-trichloropropane has not been thoroughly investigated. A 2-generation study found decreases in fertility in F1 mice (NTP 1990); however, it is not known if this was due to impaired development of the reproductive system as similar effects were observed in the P0 animals.

No populations with unusual susceptibility to health effects of 1,2,3-trichloropropane have been identified. The respiratory tract, blood, liver, and kidneys are principal targets of 1,2,3-trichloropropane in animals (see Section 2.4). It is therefore possible that people with chronic respiratory, liver, or kidney disease, or possibly people with compromised pulmonary, hepatic, or renal function, might be unusually susceptible to 1,2,3-trichloropropane.

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 1,2,3-trichloropropane 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 1,2,3-trichloropropane 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 1,2,3-trichloropropane 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

Biomarkers of exposure to 1,2,3-trichloropropane have not been established because information on levels of 1,2,3-trichloropropane or its metabolites in human tissues, fluids, or excreta or information on effects specific for 1,2,3-trichloropropane is not available. Studies with rats indicate that excretion of 1,2,3-trichloropropane in the breath or urine may be sufficient for monitoring purposes (see Section 3.1.4).

3.3.2 Biomarkers of Effect

Effects in humans that are specifically attributable to 1,2,3-trichloropropane exposure alone are not known. Principal targets of 1,2,3-trichloropropane in animals are the respiratory tract, blood, liver, and kidneys. One study with rats suggests that alterations of serum enzymes (e.g., decreased serum pseudo-cholinesterase activity) and anemia might be useful biomarkers for hepatic and hematologic effects, respectively, of 1,2,3-trichloropropane. Insufficient data exist, however, to determine whether 1,2,3-trichloropropane is likely to cause anemia in humans, and substances other than 1,2,3-trichloropropane could also cause similar hematologic and hepatic effects.

3.4 INTERACTIONS WITH OTHER CHEMICALS

Rats were exposed by inhalation to 500 ppm trichloropropane and 1,000 ppm dichloropropane alone and in combination for 4 hours (Drew et al. 1978). Activities of liver-associated serum enzymes (serum alanine aminotransferase, aspartate aminotransferase, ornithine carbamyl transferase) were increased 24–48 hours following exposure to each chemical alone. The combined exposure resulted in higher enzyme activities than with either chemical alone, but the increases were less than additive.