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

3.1 TOXICOKINETICS

- 1,2-Dibromo-3-chloropropane is rapidly absorbed through the gastrointestinal tract and is presumed to be readily absorbed through the respiratory tract and skin, based on systemic toxicity in animals exposed by these routes.
- Absorbed 1,2-dibromo-3-chloropropane is widely distributed to tissues and remains longer in fat than other tissues.
- The predominant pathway for 1,2-dibromo-3-chloropropane metabolism is cytochrome P450 oxidation to form epoxide intermediates, which can be further hydrolyzed and debrominated or undergo glutathione conjugation catalyzed by glutathione transferase.
- Most absorbed 1,2-dibromopropane is excreted as metabolites in the urine; lesser amounts are excreted in feces or exhaled air as carbon dioxide.

3.1.1 Absorption

No studies were located regarding absorption following occupational (predominantly inhalation, but may have included dermal and oral) exposure to 1,2-dibromo-3-chloropropane. However, reported systemic effects in laboratory animals exposed by inhalation or dermal routes provide evidence of absorption from these exposure routes. Animal studies show that 1,2-dibromo-3-chloropropane is rapidly and extensively absorbed from the gastrointestinal tract. The absorption of 1,2- dibromo-3-chloropropane followed first-order kinetics in rats after oral administration by gavage in a water vehicle. No dose dependence in absorption was observed with doses up to 10 mg/kg/day, and peak blood levels were reached within 5–40 minutes. The rate of absorption was slower and more erratic with oil vehicle, but the extent of absorption remained approximately the same (i.e., 68% with corn oil versus 78% with water) (Gingell et al. 1987a). Absorption from the gastrointestinal tract was 99% of the originally administered dose of ^{14}C-1,2-dibromo-3-chloropropane; only 0.223% of the administered radioactivity was recovered in the feces of bile duct-cannulated rats (Kato et al. 1979a).

3.1.2 Distribution

Following absorption in rats, 1,2-dibromo-3-chloropropane, which was administered by corn oil gavage for 10 consecutive days to pregnant rats, was rapidly and widely distributed to tissues, and tended to

remain longest in fat (Ruddick and Newsome 1979). The concentration of 1,2-dibromo-3-chloropropane in pooled fetuses and in spleens, brains, hearts, kidneys, and livers of dams was highest within 3 hours of the exposure to the last dose of 1,2-dibromo-3-chloropropane. The peak level in fat occurred after 6 hours, and 1,2-dibromo-3-chloropropane was still detectable after 24 hours. At 12 hours following the last dose, 1,2-dibromo-3-chloropropane was no longer detected in most other tissues. The detection in tissues of pooled fetuses provides evidence that 1,2-dibromo-3-chloropropane crossed the placenta.

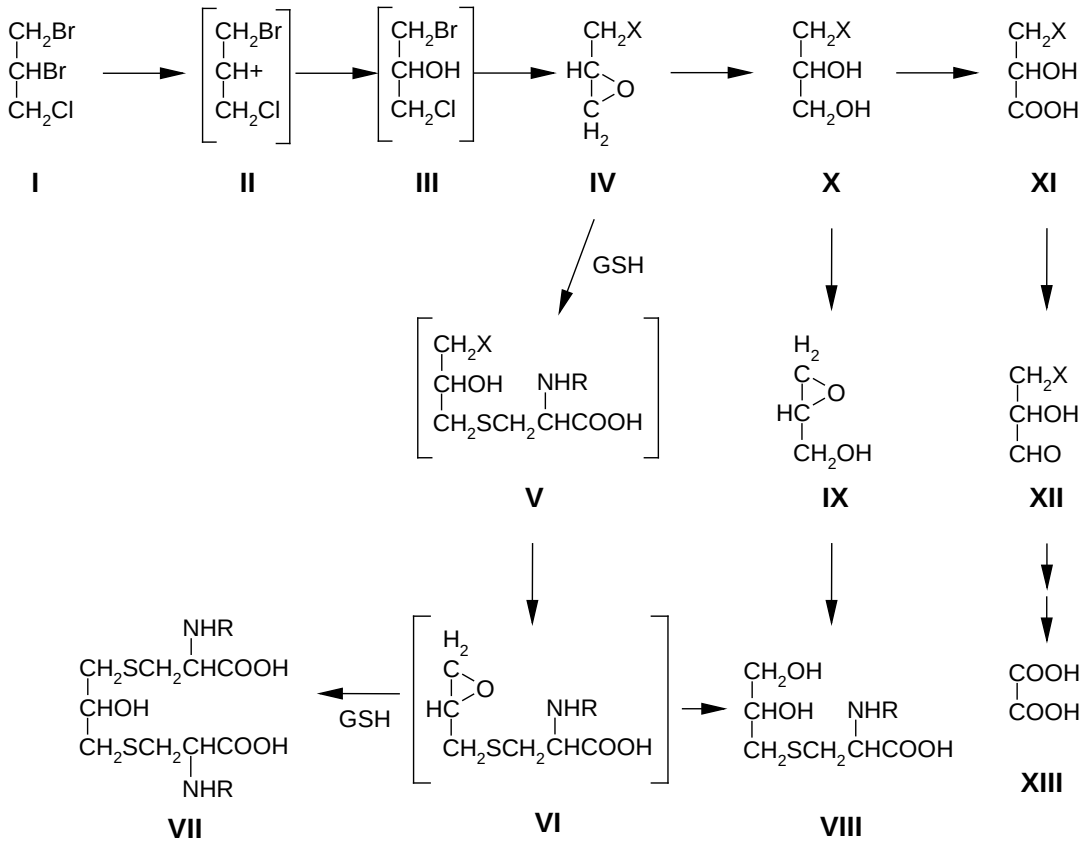
In rats administered ^{14}C-1,2-dibromo-3-chloropropane in corn oil by gavage, unchanged 1,2-dibromo-3-chloropropane accumulated only in the adipose tissues, while unextractable metabolites were found in kidneys and livers (Kato et al. 1979a). The unextractable metabolites were detected in most tissues, possibly as reactive metabolites bound to tissue macromolecules. The highest level of radioactivity was found in livers and kidneys (Kato et al. 1980) at 6 and 20 hours postexposure. As demonstrated in Sections 2.9 and 2.10, liver and kidney are targets of 1,2-dibromo-3-chloropropane toxicity.

3.1.3 Metabolism

The metabolism of 1,2-dibromo-3-chloropropane was studied in rats. The proposed metabolic pathway is shown in Figure 3-1. According to this scheme, 1,2-dibromo-3-chloropropane is converted to epoxy derivatives, which are further hydrolyzed and debrominated. Bromide accumulates in the kidneys. Beside other metabolites, epichlorohydrin and epibromohydrin were found, which can be further metabolized to oxalic acid. Mercapturic acids were detected in urine and this indicates that metabolic intermediates reacted with nonprotein sulfhydryl (NPS) groups (Jones et al. 1979).

Conjugation of the epoxide intermediates with NPS groups can occur in the liver, kidneys, lungs, stomach, and testes of rats after treatment with 1,2-dibromo-3-chloropropane (Kato et al. 1980; Kluwe et al. 1981, 1982). The greater depletion of hepatic NPS suggests that the liver is the major site of GSH conjugation with 1,2-dibromo-3-chloropropane metabolites (Kluwe et al. 1982). GSH pretreatment protected rats from 1,2-dibromo-3-propane-induced liver necrosis (Kato et al. 1980), indicating that conjugation is a detoxifying mechanism in the liver.

Figure 3-1. The Metabolism of 1,2-Dibromo-3-chloropropane in Rats



I 1,2-Dibromo-3-chloropropane
II 1-Bromo-3-chloropropylium
III 1-Bromo-3-chloropropan-2-ol
IV Epichlorohydrin or epibromohydrin
V S-[1-(2-hydroxy)propyl] cysteine
VI S-[1-(2-epoxy)propyl] cysteine
VII 1,3-(Bis-cysteine)propan-2-ol
VIII S-(2,3-dihydroxypropyl-cysteine
IX 1-Epxoy-3-hydroxypropane
X α-Chlorohydrin or α-bromohydrin
XI 3-Chloractic acid or 3-bromolactic acid
XII 3-Chlorolactadehyde or 3-bromolactaldehyde
XIII Oxalic acid
GSH Reduced glutathione

Source: Jones et al. 1979

Studies of the mechanism of 1,2-dibromo-3-chloropropane-induced testicular toxicity suggest that in the testes, conjugation with GSH with subsequent metabolism to a reactive metabolite represents a toxifying mechanism (Kluwe 1983; Omichinski et al. 1988a, 1988b).

The interspecies differences in 1,2-dibromo-3-chloropropane gonadotoxicity are probably due to interspecies differences in metabolism within the testicular cells to convert 1,2-dibromo-3-chloropropane to more reactive forms. After a single intraperitoneal injection of 1,2-dibromo-3-chloropropane, atrophy of seminiferous epithelium was more severe in rats and guinea pigs than in hamsters and mice;

furthermore, testicular DNA damage was observed only in rats and guinea pigs (Lag et al. 1989a). These findings suggest that rats and guinea pigs are sensitive to 1,2-dibromo-3-chloropropane because their testicular cells more readily activate 1,2-dibromo-3-chloropropane to a DNA-damaging intermediate(s). Species differences in metabolism were also found in *in vitro* experiments with tissues from rats and mice. Rats metabolized 1,2-dibromo-3-chloropropane in liver, kidney, testes, and stomach preparations much faster than mice, as measured by GSH-dependent debromination in cytosolic fractions (MacFarland et al. 1984). No data were located regarding potential for 1,2-dibromo-3-chloropropane to induce DNA damage in human testicular cells *in vitro*; however, effects on sperm quality and histopathological testicular changes have been associated with occupational exposure to 1,2-dibromo-3-chloropropane (see Section 2.16).

3.1.4 Excretion

Limited information was located regarding excretion following absorption of 1,2-dibromo-3-chloropropane. Excretion after administration of radioactively labeled 1,2-dibromo-3-chloropropane in rats occurred via several routes, including exhalation and biliary and urinary elimination. During 24 hours following gavage administration of ^{14}C-1,2-dibromo-3-chloropropane to male rats, captured radioactivity in urine, feces, and expired air was approximately 48, 14.4, and 17–18%, respectively, of the administered dose (Kato et al. 1979a). Expired radioactivity was primarily in the form of $^{14}CO_2$. Mercapturic acids were detected in the urine; biliary excretion accounted for approximately 23% of the administered dose. In another rat study, within 3 days of gavage administration of radioactively labeled 1,2-dibromo-3-chloropropane, 55% of the radioactivity was found in the urine, 18% in the feces, and 19.5% in the exhaled air as carbon dioxide. Less than 1% was exhaled as unchanged 1,2-dibromo-3-chloropropane (Gingell et al. 1987a).

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 PBPK models were identified for 1,2-dibromo-3-chloropropane.

3.1.6 Animal-to-Human Extrapolations

Available information indicates significant species differences in the toxicokinetics and toxicity of 1,2-dibromo-3-chloropropane, thus precluding meaningful animal-to-human extrapolation.

Soderlund et al. (1990) reported species differences in 1,2-dibromo-3-chloropropane-induced kidney lesions and DNA damage, as well as distribution and metabolism, among rats, mice, guinea pigs, and hamsters following single intraperitoneal administration. Extensive renal tubular necrosis was observed in 5/5 rats treated at 170 or 340 µmol/kg; only slight evidence of renal tubular necrosis was observed in 3/5 mice at 340 and 680 µmol/kg, and 1/5 guinea pigs and 1/5 hamsters at 680 µmol/kg.

Rats and guinea pigs exhibited similar sensitivity to 1,2-dibromo-3-chloropropane-induced DNA damage to kidney cells, whereas a 10–50-fold higher dose was necessary to produce a similar level of DNA damage to mouse and hamster kidney cells. Bjorge et al. (1996) reported a 3-fold more rapid activation of 1,2-dibromo-3-chloropropane to covalently-bound macromolecules in rat testicular cell preparations compared to human testicular cells. Comparative evaluation of 1,2-dibromo-3-chloropropane-induced DNA damage revealed dose-related increased single-strand DNA strand breaks in rat testicular cells, but no evidence of damage in human testicular cells.

Initial 1,2-dibromo-3-chloropropane kidney concentrations were substantially higher in rats and guinea pigs, and kidney elimination occurred at a significantly lower rate in rats than mice, hamsters, and guinea pigs. Kidney preparations from rats and guinea pigs were observed to debrominate 1,2-dibromo-3-chloropropane at approximately 2–3 times the rate of preparations from mice and hamsters. These results indicate that the initial higher concentration of renal 1,2-dibromo-3-chloropropane, relatively longer retention, and increased rate of metabolism may contribute to the greater susceptibility of the rat and guinea pig to 1,2-dibromo-3-chloropropane-induced nephrotoxicity.

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-dibromo-3-chloropropane are discussed in Section 5.7, Populations with Potentially High Exposures.

No data were located regarding potential age-related differences in susceptibility to 1,2-dibromo-3-chloropropane. It is unknown whether susceptibility among children is different from that of adults. Persons with impaired kidney or lung function may also be more susceptible to the toxic effects of 1,2-dibromo-3-chloropropane because the kidney and lungs are relatively sensitive targets of 1,2-dibromo-3-chloropropane toxicity. The male reproductive system has been identified as a sensitive target of 1,2-dibromo-3-chloropropane toxicity in animals; available human data suggest that the male reproductive system is a target as well.

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-dibromo-3-chloropropane 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-dibromo-3-chloropropane 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-dibromo-3-chloropropane 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

No studies were located regarding tissue, fluid, or excreta levels of 1,2-dibromo-3-chloropropane in humans.

Toxicokinetic studies performed in animals after acute exposures to 1,2-dibromo-3-chloropropane indicate that this chemical preferentially partitions to fat; however, upon termination of exposure, the accumulated chemical is rapidly lost from this tissue (Kato et al. 1979a; Ruddick and Newsom 1979). Over 80% of adipose tissue 1,2-dibromo-3-chloropropane is lost by 24 hours postexposure. 1,2-Dibromo-3-chloropropane was lost from other tissues more rapidly. Thus, determination of tissue levels of 1,2-dibromo-3-chloropropane must be made shortly after exposure. 1,2-Dibromo-3-chloro-propane may be found in exhaled air, but <1% of an administered dose was found in exhaled air during the first 24 hours after dosing (Gingell et al. 1987a).

At least 20 metabolites were detected in the urine of rats following ingestion of radioactively labeled 1,2-dibromo-3-chloropropane (Gingell et al. 1987b). However, it is not known if these metabolites occur

in human urine following exposure to 1,2-dibromo-3-chloropropane by inhalation, oral, or dermal exposures. Also, because some of the metabolites (e.g., oxalic acid) may be produced from natural body processes, the detection of these metabolites may not be specific for 1,2-dibromo-3-chloropropane exposures. Additionally, the enzymes responsible for metabolizing 1,2 dibromo-3-chloropropane function to change many substances, not just 1,2 dibromo-3-chloropropane. Therefore, changes in enzyme activity would not be a specific biomarker of exposure for 1,2 dibromo-3-chloropropane.

3.3.2 Biomarkers of Effect

Changes in sperm parameters might be considered a biomarker of effect for 1,2-dibromo-3-chloro-propane. However, such a biomarker would not be specific to 1,2-dibromo-3-chloropropane. Several studies indicated that 1,2-dibromo-3-chloropropane induced DNA damage and changes in the activity of microsomal enzymes (Kluwe 1983; Suzuki and Lee 1981); however, these changes are not specific for 1,2-dibromo-3-chloropropane exposure and cannot be used as biomarkers. It is not likely that biomarkers specific to 1,2-dibromo-3-chloropropane exist.

3.4 INTERACTIONS WITH OTHER CHEMICALS

Substances such as 3-methylcholanthrene and cobalt chloride have been reported to enhance the adverse effects of 1,2-dibromo-3-chloropropane on seminiferous tubules (Kluwe 1983).