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

3.1 TOXICOKINETICS

No studies were located regarding BCEE toxicokinetics in humans, but there are limited data from animal studies. These data are summarized below.

- Greater than 95% of BCEE is absorbed following inhalation or oral exposure. BCEE appears to be absorbed through the skin, but there are no data on the rate or extent of absorption.
- BCEE appears to be widely distributed throughout the body, with the highest levels found in the liver, kidney, and small intestine following oral exposure.
- The predominant pathway for BCEE metabolism is hydroxylation to ultimately form thiodiglycolic acid. BCEE is also metabolized via direct substitution and oxidative dehalogenation.
- BCEE is primarily excreted in the urine as the metabolite thiodiglycolic acid. Within 48 hours of oral administration, 80% of the dose is excreted.

3.1.1 Absorption

There are limited quantitative data on BCEE absorption. Gwinner et al. (1983) reported that rats placed in a chamber containing BCEE vapor absorbed >95% of the compound within 18 hours. Lingg et al. (1982) reported that only 2% of a single oral dose of BCEE administered to rats was excreted in the feces, indicating that absorption across the gastrointestinal tract was essentially complete. No studies were located regarding the rate or the extent of absorption by the dermal route. However, acute dermal toxicity studies (Smyth and Carpenter 1948) suggest that BCEE is absorbed across the skin.

3.1.2 Distribution

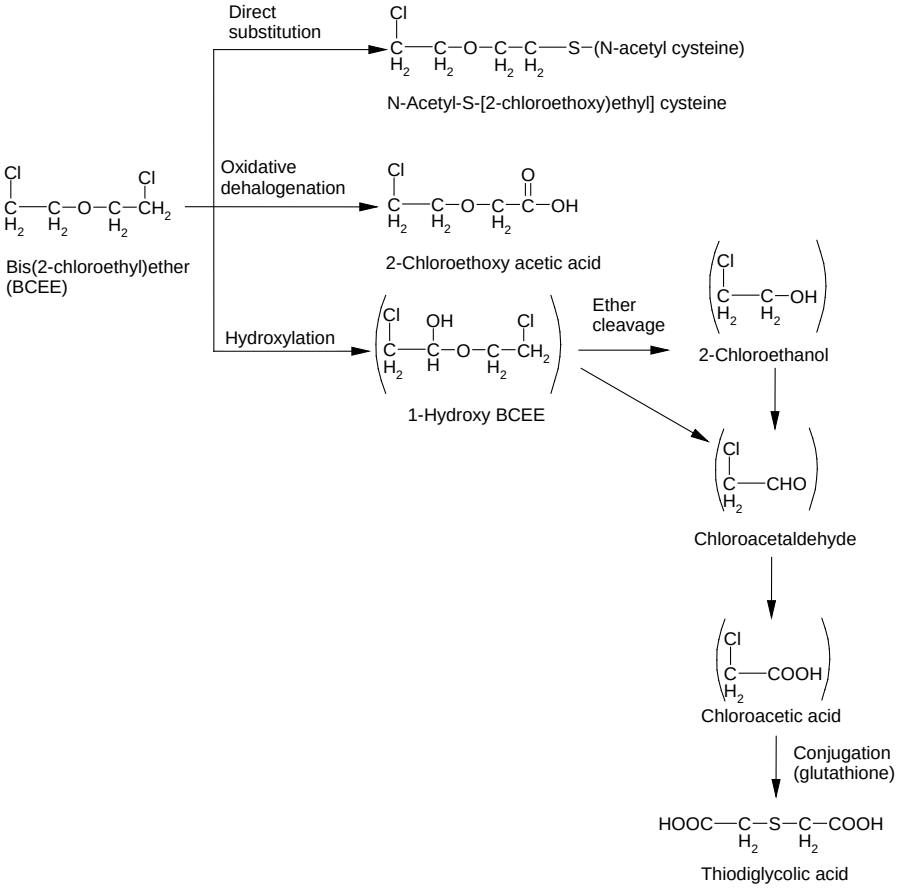
Lingg et al. (1982) administered a single oral dose of ^{14}C-labelled BCEE to rats, and measured the radioactive content of tissues 48 hours later. Only a small fraction of the dose (2.3%) was found in organs and tissues, with 0.96% in muscle, 0.56% in kidney, 0.49% in blood, 0.19% in liver, and 0.1% in other tissues. No distribution data were identified for inhalation or dermal exposure.

3.1.3 Metabolism

Studies in animals indicate that BCEE is extensively metabolized, with thiodiglycolic acid (TDGA) being the principal endproduct (Lingg et al. 1979; Norpoth et al. 1986). The pathway leading to TDGA

formation is not certain, but probably involves oxidative cleavage of the ether bond to yield chloroacetaldehyde and 2-chloroethanol, as shown in Figure 3-1 (Bolt 1984; Gwinner et al. 1983; Lingg et al. 1979, 1982; Muller and Norpoth 1979; Norpoth et al. 1986). TDGA recovered in urine usually accounts for 50% to 80% of a dose of BCEE (Lingg et al. 1979, 1982). Smaller amounts of BCEE (3–5%) are metabolized by oxidation or substitution at a chlorine without ether cleavage (see Figure 2-3), and about 12% is degraded to CO_2 (Lingg et al. 1982). Only about 2% of the dose is excreted via the lungs as unchanged BCEE (Lingg et al. 1979). Gwinner et al. (1983) exposed rats to ^{14}C-labelled BCEE vapor, and measured the amount of radioactivity irreversibly bound to tissue proteins 24 hours later. Distribution of unbound parent or metabolites was not measured. Highest levels were found in liver, kidney, and small intestine, with much lower levels in lung, spleen, and muscle. The presence of protein-bound label in these tissues suggested to the authors that reactive intermediates were formed that led to covalent adducts, but incorporation of label into protein might also have occurred through normal synthetic pathways involving nontoxic breakdown products from BCEE. No label was detectable in liver deoxyribonucleic acid (DNA) or ribonucleic acid (RNA).

Figure 3-1. Summary of Bis(2-Chloroethyl)Ether Metabolism in Rats



3.1.4 Excretion

Lingg et al. (1979, 1982) found that approximately 80% of an oral dose of BCEE administered to rats was excreted within 48 hours. Most of the dose (65%) was excreted as urinary metabolites (mostly thiodiglycolic acid), with smaller amounts excreted in feces (3%) or expired air (11% as CO_2 and <2% as parent BCEE). Only 2% of the dose remained in the body. This indicates that BCEE is effectively excreted, and that it has a low tendency to accumulate in tissues.

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 BCEE.

3.1.6 Animal-to-Human Extrapolations

There are insufficient data to evaluate possible species differences in the toxicokinetic properties of BCEE because the available studies only tested rats. Toxicity studies in rats, mice, rabbits, and guinea pigs suggest similarities in the lethality and toxicity of BCEE across species. Schrenk et al. (1933) reported nasal and eye irritation in humans briefly exposed to BCEE, irritation was also reported in guinea pigs exposed to similar concentrations.

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 BCEE are discussed in Section 5.7, Populations with Potentially High Exposures.

No data are available on the toxicity of BCEE in children and it is assumed to be similar to adults. No developmental toxicity studies have been identified for BCEE. No information was located to indicate that any human population might be especially susceptible to the toxic effects of BCEE. Based on the observation that BCEE is a powerful irritant of the respiratory tract, it may be expected that individuals with lung disease or other forms of respiratory distress might be particularly vulnerable to the effects of BCEE vapors.

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 BCEE 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 BCEE 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 BCEE 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

The use of BCEE or its principal metabolite, TDGA, as biomarkers of exposure has not been investigated.

3.3.2 Biomarkers of Effect

There are no specific biomarkers to characterize the effects caused by BCEE.

3.4 INTERACTIONS WITH OTHER CHEMICALS

No information was located on the interaction of BCEE with other chemicals.