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

3.1 TOXICOKINETICS

No information was located on the toxicokinetics of BCME in humans or animals. It is expected that BCME is rapidly degraded in the aqueous environment of tissues, forming formaldehyde and HCl.

3.1.1 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 located for BCME.

3.1.2 Animal-to-Human Extrapolations

The available suggest that BCME is a respiratory carcinogen in humans and laboratory animals. In the absence of data to the contrary, it is assumed that rodents, particularly rats, are appropriate models for humans.

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

No studies were identified that could be used to evaluate whether children would be more susceptible to the toxicity of BCME than adults; additionally, no developmental toxicity studies were located for humans or animals.

No evidence was located to suggest that any subpopulation is more susceptible to BCME than another. Since no data are available on pharmacokinetics or mechanisms of action, it is not possible to predict populations that might be unusually susceptible to BCME on the basis of genetic traits or health status.

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 BCME 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 BCME 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 BCME 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 the presence of BCME in human tissues and fluids. It is expected that BCME does not persist in tissues due to its rapid hydrolysis. Measurement of the hydrolysis products (formaldehyde and HCl) is unlikely to be a useful index of exposure, since levels of these products are highly variable due to formation from other sources, and the contribution from BCME would be extremely small and almost certainly would not be detectable against background levels.

3.3.2 Biomarkers of Effect

No biomarkers of effect were identified.

3.4 INTERACTIONS WITH OTHER CHEMICALS

No information was located regarding interactive effects of BCME with other chemicals that would be relevant to its toxicity. Chemicals of special interest include chloromethyl methyl ether, formaldehyde, and HCl, since exposure to BCME frequently occurs along with exposure to CME, and formaldehyde and HCl are formed as BCME decomposes.