

5.0 TOXICOLOGY

PRINCIPAL FINDINGS

- Contaminants such as EDB and EDC can enter the human body through dermal absorption, inhalation, and ingestion.
- Various acute and systemic effects have been reported for EDB and EDC, including gastrointestinal, cardiovascular, neurotoxic, nephrotoxic, and hepatotoxic effects.
- EDB has been shown to be a potent mutagen, both *in vivo* and *in vitro*.
- Both EDB and EDC are probable human carcinogens
- The drinking water MCLs for EDB and EDC are 0.05 and 5 µg/L, respectively.

EPA's National Center for Environmental Assessment (NCEA) identified the ATSDR toxicological profiles for EDB and EDC completed in 1992 and 2001, respectively, as the primary sources of information for the health effects of these compounds (5-10). Information from these profiles is summarized below. Information about the carcinogenic effects of EDB and EDC were obtained from EPA's Integrated Risk Information System (IRIS), which provides reference values for inhalation and oral exposure of humans to these compounds (Refs. 5-14 and 5-16).

5.1 EXPOSURE PATHWAYS

Contaminants such as EDB and EDC must enter the body through one or more exposure pathways before causing damage to a 'target' tissue or organ. There are three major pathways of exposure to these contaminants: dermal absorption, inhalation exposure, and oral exposure or ingestion (Refs. 5-1 and 5-3). Biochemical pathways have been proposed for the metabolism of both EDB and EDC (Refs. 5-1 and 5-3) as shown in Figures 5-1 and 5-2.

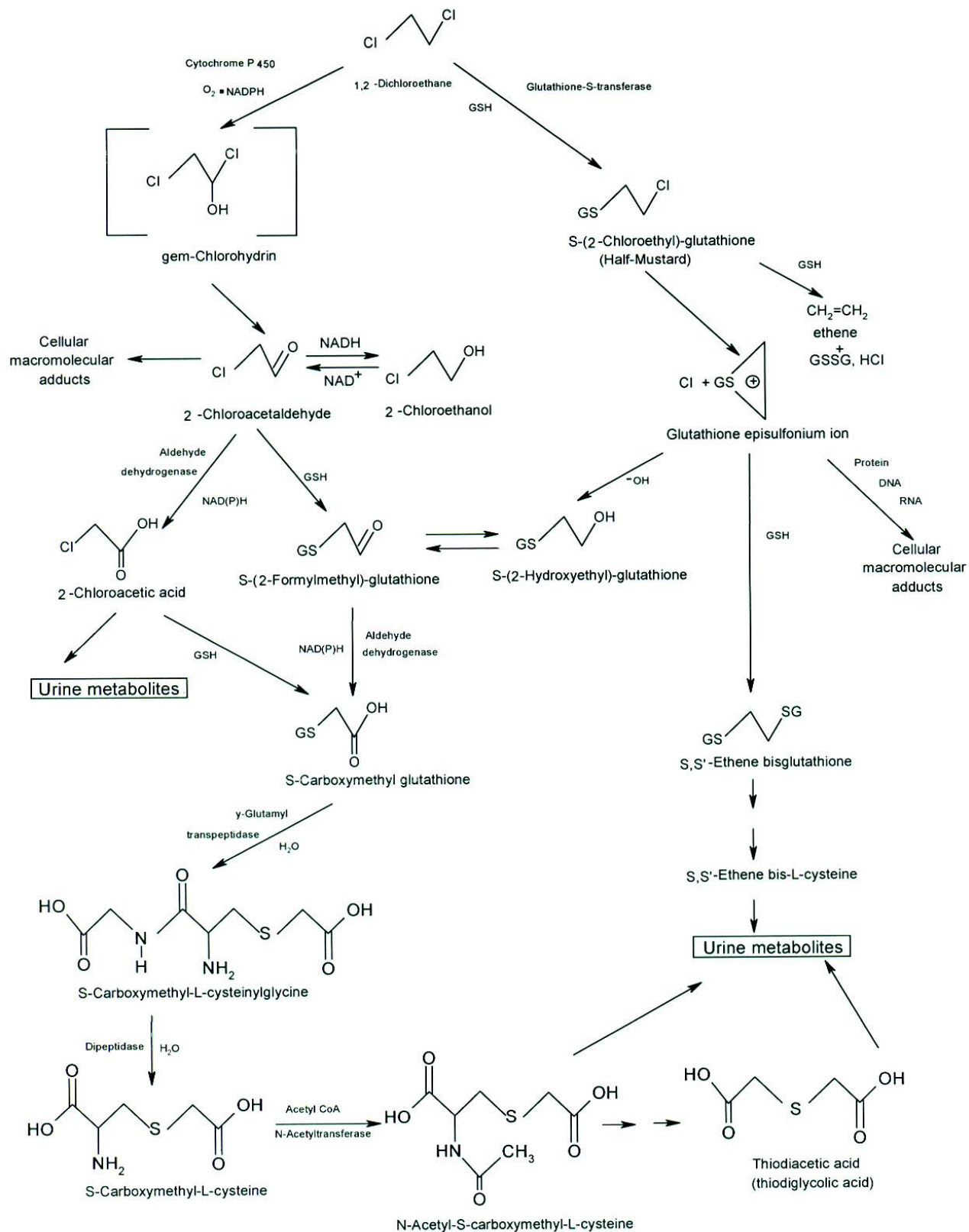


Figure 5-2. Proposed Pathways for Metabolism of EDC (Ref. 5-3)

The three pathways of EDB and EDC exposure are briefly discussed below.

5.1.1 Dermal Absorption

Dermal Absorption of EDB: EDB can be absorbed via the dermal pathway of human exposure. EDB is then distributed to various organs in the body and is metabolized in various tissues into toxic metabolites such as 2-bromoacetaldehyde (Ref. 5-1). EDB metabolism can occur via two pathways:

- ◆ Microsomal oxidation using cytochrome P-450 leads to formation of 2-bromoacetaldehyde, an intermediate that binds to cellular proteins. The 2-bromoacetaldehyde can be further metabolized into 2-bromoethanol, which is highly genotoxic (Ref. 5-1).
- ◆ Conjugation of EDB with glutathione leads to formation of S-(2-bromoethyl) glutathione, a highly reactive alkylating agent that can bind to deoxyribose nucleic acid (DNA), leading to genotoxic and probably carcinogenic effects (Ref. 5-1).

Dermal Absorption of EDC: EDC is absorbed into the skin following dermal exposure of humans. Percutaneous absorption of EDC (with possible concurrent inhalation exposure) has been reported to cause increased levels of EDC in the breast milk of nursing women. EDC was found to be excreted unchanged in exhaled air following dermal exposure. The concentration of EDC in exhaled air was greatest immediately after skin contact and decreased gradually with time (Ref. 5-3).

5.1.2 Inhalation Exposure

Inhalation Exposure to EDB: Inhalation is an important pathway of EDB exposure for humans. The respiratory tract, particularly the nasal cavity, is the point-of-contact target organ affected by inhalation of EDB (Ref. 5-1). Kidney and liver lesions that develop as a result of inhalation exposure to EDB are indicative of the distribution of EDB to these organs. EDB is extensively metabolized in various tissues and organs into 2-bromoacetaldehyde as well as other toxic metabolites. Excretion of the metabolites occurs primarily in the urine (Ref. 5-1).

Inhalation Exposure to EDC: The general population may be exposed to EDC through inhalation of air containing EDC. Air emissions comprise the largest component of releases of EDC into the environment (Ref. 5-3). People living at or near uncontrolled hazardous waste sites or working in a factory where EDC is used may be exposed to higher EDC concentrations (Ref. 5-5). The absorption and distribution of EDC following inhalation are rapid and complete (Ref. 5-7). The high vapor pressure and high serum-air partition coefficient of EDC allow it to be easily absorbed through the lungs following inhalation exposure (Ref. 5-3). EPA also found that inhalation exposure to EDC causes its accumulation in the breast milk of nursing women, mainly because of its high lipid-water partition coefficient. EDC was also detected in the breath of these nursing women shortly after they left the contaminated location, indicating rapid distribution of EDC in the body following inhalation exposure.

5.1.3 Ingestion

EDB and EDC can enter the human bloodstream through the digestive tract. Millions of villi (projections) in the small intestine provide surface area for absorbing toxic substances into the bloodstream. Absorption of toxic substances in the intestines depends on the specific contaminant, its molecular size, and its lipid solubility (Refs. 5-1 and 5-3).

Ingestion of EDB: The general population may be exposed to EDB in drinking water. EDB can be absorbed through the digestive tract in humans and is extensively metabolized into toxic 2-bromoacetaldehyde. Excretion of the metabolite occurs primarily in the urine (Ref. 5-1).

Ingestion of EDC: The general population may be exposed to EDC in drinking water. However, industrial releases of EDC to surface water are relatively minor compared to atmospheric releases (Ref. 5-3). EDC is rapidly absorbed into the systemic circulation following oral exposure. Because of its lipophilicity, EDC is absorbed largely via passive diffusion across the mucosal membrane of the gastrointestinal tract (Ref. 5-3). Available information suggests that oral absorption of an aqueous solution of EDC is rapid and complete (Ref. 5-7); hence, ingestion of water contaminated with EDC is of particular concern. However, limited information is available regarding health effects resulting from long-term exposure to low levels of EDC in drinking water. The different types of effects that occur upon ingestion of EDC suggest that it is widely distributed in the human body (Ref. 5-3).

5.2 SITE OF EFFECT

Once EDB or EDC enters the human body, the effects of the exposure may be either *localized* or *systemic*.

5.2.1 Localized Effects

If the effects are *localized*, the immediate site of entry of EDB or EDC is affected.

Skin exposure to EDB has been shown to result in severe irritation, reddening, blistering, and burning. Direct eye exposure to EDB could cause severe damage (Ref. 5-12). Skin exposure of EDC can cause severe irritation and moderate edema. Direct eye exposure to EDC can cause immediate discomfort with conjunctival hyperemia and slight corneal injury (Ref. 5-3).

5.2.2 Systemic Effects

In *systemic* effects, the effects of EDB or EDC occur at other sites in the body. Either compound may affect an organ or the central nervous system and thus affect body functions. For systemic effects to occur, the rate of accumulation of EDB or EDC must exceed the body's ability to eliminate (or excrete) the compound or transform it into a less harmful substance (Refs. 5-1 and 5-3).

Systemic Effects of EDB: The systemic effects of EDB are primarily due to the metabolic conversion of EDB to the toxic by-product 2-bromoacetaldehyde (Ref. 5-6). Both acute

inhalation and dermal exposures to high concentrations of EDB have been shown to cause mucous membrane irritation, central nervous system depression, metabolic acidosis, liver and kidney damage, and death in humans. Ingestion of a lethal (4.5 milliliters) or sublethal amount of EDB has been shown to cause gastrointestinal effects as well as massive kidney and liver damage, depression, disorientation, and collapse in humans (Ref. 5-1).

Systemic Effects of EDC: Acute and occupational inhalation exposure to EDC vapors has been shown to cause adverse health effects in humans, including nephrotoxic and hepatotoxic effects, respiratory distress, cardiac arrhythmia, nausea, and vomiting (Ref. 5-3). Ingestion of EDC can lead to systemic effects such as respiratory failure, gastrointestinal effects, cardiovascular dysfunction, hematological effects, and acute renal damage (Ref. 5-3). Nervous system disorders have also been reported in humans ingesting or inhaling large quantities of EDC (Ref. 5-5).

5.3 HEALTH EFFECTS

This section provides an overall perspective of the toxicology of EDB and EDC in light of various adverse acute and chronic health effects. Short-, intermediate-, and long-term health effects can result from inhalation or ingestion of, or dermal contact to EDB and EDC. Acute and chronic effects are discussed below.

5.3.1 Acute Effects

Acute effects arise shortly after human contact with EDB and EDC.

Acute Effects of EDB: EPA has found EDB to potentially cause acute health effects after exposure to EDB levels above MCL for relatively short periods of time (Ref. 5-17). Early symptoms of acute exposure to EDB include irritation of the nose and throat (Ref. 5-6). Symptoms of acute toxicity when EDB is ingested include oropharyngeal ulceration; erosion of the mouth, pharynx, and gastric mucosa; vomiting; watery diarrhea; anuresis; depression; and collapse. In some cases, massive hepatic centrilobular necrosis and proximal tubular epithelial damage of the kidneys have been reported in autopsies (Ref. 5-1). Occupational exposure (inhalation or dermal exposure) to EDB is known to have caused death (Ref. 5-1). EDB may be lethal to humans after a single oral dose of 65 milligrams per kilogram (mg/kg) (Ref. 5-22).

Acute Effects of EDC: EPA has found EDC to potentially cause acute health effects after exposure to EDC levels above MCL for relatively short periods of time (Ref. 5-18). Inhalation of EDC has been reported to cause many acute effects. Respiratory effects following acute exposure included severe pulmonary congestion, edema, and chronic bronchitis. Degenerative changes of the myocardium such as fragmentation, loss of nuclei of myocardial fibers, interstitial edema, and death because of cardiac arrhythmia were also reported. Epigastric pain, nausea, and vomiting were some of the gastrointestinal symptoms observed in people exposed to unreported air concentrations of EDC in a packing plant for 2 to 5 months. Nausea, vomiting, and unspecified blood changes were also reported in a study of workers exposed to 10 to 37 parts per million (ppm) of EDC in air (Ref. 5-8). Hematological effects included transient leukocytosis 5 days after a single 4-hour occupational exposure of factory workers to EDC in air. Hepatic effects resulted in liver enlargement, high serum levels of lactate and ammonia, increased serum

levels of glutamic oxaloacetic transaminase (SGOT) and glutamic pyruvic transaminase (SGPT) indicating liver damage, and extensive centrilobular necrosis that eventually contributed to death. EDC is acutely nephrotoxic in humans following inhalation exposure, causing increased kidney weight and tubular degeneration (Ref. 5-3).

Ingestion of EDC has been shown to cause acute health effects such as congestion, pulmonary edema, dyspnea, and bronchitis. Cardiovascular insufficiency and hemorrhage have also contributed to death following acute ingestion of EDC. Gastrointestinal symptoms such as nausea, vomiting, and diarrhea were reported prior to death after oral exposure to 500 to 700 mg/kg-day of EDC. Autopsies of the patients revealed hemorrhagic colitis, hemorrhagic gastritis, and focal hemorrhages of the gastrointestinal tract. Adverse hematological effects such as increased prothrombin time and reduction in blood clotting factors were observed in patients after their ingestion of 570 mg/kg of EDC. EDC has been shown to be a hepatotoxin in humans, causing severe hepatocellular damage, liver atrophy, and necrosis after acute oral exposure. Acute renal damage resulting from EDC ingestion is also reported to have caused bleeding and hyperemia of the kidney (Ref. 5-3).

5.3.2 Chronic Effects

Chronic health effects result from long-term exposure to EDB and EDC (Refs. 5-1 and 5-3).

5.3.2.1 Reference Concentration for Chronic Inhalation Exposure

The reference concentration (RfC) is an estimate of a daily inhalation exposure of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfC takes into account toxic effects on the respiratory system (port of entry) and peripheral effects. The inhalation RfC, which is expressed in milligrams per cubic meter (mg/m^3), is analogous to the oral RfD and is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis (Ref. 5-16). The RfC for EDB has been found to be $9 \text{ E}^{-3} \text{ mg}/\text{m}^3$ (5-20). The RfC for EDC is not available at this time (Ref. 5-10). An updated IRIS file for EDC is scheduled to be released by November 2005 (Ref. 5-10).

5.3.2.2 Reference Dose for Chronic Oral Exposure

The reference dose (RfD) is an estimate of a daily oral exposure of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfD is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis and is expressed in $\text{mg}/\text{kg}\text{-day}$ (Ref. 5-16). The RfD for EDB has been found to be $9 \text{ E}^{-3} \text{ mg}/\text{kg}\text{-day}$ (Ref. 5-20). The RfD for EDC is not available at this time (Ref. 5-10).

5.3.2.3 Carcinogenicity

EDB: ATSDR reported that epidemiological studies are inadequate to determine whether a correlation exists between environmental exposure to EDB and increased risk of cancer in

humans (Ref. 5-1). Carcinogenic effects were observed in workers who were occupationally exposed to EDB, primarily via the respiratory route (Ref. 5-1). EPA has designated EDB as a probable¹ human carcinogen (Ref. 5-20), and the U.S. Department of Health and Human Services (DHHS) has determined that EDB may be reasonably anticipated to be a carcinogen (Ref. 5-4).

EDC: Several agencies have determined that EDC has carcinogenic potential; DHHS has determined that EDC may reasonably be expected to cause cancer; EPA has determined that EDC is a probable human carcinogen while the International Agency for Research on Cancer (IARC²) considers EDC to be a possible³ human carcinogen (Ref. 5-5). In animal studies, increases in the occurrence of cancers of the stomach, mammary gland, liver, lung, and endometrium have been observed (Ref. 5-5). Studies of the carcinogenicity of EDC in human subjects after oral or inhalation exposure were considered inconclusive and could not specifically link EDC exposure to cancer occurrence (Ref. 5-3).

5.3.2.4 Reproductive and Developmental Effects

EDB: There is inconclusive but suggestive evidence that EDB may cause abnormal sperm and decreased male fertility (Ref. 5-1). A study of agricultural workers exposed to EDB used as a fumigant revealed statistically significant decreases in sperm counts and in the percentages of viable and motile sperm as well as significant increases in sperm with morphological abnormalities (Ref. 5-1). Another study concluded that human exposure to EDB concentrations between 0.5 and 5.0 ppm was associated with lower sperm counts (Ref. 5-8).

EDC: It is not known whether inhalation, ingestion, or dermal exposure to EDC can cause birth defects or other developmental effects in humans (Ref. 5-5).

5.3.2.5 Mutagenic Effects

EDB: EDB is a potent mutagen and can cause genetic damage, including point mutations, chromosomal aberration, and primary DNA damage in both *in vivo* and *in vitro* systems. Chromosomal aberrations and sister chromatid exchanges were seen in cultured mammalian cells (Ref. 5-22).

¹ Based on the 1986 EPA classification of carcinogens, “probable” carcinogens (Group B) include those agents for which the weight of evidence of human carcinogenicity based on epidemiological studies is “limited” and those agents for which the weight of evidence of human carcinogenicity based on animal studies is “sufficient” (Ref. 5-19).

² IARC is part of the World Health Organization. IARC coordinates and conducts research on the causes of human cancer and the mechanisms of carcinogenesis and develops scientific strategies for cancer control. IARC also disseminates scientific information through publications, meetings, courses, and fellowships. Its online address is <http://www.iarc.fr>.

³ Based on the 1986 EPA classification of carcinogens, “possible” carcinogens (Group C) include those agents for which there is limited evidence of carcinogenicity in animals in the absence of human data (Ref. 5-19).

EDC: *In vitro* genotoxicity studies have shown that EDC can interact with human DNA and produce point mutations in human cells (Ref. 5-3).

5.4 STANDARDS AND GUIDELINES

A range of agencies is responsible for standards and guidelines to protect the public and workers from exposure. Drinking water standards are part of the Safe Drinking Water Act requirements and are set by EPA to control the level of contaminants in the nation's drinking water. There are two categories of drinking water standards: primary standards (also known as MCLs) and secondary standards. Public water systems (PWS), which provide water for human consumption through at least 15 service connections, or regularly serve at least 25 individuals, are required to comply with drinking water standards (Ref. 5-21). Recommendations for workplace exposure are provided by NIOSH and American Conference of Governmental Industrial Hygienist (ACGIH). The Occupational Safety and Health Administration (OSHA) sets legally enforceable workplace exposure limits. Table 5-1 provides information about selected federal standards and guidelines for EDB and EDC. Table 5-2 provides information about selected state drinking water standards for EDB and EDC.

Table 5-1: Selected Federal Standards and Guidelines for EDB and EDC

Standard/ Guideline	EDB	EDC
MCL	The drinking water MCL is 0.05 µg/L. EPA requires that spills of 1,000 pounds or more be reported (Refs. 5-9 and 5-15).	The drinking water MCL is 5 µg/L (Refs. 5-9 and 5-15).
OSHA	The legal airborne permissible exposure limit (PEL) is 20 ppm averaged over an 8-hour workshift; 30 ppm is an acceptable ceiling; 50 ppm is the maximum peak above the acceptable ceiling and is not to be exceeded during any 5-minute work period (Ref. 5-13).	The OSHA limit is 50 ppm in workplace air for 8-hour shifts and 40-hour work week (Ref. 5-13).
NIOSH	The recommended airborne exposure limits are 0.045 ppm averaged over a 10-hour workshift and 0.13 ppm, which should not be exceeded during any 15-minute work period (Ref. 5-11).	1 ppm (Ref. 5-11)
ACGIH	ACGIH recommends that exposure by all routes be controlled to keep levels as low as possible (Ref. 5-2).	Not provided

Table 5-2: Selected State Drinking Water Standards for EDB and EDC

Standard/ Guideline	EDB	EDC
California ¹	0.05 µg/L	0.5 µg/L
Kansas ²	0.05 µg/L	5 µg/L
New Jersey ³	0.05 µg/L	2 µg/L
South Carolina ⁴	0.05 µg/L	5 µg/L

Notes:

1. Title 22 – *California Code of Regulations*. June 2004. Pages 91 and 126.
<http://www.dhs.ca.gov/ps/ddwem/publications/lawbook/dwregulations-06-01-04.pdf>
2. Kansas Department of Health and Environment, Bureau of Water, Public Water Supply Section. Website Accessed on October 5, 2004. <http://www.kdhe.state.ks.us/pws/dmdu.html>
3. New Jersey Department of Environmental Protection, Water Supply Administration. Website Accessed on October 6, 2004. <http://www.state.nj.us/dep/watersupply/standard.htm>
4. South Carolina Department of Health and Environmental Control, Bureau of Water. State Primary Drinking Water Regulations. September 2003.
<http://www.scdhec.net/water/regs/r.61-58/61-58.5.pdf>

5.5 REFERENCES

- 5-1 Agency for Toxic Substances and Disease Registry (ATSDR). 1992. Toxicological Profile for 1,2-Dibromoethane. U.S. Department of Health and Human Services, Public Health Service.
- 5-2 American Conference of Governmental Industrial Hygienists (ACGIH). 2004. TLVs[®] and BEIs[®] Based on Documentation of the Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices.
- 5-3 ATSDR. 2001. Toxicological Profile for 1,2-Dichloroethane. U.S. Department of Health and Human Services, Public Health Service.
- 5-4 ATSDR. 2004. ToxFAQs[™]: 1,2-Dibromoethane. Website Accessed on March 26, 2004. <http://www.atsdr.cdc.gov/tfacts37.html>
- 5-5 ATSDR. 2004. ToxFAQs[™]: 1,2-Dichloroethane. Website Accessed on August 17, 2004. <http://www.atsdr.cdc.gov/tfacts38.html>
- 5-6 ATSDR. 2004. Medical Management Guidelines for Ethylene Dibromide. Accessed on March 26, 2004. <http://www.atsdr.cdc.gov/MHMI/mmg37.html>
- 5-7 California, State of. 2000. Determination of Noncancer Chronic Reference Exposure Levels, Batch 2A. Chronic Toxicity Summary - Ethylene Dichloride. Office of Environmental Health Hazards Assessment. <http://www.oehha.ca.gov>

- 5-8 California, State of. 2001. Determination of Noncancer Chronic Reference Exposure Levels, Batch 2B. Chronic Toxicity Summary - Ethylene Dibromide. Office of Environmental Health Hazards Assessment. <http://www.oehha.ca.gov>
- 5-9 *Code of Federal Regulations* (CFR). Title 40. Section 141.61. "National Primary Drinking Water Regulations".
- 5-10 EPA. 1993. Integrated Risk Information System (IRIS) File on 1,2-Dichloroethane. National Center for Environmental Assessment, Office of Research and Development, Washington, DC. Website Accessed on September 29, 2005. <http://www.epa.gov/iris/subst/0149.htm>
- 5-11 National Institute for Occupational Safety and Health (NIOSH). 1997. *Pocket Guide to Chemical Hazards*. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention. Cincinnati, Ohio.
- 5-12 New Jersey Department of Health and Senior Services. 2001. Hazardous Substance Factsheet on Ethylene Dibromide.
- 5-13 Occupational Safety and Health Administration (OSHA). 1998. CFR. Title 29. Section 1910.1000. "Occupational Safety and Health Standards, Toxic and Hazardous Substances".
- 5-14 U.S. Environmental Protection Agency (EPA). 1991. Integrated Risk Information System (IRIS) File on 1,2-Dichloroethane. National Center for Environmental Assessment, Office of Research and Development. Washington, DC. Website Accessed on September 23, 2004. <http://www.epa.gov/iris/subst/0361.htm>
- 5-15 EPA. 2003. National Primary Drinking Water Standards. EPA 816-F-03-016.
- 5-16 EPA. 2004. Integrated Risk Information System (IRIS) File on 1,2-Dibromoethane. National Center for Environmental Assessment, Office of Research and Development, Washington, DC. Website Accessed on September 23, 2004. <http://www.epa.gov/iris/subst/0361.htm>
- 5-17 EPA. 2004. Consumer Factsheet on Ethylene Dibromide. Website Accessed on October 5, 2004. http://www.epa.gov/safewater/contaminants/dw_contamfs/ethylene.html
- 5-18 EPA. 2004. Consumer Factsheet on Ethylene Dichloride. Website Accessed on October 5, 2004. http://www.epa.gov/safewater/contaminants/dw_contamfs/12-dichl.html
- 5-19 EPA. 2004. Evaluating Pesticides for Carcinogenic Potential. Website Accessed on October 5, 2004. <http://www.epa.gov/pesticides/health/cancerfs.htm>

- 5-20 EPA. 2004. Toxicological Review of 1,2-Dibromoethane: In Support of Summary Information on the Integrated Risk Information System (IRIS). EPA 635/R-04/067.
- 5-21 EPA. 2005. Setting Standards for Safe Drinking Water. Website Accessed on July 18, 2005. <http://www.epa.gov/safewater/standard/setting.html>
- 5-22 Virginia Department of Health. 1996. Factsheet on Ethylene Dibromide. Bureau of Toxic Substances.