# TOXICOLOGICAL PROFILE FOR ETHYLENE OXIDE

Agency for Toxic Substances and Disease Registry
U.S. Public Health Service

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# DISCLAIMER

The use of company or product name(s) is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry.

# FOREWORD

The Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) extended and amended the Comprehensive EnvironmentalResponse, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed the Agency for Toxic Substances and DiseaseRegistry (ATSDR) to prepare toxicological profiles for hazardous substances which are most commonly found at facilities on the CERCLA National Priorities List and which pose the most significant potential threat to human health, as determined by ATSDR and the Environmental Protection Agency (EPA). The lists of the 250 most significant hazardous substances were published in the Federal Register on April 17, 1987, on October 20, 1988, on October 26, 1989, and on October 17, 1990.

Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. Each profile must include the following content:

(A) An examination, summary, and interpretation of available toxicological information and epidemiological evaluations on the hazardous substance in order to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects,

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure which present a significant risk to human health of acute, subacute, and chronic health effects, and

(C) Where appropriate, an identification of toxicological testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

This toxicological profile is prepared in accordance with guidelines developed by ATSDR and EPA. The original guidelines were published in the Federal Register on April 17, 1987. Each profile will be revised and republished as necessary, but no less often than every three years, as required by CERCLA, as amended.

The ATSDR toxicological profile is intended to characterize succinctly the toxicological and adverse health effects information for the hazardous substance being described. Each profile identifies and reviews the key literature (that has been peer-reviewed) that describes a hazardous substance's toxicological properties. Other pertinent literature is also presented but described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

*Foreword*

Each toxicological profile begins with a public health statement, which describes in nontechnical language a substance's relevant toxicological properties. Following the public health statement is information concerning significant health effects associated with exposure to the substance. The adequacy of information to determine a substance's health effects is described. Data needs that are of significance to protection of public health will be identified by ATSDR, the National Toxicology Program (NTP) of the Public Health Service, and EPA. The focus of the profiles is on health and toxicological information; therefore, we have included this information in the beginning of the document.

The principal audiences for the toxicological profiles are health professionals at the federal, state, and local levels, interested private sector organizations and groups, and members of the public.

This profile reflects our assessment of all relevant toxicological testing and information that has been peer reviewed. It has been reviewed by scientists from ATSDR, the Centers for Disease Control, the NTP, and other federal agencies. It has also been reviewed by a panel of nongovernment peer reviewers and is being made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

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Administrator
Agency for Toxic Substances and
Disease Registry

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# 1. PUBLIC HEALTH STATEMENT

This Statement was prepared to give you information about ethylene oxide and to emphasize the human health effects that may result from exposure to it. The Environmental Protection Agency (EPA) has identified 1,177 sites on its National Priorities List (NPL). Ethylene oxide has not been definitely identified at any NPL site. However, it has been tentatively identified at three of these sites. As EPA evaluates more sites, the number of sites at which ethylene oxide is found may change. This information is important for you to know because ethylene oxide may cause harmful health effects and because these sites are potential or actual sources of human exposure to ethylene oxide.

When a chemical is released from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment as a chemical emission. This emission, which is also called a release, does not always lead to exposure. You can be exposed to a chemical only when you come into contact with the chemical. You may be exposed to it in the environment by breathing, eating, or drinking substances containing the chemical or from skin contact with it.

If you are exposed to a hazardous substance such as ethylene oxide, several factors will determine whether harmful health effects will occur and what the type and severity of those health effects will be. These factors include the dose (how much), the duration (how long), the route or pathway by which you are exposed (breathing, eating, drinking, or skin contact), the other chemicals to which you are exposed, and your individual characteristics such as age, sex, nutritional status, family traits, life style, and state of health.

## 1.1 WHAT IS ETHYLENE OXIDE?

Ethylene oxide (also known as ET0 or oxirane) is a flammable gas with a somewhat sweet odor. It dissolves easily in water, alcohol, and most organic solvents.

Ethylene oxide is produced in large volumes and is used to make other chemicals, especially ethylene glycol, a chemical used to make antifreeze and polyester. Most ethylene oxide is used up in the factories where it is produced. A very small amount (less than 1%) is used to control insects on stored agricultural products such as nuts and spices. Ethylene oxide is also used in very small amounts in hospitals to sterilize medical equipment and supplies.

When ethylene oxide is produced or used, some of the gas is released to air and water. If it is released into the air, humidity and sunlight

cause it to break down within a few days. In water, ethylene oxide will either break down or be destroyed by bacteria within a few days.

Further information on the properties and uses of ethylene oxide can be found in Chapters 3, 4 and 5.

**1.2 HOW MIGHT I BE EXPOSED TO ETHYLENE OXIDE?**

You are not likely to be exposed to ethylene in the general environment. In studies of the air quality in Texas and California, no ethylene oxide was found. There is also no evidence that ethylene oxide is commonly found in water. Because of the limited information about ethylene oxide in air, water, or soil at hazardous waste sites, we do not know how likely it is that you might be exposed to ethylene oxide at or near these sites.

You may be exposed to ethylene oxide if you work where it is produced or used. Health care workers, such as technicians, nurses, and physicians in hospitals and clinics, may have contact with ethylene oxide because it is used to sterilize medical equipment and supplies. Since ethylene oxide is used as a fumigant to spray agricultural products, if you are a farmer or work on a farm where ethylene oxide is used, you may also be exposed to this substance.

It is not known if food crops are a source of exposure to ethylene oxide for the general public. Ethylene oxide has been found at levels up to 3.5 parts of ethylene oxide per one million parts of food (3.5 ppm) in some foods shortly after being sprayed with pesticide that contains it. These levels decrease with time as ethylene oxide evaporates or breaks down into other substances, and thus little or none may remain when the food is eaten.

Further information on the ways that you can be exposed to ethylene oxide is presented in Chapter 5.

**1.3 HOW CAN ETHYLENE OXIDE ENTER AND LEAVE MY BODY?**

Ethylene oxide can enter your body when air containing this substance is breathed into your lungs. Because ethylene oxide evaporates very easily, it is unlikely that it remains in or on food or remains dissolved in water long enough to be eaten or swallowed, although this is not known for certain. It is not known if ethylene oxide can enter the body through the skin.

After a person has been exposed to ethylene oxide, it leaves the body through the urine or feces or by breathing it out through the lungs. This probably occurs very rapidly, perhaps within 2 or 3 days.

## 1.4 HOW CAN ETHYLENE OXIDE AFFECT MY HEALTH?

Ethylene oxide can cause a wide variety of harmful health effects in exposed persons. In general, with higher levels of exposure to this chemical, more severe effects will occur. The major effects seen in workers exposed to ethylene oxide at low levels for several months or years are irritation of the eyes, skin, and mucous membranes and problems in the functioning of the brain and nerves. At higher levels of exposure to ethylene oxide, which may result from accidents or equipment breakdown, the types of effects are similar, but they are more severe and harmful. There is also some evidence that exposure to ethylene oxide can cause an increased rate of miscarriages in female workers exposed to ethylene oxide.

Studies in animals have shown that breathing ethylene oxide at high levels can interfere with their ability to reproduce. Litter sizes have been smaller than usual, and the babies of exposed animals have weighed less than normal and have had delayed bone formation.

Some studies of workers exposed to ethylene oxide in ethylene oxide factories or hospital sterilizing rooms have shown an increased incidence of leukemia, stomach cancer, cancer of the pancreas and Hodgkin's disease. Ethylene oxide has also been shown to cause cancer in laboratory animals. Leukemia, brain tumors, lung tumors and tumors of the tear glands of the eye have been found.

Further information on the health effects of ethylene oxide is presented in Chapter 2.

## 1.5 WHAT LEVELS OF EXPOSURE HAVE RESULTED IN HARMFUL HEALTH EFFECTS?

Tables 1-1 through 1-4 show the relationship between exposure to ethylene oxide and known health effects. Skin contact with ethylene oxide can result in blisters and burns that may appear to be similar to frostbite. With longer times of contact, there is a more severe reaction. Eye damage can also result from ethylene oxide contact.

It is possible to smell ethylene oxide if it is present in water at or above 140 mg per liter (about one quart) of water. It can also be smelled in air if it is present at or above 430 ppm (430 parts of ethylene oxide per million parts of air).

A Minimal Risk Level (MRL) is also included in Table l-l. This MRL was derived from animal data for long-term exposure, as described in Chapter 2 and in Table 2-l. The MRL provides a basis for comparison with levels that people might encounter in the air. If a person is exposed to ethylene oxide at an amount below the MRL, it is not expected that harmful (noncancer) health effects will occur. Because this level

**TABLE 1-1. Human Health Effects from Breathing Ethylene Oxide***

| Short-term Exposure (less than or equal to 14 days) | | |
|---|---|---|
| Levels in Air | Length of Exposure | Description of Effects |
| | | The health effects resulting from short-term exposure of humans to air containing specific levels of ethylene oxide are not known. |
| **Long-term Exposure (greater than 14 days)** | | |
| Levels in Air (ppm) | Length of Exposure | Description of Effects** |
| 0.09 | 14 weeks | Minimum risk level (MRL) for intermediate exposure to ethylene oxide. Based on a study in mice. |
| 3-430 | 5-20 years | Problems with hand/eye coordination. |
| 10-400 | 2 years | Eye and nose irritation. |
| 700 | 2 months | Seizures, cataracts. |

*See Section 1.2 for a discussion of exposures encountered in daily life.
**These effects are listed at the lowest level at which they were first observed. They may also be seen at higher levels.

**TABLE 1-2. Animal Health Effects from Breathing Ethylene Oxide**

| Short-term Exposure (less than or equal to 14 days) | | |
|---|---|---|
| Levels in Air (ppm) | Length of Exposure | Description of Effects* |
| 100 | 10 days of pregnancy | Decreased litter size and smaller newborn rats. |
| 800 | 4 days | Death in mice. |
| **Long-term Exposure (greater than 14 days)** | | |
| Levels in Air (ppm) | Length of Exposure | Description of Effects* |
| 50 | 10-11 weeks | Decreased physical activity in mice. |
| 100 | 14 weeks | Kidney damage in mice. |
| 200 | 14 weeks | Nasal inflammation in mice. |
| 400 | 14 weeks | Death in mice. |

*These effects are listed at the lowest level at which they were first observed. They may also be seen at higher levels.

**TABLE 1-3. Human Health Effects from Eating or Drinking Ethylene Oxide***

| Short-term Exposure (less than or equal to 14 days) | | |
|---|---|---|
| Levels in Food | Length of Exposure | Description of Effects |
| | | The health effects resulting from short-term exposure of humans to food containing specific levels of ethylene oxide are not known. |
| Levels in Water | | The health effects resulting from short-term exposure of humans to water containing specific levels of ethylene oxide are not known. |
| **Long-term Exposure (greater than 14 days)** | | |
| Levels in Food | Length of Exposure | Description of Effects |
| | | The health effects resulting from long-term exposure of humans to food containing specific levels of ethylene oxide are not known. |
| Levels in Water | | The health effects resulting from long-term exposure of humans to water containing specific levels of ethylene oxide are not known. |

*See Section 1.2 for a discussion of exposures encountered in daily life.

**TABLE 1-4. Animal Health Effects from Eating or Drinking Ethylene Oxide**

| Short-term Exposure (less than or equal to 14 days) | | |
|---|---|---|
| Levels in Food (ppm) | Length of Exposure | Description of Effects* |
| 4,000 | 1 day | Death in rats. |
| Levels in Water | | The health effects resulting from short-term exposure of animals to water containing specific levels of ethylene oxide are not known. |
| **Long-term Exposure (greater than 14 days)** | | |
| Levels in Food | Length of Exposure | Description of Effects |
| 2,000 | 21-30 days | Liver damage and stomach irritation in rats. |
| Levels in Water | | The health effects resulting from long-term exposure of animals to water containing specific levels of ethylene oxide are not known. |

*These effects are listed at the lowest level at which they were first observed. They may also be seen at higher levels.

is based only on information currently available, some uncertainty is always associated with it. Also, because the method for deriving MRLs does not use any information about cancer, an MRL does not imply anything about the presence, absence, or level of risk for cancer.

Further information on exposure levels of ethylene oxide that cause health effects in humans and animals is presented in Chapter 2.

## 1.6 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO ETHYLENE OXIDE?

There are two kinds of tests that can determine if you have been exposed to ethylene oxide within the last couple of days. These tests are not routinely done in a doctor's office, but can be done in a special laboratory. One test measures this substance in blood, the other measures it in air that you breathe out of your lungs. If you were exposed to ethylene oxide more than two or three days ago, there may be no ethylene oxide remaining in your body. In addition, if you have been exposed to very low levels of ethylene oxide, these tests may not detect it. The results of these tests cannot be used to predict the type or severity of health effects resulting from exposure.

Further information on this topic is presented in Chapter 2 and 6.

## 1.7 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

In order to protect the general population from exposure to ethylene oxide, the federal government has established a number of guidelines and regulations related to its use and disposal.

The EPA is considering listing ethylene oxide as a hazardous air pollutant and regulating industrial emissions. The Food and Drug Administration (FDA) has set limits on the levels of ethylene oxide that may remain on food products fumigated with this chemical. In order to protect workers who use ethylene oxide while on the job, the Occupational Safety and Health Administration (OSHA) has established a limit of 1 ppm in workplace air for an 8-hour work day and a limit of 5 ppm for a 15-minute period.

More detailed information on federal and state regulations regarding ethylene oxide is given in Chapter 7.

## 1.8 **WHERE CAN I GET MORE INFORMATION?**

If you have any more questions or concerns not covered here, please contact your State Health or Environmental Department or:

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road, E-29
Atlanta, Georgia 30333

This agency can also give you information on the location of the nearest occupational and environmental health clinics. Such clinics specialize in recognizing, evaluating, and treating illnesses that result from exposure to hazardous substances.

# 2. HEALTH EFFECTS

## 2.1 INTRODUCTION

This chapter contains descriptions and evaluations of studies and interpretation of data on the health effects associated with exposure to ethylene oxide. Its purpose is to present levels of significant exposure for ethylene oxide based on toxicological studies, epidemiological investigations and environmental exposure data. This information is presented to provide public health officials, physicians, toxicologists and other interested individuals and groups with (1) an overall perspective of the toxicology of ethylene oxide and (2) a depiction of significant exposure levels associated with various adverse health effects.

## 2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals address the needs of persons living or working near hazardous waste sites, the data in this section are organized first by route of exposure -- inhalation, oral and dermal -- and then by health effect -- death, systemic, immunological, neurological, developmental, reproductive, genotoxic and carcinogenic effects. These data are discussed in terms of three exposure periods -- acute, intermediate and chronic.

Levels of significant exposure for each exposure route and duration (for which data exist) are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. These distinctions are intended to help the users of the document identify the levels of exposure at which adverse health effects start to appear, determine whether or not the intensity of the effects varies with dose and/or duration and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown on the tables and figures may differ depending on the user's perspective. For example, physicians concerned with the interpretation of clinical findings in exposed persons or with the identification of persons with the potential to develop such disease may be interested in levels of exposure associated with "serious" effects. Public health officials and project managers concerned with response actions at Superfund sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAELs) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels, MRLs) are of interest to health professionals and citizens alike.

# 2. HEALTH EFFECTS

For certain chemicals, levels of exposure associated with carcinogenic effects may be indicated in the figures. These levels reflect the actual doses associated with the tumor incidences reported in the studies cited. Because cancer effects could occur at lower exposure levels, the figures also show estimated excess risks, ranging from a risk of one in 10,000 to one in 10,000,000 ($10^{-4}$ to $l0^{-7}$), as developed by EPA.

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made, where data were believed reliable, for the most sensitive noncancer end point for each exposure duration. MRLs include adjustments to reflect human variability and, where appropriate, the uncertainty of extrapolating from laboratory animal data to humans. Although methods have been established to derive these levels (Barnes et al. 1987; EPA 1989), uncertainties are associated with the techniques.

### 2.2.1 Inhalation Exposure

Most information on the health effects of ethylene oxide is derived from animal inhalation studies or epidemiological or case studies of persons in occupational settings. The most relevant route of exposure to a volatile compound such as ethylene oxide in an occupational setting is via inhalation. It is important to note, however, that there may be dermal exposure, either directly or through the air, and any food on the premises may similarly be contaminated, resulting in possible oral exposure.

#### 2.2.1.1 Death

The available studies on humans exposed to ethylene oxide in the workplace indicate that there is no increase in mortality associated with those exposures (Gardner et al. 1989; Greenberg et al. 1990; Kiesselbach et al. 1990).

Estimates of lethal ethylene oxide inhalation levels in animals depend on the exposure duration. In mice, exposures to 800 ppm for four hours resulted in 80-100% mortality, whereas 400 ppm exposures for 14 days did not result in death (NTP 1987). Jacobson et al. (1956) reported that the 4-hour $LC_{50}$ values for rats, mice and dogs were 1,460, 835 and 960 ppm, respectively.

In two-year studies using mice (NTP 1987*)* and monkeys (Lynch et al. 1984a), exposure to 100 ppm did not result in increased mortality in the test animals.

The highest NOAEL values and all reliable LOAEL values for death in each species are presented in Table 2-l and plotted in Figure 2-1.

**2.2.1.2 Systemic Effects**

**Respiratory Effects**. Inhalation of ethylene oxide is irritating to mucous membranes including those associated with the respiratory system. Inhalation exposure of workers to high concentrations of ethylene oxide for brief periods has resulted in bronchitis, pulmonary edema, and emphysema (Theiss 1963). Studies on long-term human exposure to ethylene oxide do not address the incidence of respiratory problems.

Respiratory irritation has been reported in animal studies at various exposure levels. In lethality studies, mice exposed to 200 ppm and above for 14 weeks exhibited nasal irritation, necrosis of epithelium, and loss of cilia (NTP 1987). These lesions were not seen in mice exposed to 100 ppm for two years (NTP 1987).

The highest NOAEL values and all reliable LOAEL values for respiratory effects in each species and duration category are presented in Table 2-l and plotted in Figure 2-l.

**Cardiovascular Effects**. Studies of humans and animals exposed to ethylene oxide via inhalation have not reported evidence of injury to the cardiovascular system. In a study of male monkeys exposed to ethylene oxide at levels up to 100 ppm for two years, no treatment related changes were observed in routine electrocardiograms taken throughout the study (Lynch et al. 1984a).

**Gastrointestinal Effects**. Studies of humans and animals exposed to ethylene oxide via inhalation have not addressed the potential gastrointestinal effects of these exposures. Nausea and vomiting have been reported, but these are considered to be secondary effects due to neurotoxicity rather than a primary effect of inhaled ethylene oxide on the gastrointestinal tract. (See Section 2.2.1.4)

**Hematological Effects**. Most studies of human exposure to ethylene oxide via inhalation have not examined the potential adverse hematological effects of this compound. Joyner (1964) reported no effects on hemoglobin levels or red or white blood cell counts in workers exposed to ethylene oxide at about 5-10 ppm for approximately 10 years. Data reported in case studies of individuals exposed to ethylene oxide in occupational settings do not provide quantifiable information due to the small numbers of subjects and lack of information on the level of ethylene oxide exposure.

A 10-week exposure of mice to ethylene oxide at 250 ppm resulted in slight but statistically significant decreases in red blood cell numbers and blood hemoglobin concentrations. These effects were not seen at 100 ppm or below (Snellings et al. 1984a). Two-year studies of rats,

**TABLE 2-1. Levels of Significant Exposure to Ethylene Oxide - Inhalation**

| Figure Key[a] | Species | Exposure Frequency/ Duration | Effect | NOAEL (ppm) | LOAEL (Effect) Less Serious (ppm) | LOAEL (Effect) Serious (ppm) | Reference |
|---|---|---|---|---|---|---|---|
| ACUTE EXPOSURE | | | | | | | |
| Death | | | | | | | |
| 1 | Mouse | 4 hr | | 400 | | 800[b] (80-100% death) | NTP 1987 |
| Developmental | | | | | | | |
| 2 | Rat | 12 wk Gd0-19 6hr/d | | 33 | | 100[b] (decreased fetal weight) | Snellings et al. 1982a |
| Reproductive | | | | | | | |
| 3 | Rat | 12 wk + Gd0-19 6hr/d | | 33 | | 100[b] (decreased fetal implants) | Snellings et al. 1982b |
| INTERMEDIATE EXPOSURE | | | | | | | |
| Death | | | | | | | |
| 4 | Mouse | 14 wk 5d/wk 6hr/d | | 200 | | 400 (100% mortality) | NTP 1987 |
| Systemic | | | | | | | |
| 5 | Mouse | 10-11 wk 5d/wk 6hr/d | Hepatic Hemato | 250 100 | 250 (decreased RBCs, Hb) | | Snellings et al. 1984a |
| 6 | Mouse | 14 wk 5d/wk 6hr/d | Resp | 100 | 200[b] (nasal inflammation) | 400 (necrosis) | NTP 1987 |
| 7 | Mouse | 14 wk 5d/wk 6hr/d | Renal | 50[c] | 100[b] (tubular degeneration) | 600 (tubular necrosis) | NTP 1987 |

**TABLE 2-1 (Continued)**

| Figure Key[a] | Species | Exposure Frequency/ Duration | Effect | NOAEL (ppm) | LOAEL (Effect) Less Serious (ppm) | LOAEL (Effect) Serious (ppm) | Reference |
|---|---|---|---|---|---|---|---|
| Immunological | | | | | | | |
| 8 | Mouse | 14 wk 5d/wk 6hr/d | | 100 | 200 (hypoplasia) | 600 (thymic lymph. necrosis) | NTP 1987 |
| Neurological | | | | | | | |
| 9 | Mouse | 10-11 wk 5d/wk 6hr/d | | 10 | 50[b] (decreased locomotor activity) | | Snellings et al. 1984a |
| Developmental | | | | | | | |
| 10 | Rabbit | 13-19 d 7hr/d | | 150 | | | Hardin et al. 1983 |
| Reproductive | | | | | | | |
| 11 | Rat | 16-37 d 7hr/d | | | | 150 (increased resorption) | Hardin et al. 1983 |
| CHRONIC EXPOSURE | | | | | | | |
| Death | | | | | | | |
| 12 | Human | 5+ yr 5d/wk 8hr/d | | | | | Morgan et al. 1981 |
| 13 | Mouse | 2 yr 5d/wk 6hr/d | | 100 | | | NTP 1987 |
| 14 | Monkey | 24 mo 5d/wk 7hr/d | | 100 | | | Lynch et al. 1984a |

**TABLE 2-1 (Continued)**

| Figure Key[a] | Species | Exposure Frequency/ Duration | Effect | NOAEL (ppm) | LOAEL (Effect) Less Serious (ppm) | LOAEL (Effect) Serious (ppm) | Reference |
|---|---|---|---|---|---|---|---|
| Systemic | | | | | | | |
| 15 | Human | 11 yr 5d/wk 8hr/d | Renal | 10 | | | Joyner 1964 |
| 16 | Human | 2 yr | Resp | | 10[d] (nasal irritation) | | Zampollo et al. 1984 |
| 17 | Human | 2 yr | Hemato | 10 | | | Zampollo et al. 1984 |
| 18 | Human | 11 yr 5d/wk 8hr/d | Hepatic | 10 | | | Joyner 1964 |
| 19 | Mouse | 2 yr 5d/wk 6hr/d | Renal | 100 | | | NTP 1987 |
| 20 | Monkey | 24 mo 5d/wk 7hr/d | Cardio | 100 | | | Lynch et al. 1984a |
| 21 | Monkey | 24 mo 5d/wk 7hr/d | Hemato | 100 | | | Lynch et al. 1984a |
| Neurological | | | | | | | |
| 22 | Human | 5-20 yr 5d/wk 8hr/d | | | 3[d] (hand/eye coordination) | | Estrin et al. 1987 |
| 23 | Human | 2 yr | | | 10 (peripheral neuropathy) | | Zampollo et al. 1984 |
| 24 | Monkey | 24 mo 5d/wk 7hr/d | | 50 | 100 (slight demyelination) | | Lynch et al. 1984a |

**TABLE 2-1 (Continued)**

| Figure Key[a] | Species | Exposure Frequency/ Duration | Effect | NOAEL (ppm) | LOAEL (Effect) Less Serious (ppm) | LOAEL (Effect) Serious (ppm) | Reference |
|---|---|---|---|---|---|---|---|
| Reproductive | | | | | | | |
| 25 | Monkey | 24 mo 5d/wk 7hr/d | | | | 50 (decreased sperm counts and motility) | Lynch et al. 1984a |
| Cancer | | | | | | | |
| 26 | Rat | 2 yr 5d/wk 7hr/d | | | | 50 CEL (peritoneal mesothelioma, MNCL)<br>100 CEL (brain) | Lynch et al. 1984b |
| 27 | Rat | 24 mo 5d/wk 6hr/d | | | | 33 CEL (brain, MNCL, mesothelioma) | Snellings et al. 1984b |
| 28 | Mouse | 2 yr 5d/wk 6hr/d | | | | 50 CEL (hard. gland, lung)<br>50 CEL (F:mammary)<br>100 CEL (F:lymphoma, uterine gland) | NTP 1987 |

[a]The number corresponds to entries in Figure 2-1.
[b]Presented in Table 1-2.
[c]Used to derive the intermediate inhalation MRL; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans, and 10 for human variability), resulting in an MRL of 0.09 ppm. This MRL has been presented in Table 1-1.
[d]Presented in Table 1-1.

LOAEL = lowest-observed-adverse effect level; NOAEL = no-observed-adverse effect level; hr = hour; Gd = gestational day; d = day; wk = week; mo = month; RBC = red blood cells; Hb = hemoglobin; Hemato = hemotological; lymph = lymphocyte; Resp = respiratory; yr = year; Cardio = cardivascular; CEL = cancer effect level; F = females; MNCL = mononuclear cell leukemia

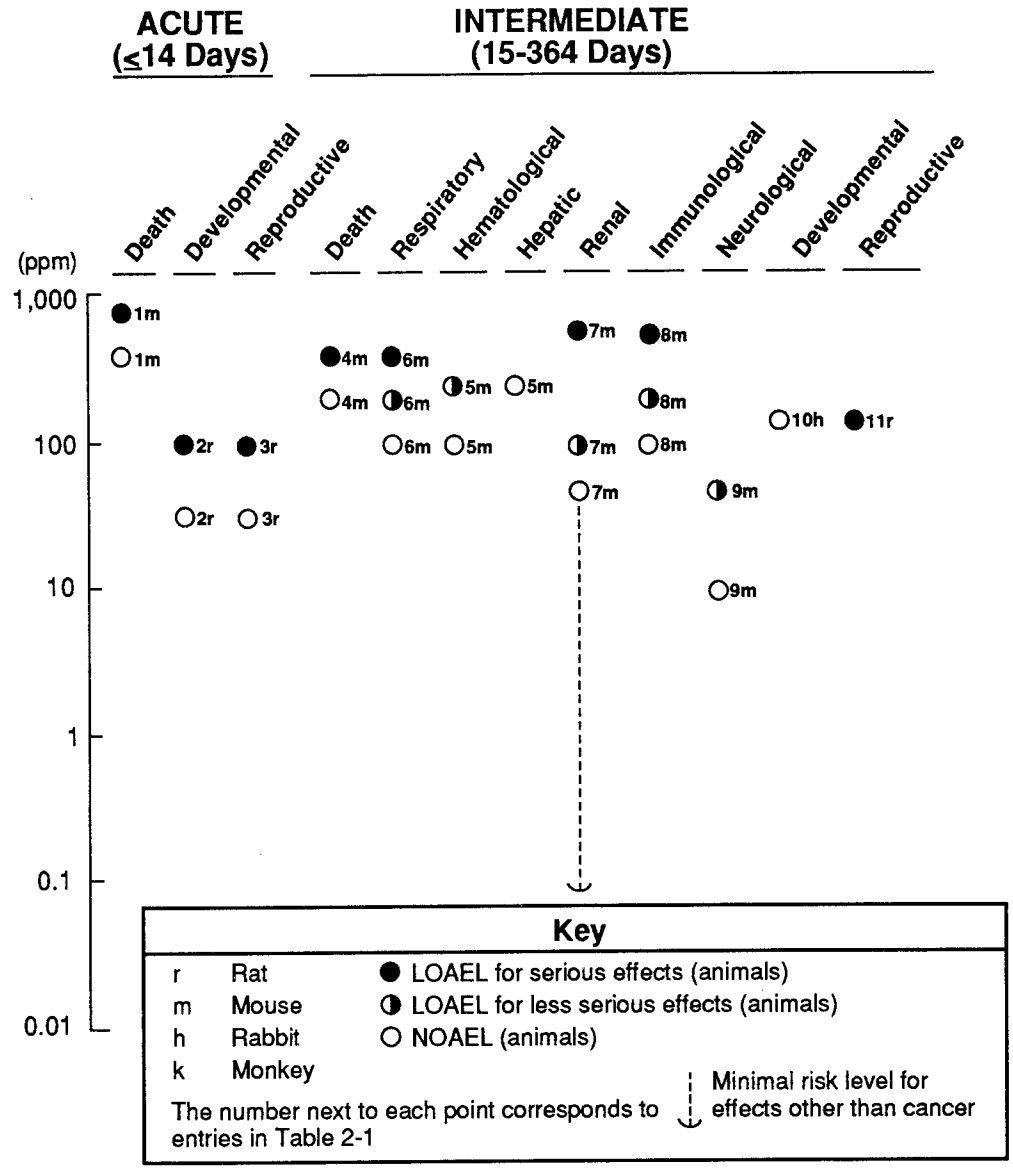



**FIGURE 2-1. Levels of Significant Exposure to Ethylene Oxide – Inhalation**

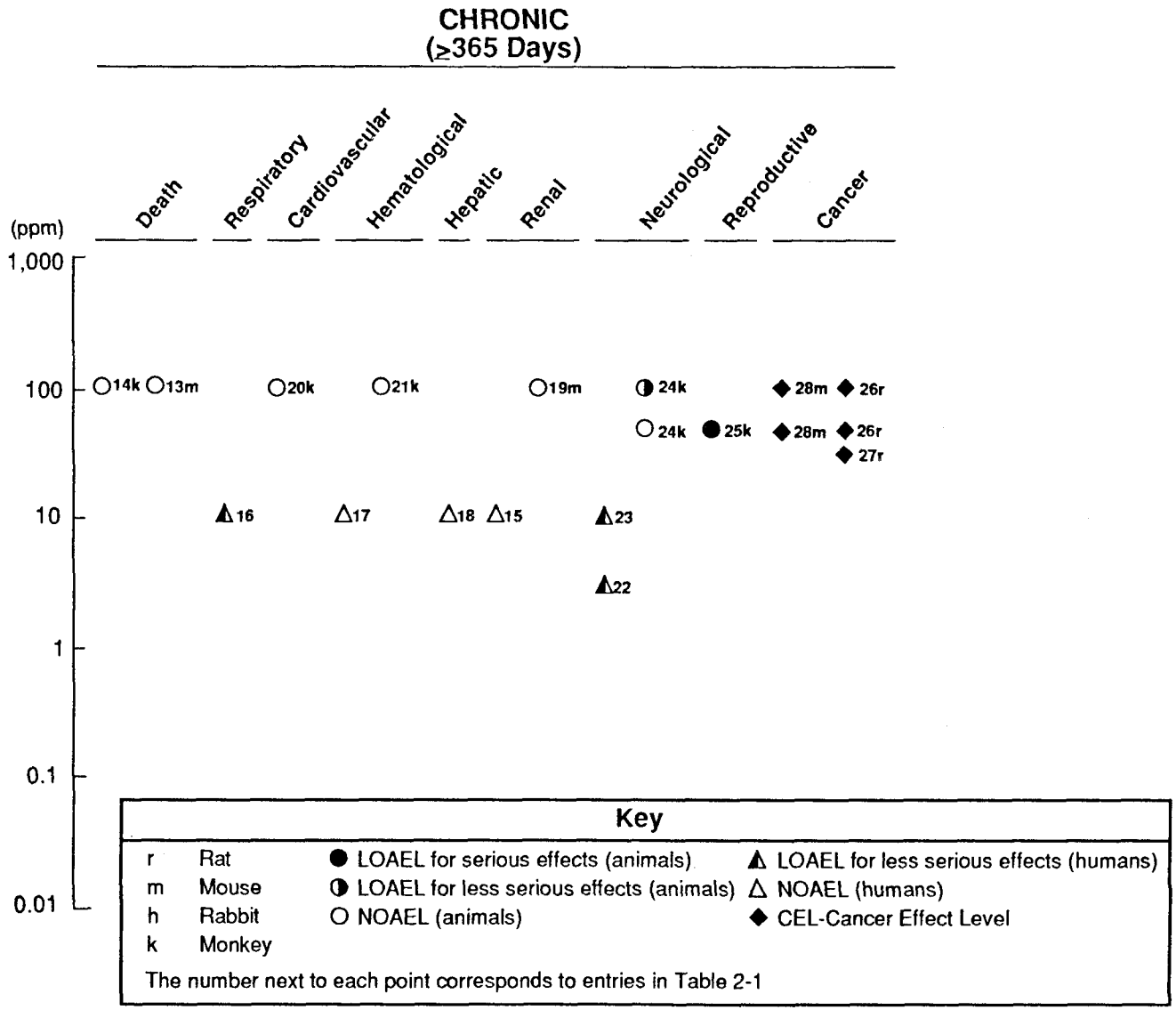



**FIGURE 2-1 (Continued)**

monkey (Lynch et al. 1984a) and mice (NTP 1987) have reported that chronic exposure to 100 ppm did not have any observable hematological effects.

Thus, it is not clear if hematological effects are an area of Concern associated with inhalation exposure to ethylene oxide.

**Musculoskeletal Effects.** No studies were located regarding Musculoskeletal effects in humans after inhalation exposure to ethylene oxide.

Lynch et al. (1984b) reported an increased incidence of skeletal Muscle myopathy in rats exposed to ethylene oxide at 100 ppm by Inhalation. Lesions consisted of multifocal areas of atrophy and Degeneration of skeletal muscle fibers.

**Hepatic Effects.** Information regarding hepatic effects in humane After inhalation exposure to ethylene oxide is limited to a report by Joyner (1964) which indicated that workers exposed to about 5-10 ppm for 10 years did not have major signs of hepatic toxicity such as jaundice or palpable liver.

The data on hepatic effects in animal studies are sparse. Qualitative evidence of liver damage is available in an earlier acute-duration study by Hollingsworth et al. (1956) Rats and guinea pigs given two and three sever-hour exposures, respectively, to ethylene oxide at 841 ppm were reported to have light coloration and fatty degeneration of the liver. Because the authors did not specify which species was observed to have the stated lesions, or what observations were made in control animals, the reported results are difficult to Interpret.

Adverse hepatic effects have not been reported in the more recent literature, most notably in the NTP (1987) 14-week study in which mice were exposed to ethylene oxide at doses up to 600 ppm. Snellings et al. (1984a) reported an elevation in the liver to body weight ratio in female mice exposed to ethylene oxide at 250 ppm for 11 weeks; however, histological examination showed that the livers were normal at this and all other lower exposure levels for both sexes in this study. No hepatic effects have been reported in chronic studies.

The highest NOAEL value and all reliable LOAEL values for each Species and duration category are presented in Table 2-1 and plotted in Figure 2-1.

**Renal Effects**. Information regarding renal effects in humans after inhalation exposure to ethylene oxide is limited to a report by Joyner (1964) which indicates that there was no evidence of nephritis or other parenchymal disease among workers exposed to ethylene oxide at 5-10 ppm for 10 years.

In animal studies, qualitative evidence of renal effects resulting from acute exposure was presented in an earlier study, Hollingsworth et al. (1956), in which rats and guinea pigs were given two and three seven-hour exposures, respectively, to ethylene oxide at 841 ppm. Renal enlargement and slight congestion and cloudy swelling of the convoluted tubules were reported. As described previously, there are certain limitations in this study (i.e., the results observed in controls were not indicated and the authors did not indicate the species in which each lesion was observed).

Renal lesions have also been reported in a 14-week study in mice by NTP (1987). Exposure to 100 ppm resulted in tubular degeneration in male mice and to 600 ppm in tubular necrosis in both sexes. No renal lesions were observed in mice exposed to ethylene oxide at 50 ppm. This value has been used to calculate the minimum risk level (MRL) for intermediate inhalation exposure as shown in Figure 2-l. Renal lesions seen at 100 ppm in the 14-week study, however, were not observed at that level (the highest tested) in the two-year study in mice by NTP (1987). The authors attributed this disparity to the confounding influence of subtle age-related lesions in the kidneys of mice in the two-year study.

Therefore, renal effects appear to be an area of some concern for inhalation exposure to ethylene oxide. The highest NOAEL values and all reliable LOAEL values for renal effects in each species and duration category are presented in Table 2-l and plotted in Figure 2-1.

**Dermal/Ocular Effects**. There is some evidence that occupational exposure to high levels of ethylene oxide can result in cataracts. This is based on the cases of four sterilizer operators who were exposed to ethylene oxide from a leaking sterilizer for up to two months (Gross et al. 1979). In the next 2.5 to 3.5 years, Jay et al. (1982) found that all four men had developed cataracts. Because these persons could intermittently smell the fumes, a level of 700 ppm or more was estimated by the authors in retrospect. Although none of the patients were examined before this accidental exposure, the occurrence of cataracts was viewed as unlikely to be a chance occurrence in all four persons in this age range (31 to 35 years old) who had no systemic or ocular disease that might be associated with cataract formation.

Lynch et al. (1984a) observed a dose-related but not statistically significant increase in the incidence of cataracts in rats exposed to ethylene oxide at 50 and 100 ppm for two years. Therefore, the potential for adverse ocular effects may be an area of concern in cases of chronic or high level inhalation exposure to ethylene oxide. The available data, however, are not useful to serve as the basis for quantifying effect levels for cataract formation in humans.

**Other Effects**. Proliferative and degenerative lesions of the adrenal cortex, consisting of vacuolation and hyperplasia or hypertrophy of the zona fascicularis, have been reported in rats exposed to ethylene oxide at 50 or 100 ppm in a 2-year study by Lynch et al. (1984b). Focal to multifocal splenic fibrosis and extramedullary hematopoiesis were also reported in these rats.

### 2.2.1.3 Immunological Effects

The immunological effects of human inhalation exposure to ethylene oxide were studied in workers in an ethylene oxide manufacturing plant for up to 14 years. Atmospheric concentrations were generally below 0.05 ppm (the detection limit of the analytical method) with occasional peaks of 8 ppm during the 4 years that the air was monitored. There was no effect on any of the blood parameters relating to immune function that were investigated, including T and B lymphocyte counts, lymphocyte activation, and serum IgG, IgM, and IgA levels (Van Sittert et al. 1985). Theiss (1963) did not observe skin sensitization in ethylene oxide plant workers (average exposure: 10.4 years) who were challenged with a single dermal application of 1% ethylene oxide.

In mice exposed to ethylene oxide during a 14-week study, lymphocytic hypoplasia of the thymus was seen in males in the 200 ppm exposure group. At 600 ppm, lymphocytic necrosis of the thymus was seen in most mice of both sexes, and lymphocytic necrosis of the spleen was seen in males.

### 2.2.1.4 Neurological Effects

Neurological effects have frequently been reported in association with human and animal exposure to ethylene oxide via inhalation at a wide range of concentrations and exposure durations.

In humans exposed to high levels of ethylene oxide in occupational settings, headache, nausea and vomiting have been reported for decades (Blackwood and Erskine 1938; von Oettingen 1939; Sexton and Henson 1949). Exposure levels were not measured or estimated in these situations.

Peripheral neuropathy, impaired hand-eye coordination, and memory loss have also been reported in more recent case studies of workers exposed to ethylene oxide for various durations (Crystal et al. 1988; Estrin et al. 1987; Finelli et al. 1983; Kuzuhara et al. 1983; Salinas et al. 1981; Schroeder et al. 1985; Zampollo et al. 1984). These effects were seen at estimated average exposure levels as low as 3 ppm; however, short-term exposures may have been as high as 700 ppm for some of these workers. Two of these studies indicated that sural nerve biopsies showed axonal degeneration and regeneration (Kuzuhara et al. 1983; Schroeder et al. 1985).

Information on the neurological effects of inhalation exposure to ethylene oxide has also been derived from case studies of longer-term occupational exposure. Four sterilizer operators exposed to ethylene oxide for up to two months on an intermittent basis at levels of approximately 700 ppm (estimated by the authors based on the fact that the exposed workers could smell the vapors emitted from a leaking apparatus) reported headaches, nausea, vomiting, clumsiness, blunting of the senses, lethargy, numbness and weakness in the extremities, and, in the case of one operator, recurrent major motor seizures at 20- to 30-minute intervals near the end of the work shift. Nerve conduction studies indicated sensimotor neuropathy. These conditions were reversed in the case of one of these operators who was returned to a position without ethylene oxide exposure, but the results of nerve conduction studies remained abnormal in the cases of two of the three workers who were returned to positions of lower ethylene oxide exposure (50 ppm or less) (Gross et al. 1979). However, the possibility of occasional short-term exposure to high levels of ethylene oxide after that point was not addressed.

In subchronic studies in mice, exposure to ethylene oxide at 50 ppm and above for l0-11 weeks resulted in hunched posture, reduced locomotor activity and abnormal righting reflexes (Snellings et al. 1984a).

In earlier animal studies, exposures of various species to moderately high levels of ethylene oxide (357 ppm) for up to 6 months resulted in neurological impairment, including reversible hind leg paralysis and atrophy, abnormal knee and extensor reflexes and diminished pain perception (Hollingsworth et al. 1956). The exposure of monkeys to 200 ppm for about 7 months in another phase of this study resulted in partial paralysis, muscular atrophy of the hind legs and suppression of reflexes. Due to inconsistencies in the testing protocol and reporting of results, the Hollingsworth et al. (1956) study can be viewed only as qualitative evidence of a broad range of neurological effects associated with inhalation of ethylene oxide at these levels.

In a 9-month study of rats exposed to ethylene oxide at 250 ppm, distal axonal degeneration of myelinated fibers in both sural nerves and gracile fascicles was reported (Ohnishi et al. 1986). Observations of

neurological effects in two-year studies have ranged from no effects observed in mice exposed to 100 ppm (NTP 1987) to slight demyelination of the brain of monkeys exposed at the same level (Lynch et al. 1984a) and brain lesions seen in rats exposed at 50 ppm (Lynch et al. 1984a, 1984b).

The highest NOAEL values and all reliable LOAEL values for neurotoxicity in each species and duration category are presented in Table 2-l and plotted in Figure 2-l.

**2.2.1.5 Developmental Effects**

No studies were located regarding developmental effects in humans after inhalation exposure to ethylene oxide.

Data available from animal studies indicate that ethylene oxide was not teratogenic in rats exposed at 100 ppm during gestation (Snellings et al. 1982a) or in rats or rabbits at an exposure level of 150 ppm during gestation (Hardin et al. 1983).

Embryo and fetal toxicities, however, were evident in rats exposed to 100 ppm in the Snellings et al. (1982a) study, as indicated by an increased incidence of resorption and reductions in fetal body weight and crown-rump length and reduced skeletal ossification of the skull and sternebrae. The highest NOAEL values and all reliable LOAEL values for developmental toxicity in each species and duration category are presented in Table 2-l and plotted in Figure 2-l.

**2.2.1.6 Reproductive Effects**

There is limited evidence in both animal and human studies that inhalation exposure to ethylene oxide can result in adverse reproductive effects, although there is currently no clear pattern in the nature of those effects.

Data in humans are limited. In an epidemiological study by Hemminki et al. (1982), the spontaneous abortion rates in ethylene oxide sterilizer personnel in hospitals in Finland were found to be significantly higher than those of non-exposed workers. Although exposure levels were not measured, the authors estimated that 8-hour weighted mean concentrations ranging from 0.1 to 0.5 ppm with peaks to 250 ppm were associated with adverse outcomes. Various limitations have been described in the design and implementation of this study including recall bias, prior knowledge of the questionnaires and analysis based on too few pregnancies (Golberg 1986). Decreased sperm counts in ethylene oxide workers were reported by Abrahams (1980). However, based on the small number of sperm samples obtained, the author viewed the results as inconclusive.

Various adverse reproductive effects have also been noted in animal studies, including a decreased number of implantation sites in rats exposed to ethylene oxide at 100 ppm during gestation (Snellings et al. 1982b), decreased testicular weights in mice exposed to 50 ppm or more for 10 weeks (Snellings et al. 1984a), decreased testicular weights and testicular degeneration in guinea pigs exposed to 375 ppm for about 6 months, and testicular degeneration in rats exposed to 204 ppm for about 6 months (Hollingsworth et al. 1956). In Cynomolgus monkeys exposed to ethylene oxide at 50 or 100 ppm for two years, sperm concentration, motility and drive range, as well as decreased testicular and epididymal weights, were observed (Lynch et al. 1984a). Appelgren et al. (1977) demonstrated that in mice intravenously injected with $^{14}$C-ethylene oxide, the $^{14}$C-label was detected in the testes and epididymis (at undetermined levels) within four hours. This study indicates that ethylene oxide or one of its degradation products can be distributed to the male reproductive system.

Therefore, it appears that both female and male reproductive systems are potential targets of ethylene oxide toxicity.

The highest NOAEL values and all reliable LOAEL values for reproductive toxicity in each species and duration category are presented in Table 2-1 and plotted in Figure 2-1.

**2.2.1.7 Genotoxic Effects**

In studies of workers exposed to ethylene oxide, analysis of peripheral blood lymphocytes resulted in the detection of various chromosomal aberrations including breaks, gaps, and exchanges and supernumerary chromosomes (Pero et al. 1981; Galloway et al. 1986; Sarto et al. 1984a; Theiss et al. 1981). An increased incidence of sister chromatid exchange (SCE) in the peripheral lymphocytes of ethylene oxide workers has also been reported by Galloway et al. (1986), Garry et al. (1979), Lambert and Lindblad (1980), Sarto et al. (1984a, 1984b), Stolley et al. (1984), and Yager et al, (1983).

Inhalation studies with rats indicate that ethylene oxide at 50 ppm or more for 3 days resulted in an increase in SCE (Kligerman et al. 1983). Increased incidences of SCE and chromosomal aberrations in the peripheral blood of monkeys exposed to ethylene oxide at 500 or 100 ppm were reported by Lynch et al. (1984a). A follow-up study in these same monkeys by Kelsey et al. (1988) indicated that high SCE counts persisted 6 years after exposure.

In dominant lethal assays, ethylene oxide administered via inhalation has resulted in a positive response in mice (Cumming and Michaud 1979; Generoso et al. 1986, 1988) and rats (Embree et al. 1977). Dose-rate studies by Generoso et al. (1986) have demonstrated that short

bursts of ethylene oxide at high concentrations, such as those that may occur in the workplace, may present a greater risk to germ cell damage than does cumulative, long-term exposure to lower levels. Data from these studies are viewed as providing support to the concern for the potential genotoxicity of this compound.

**2.2.1.8 Cancer**

There is some evidence from inhalation data in both humans and animals that ethylene oxide is carcinogenic by this route. However, the available data in humans are considered to be limited and inconclusive. Epidemiological studies of workers exposed to ethylene oxide in hospital sterilizing operations and in manufacturing plants (Hogstedt et al. 1979, 1986) have reported increased incidences of leukemia and stomach cancer. The Hogstedt data are viewed as having certain limitations, however, such as the small cohort size, the small number of deaths that occurred, and uncertainties about the exposure levels (Golberg 1986). Data (originally reported as negative) by Morgan et al. (1981), when reanalyzed by EPA (1985a), showed an increased rate of mortality from pancreatic cancer and Hodgkin's disease in ethylene oxide-exposed workers. No clear excess in any of these cancers, however, was found by Gardner et al. (1989), Greenberg et al. (1990) or Kiesselbach et al. (1990).

In two-year studies of rats exposed to ethylene oxide at 33 to 100 ppm and 50 to 100 ppm, increased incidences of mononuclear cell leukemia, peritoneal mesotheliomas, and various brain tumors have been reported at all dose levels tested (Lynch et al. 1984b; Snellings et al. 1984b). The finding of mononuclear cell leukemia in rats may be of dubious significance to humans because this is a spontaneous tumor in Fischer-344 rats and because the human equivalent of this disease is T-gamma lymphoproliferative disease (lymphocytosis), not leukemia.

In an NTP (1987) two-year inhalation study of mice at 50 and 100 ppm, alveolar/bronchiolar carcinomas and adenomas, papillary cystadenomas of the harderian gland, malignant lymphomas, uterine adenocarcinomas, and mammary gland tumors were increased in one or more exposure groups. The cancer effect levels (CEL'S) are presented in Table 2-l and plotted in Figure 2-l.

On the basis of the combined incidence of mononuclear cell leukemia and gliomas in female rats in the Snellings et al. (1984b) inhalation study, an upper-limit carcinogenicity potency value for ethylene oxide has been calculated as $3.5 \times 10^{-1}$ $(mg/kg/day)^{-1}$ by EPA (1985a) using the linearized multistage model.

EPA's Cancer Assessment Group has found the evidence in animal studies to be "sufficient" and the human evidence to be "limited" bordering on inadequate to establish ethylene oxide as a probable human carcinogen (EPA 1985a). This results in a Group Bl bordering on B2 carcinogenicity classification for this compound. Similarly, according to IARC guidelines, ethylene oxide has been classified in Group 2A bordering on 2B due to the limitations in human evidence (IARC 1987).

### 2.2.2 Oral Exposure

Data on the toxic effects following oral administration of ethylene oxide are extremely limited and no studies are considered appropriate for the calculation of Minimal Risk Levels. As mentioned previously, inhalation is considered to be the most important route of exposure for this chemical.

#### 2.2.2.1 Death

No information was located on the lethal effects in humans after oral exposure to ethylene oxide.

In a study using rats, Hollingsworth et al. (1956) found that a single gavage dose of ethylene oxide at 200 mg/kg resulted in the death of all test animals. At 100 mg/kg, all animals survived 15 doses administered in 21 days. Based on these results, the oral $LD_{50}$ would probably be somewhere between these two dosage levels. It should be noted that this study used a small number of test animals (5/dose) and the results should be viewed in consideration of this study limitation.

These values are presented in Table 2-2 and plotted in Figure 2-2.

#### 2.2.2.2 Systemic Effects

No studies were located on the respiratory, cardiovascular, musculoskeletal, renal or dermal effects in humans or animals after oral exposure to ethylene oxide.

**Gastrointestinal Effects.** No studies were located on the gastrointestinal effects in humans after oral exposure to ethylene oxide.

Hollingsworth et al. (1956) reported gastric irritation in female rats receiving 15 doses of ethylene oxide by gavage at 100 mg/kg/day for 21 days. This effect was not observed at doses of 30 mg/kg/day or below in rats dosed 22 times in 30 days. Due to the small number of test animals used (5/dose) and the lack of detail in reporting results, especially in control animals, the value of this study is limited.

**TABLE 2-2. Levels of Significant Exposure to Ethylene Oxide - Oral**

| Figure Key[a] | Species | Route | Exposure Frequency/ Duration | Effect | NOAEL (mg/kg/day) | LOAEL (Effect) Less Serious (mg/kg/day) | LOAEL (Effect) Serious (mg/kg/day) | Reference |
|---|---|---|---|---|---|---|---|---|
| ACUTE EXPOSURE | | | | | | | | |
| Death | | | | | | | | |
| 1 | Rat | (G) | 1 d | | 100 | | 200[b] (all died) | Hollingsworth et al. 1956 |
| INTERMEDIATE EXPOSURE | | | | | | | | |
| Systemic | | | | | | | | |
| 2 | Rat | (G) | 21-30 d 5d/wk | Gastro | 30 | 100[c] (gastric irritation) | | Hollingsworth et al. 1956 |
| 3 | Rat | (G) | 21-30 d 5d/wk | Hepatic | 30 | 100[c] (slight damage) | | Hollingsworth et al. 1956 |
| CHRONIC EXPOSURE | | | | | | | | |
| Death | | | | | | | | |
| 4 | Rat | (G) | 150 wk 2d/wk | | 7.5 | | 30 (earlier death) | Dunkelberg 1982 |
| Cancer | | | | | | | | |
| 5 | Rat | (G) | 150 wk 2d/wk | | | | 7.5 CEL (forestomach) | Dunkelberg 1982 |

[a]The number corresponds to entries in Figure 2-2.
[b]Converted to 4,000 ppm in food for presentation in Table 1-4.
[c]Converted to 2,000 ppm in food for presentation in Table 1-4.

LOAEL = lowest-observed-adverse effect level; NOAEL = no-observed-adverse-effect level; d = day; (G) = gavage; wk = week; Gastro = gastrointestinal; CEL = cancer effect level.

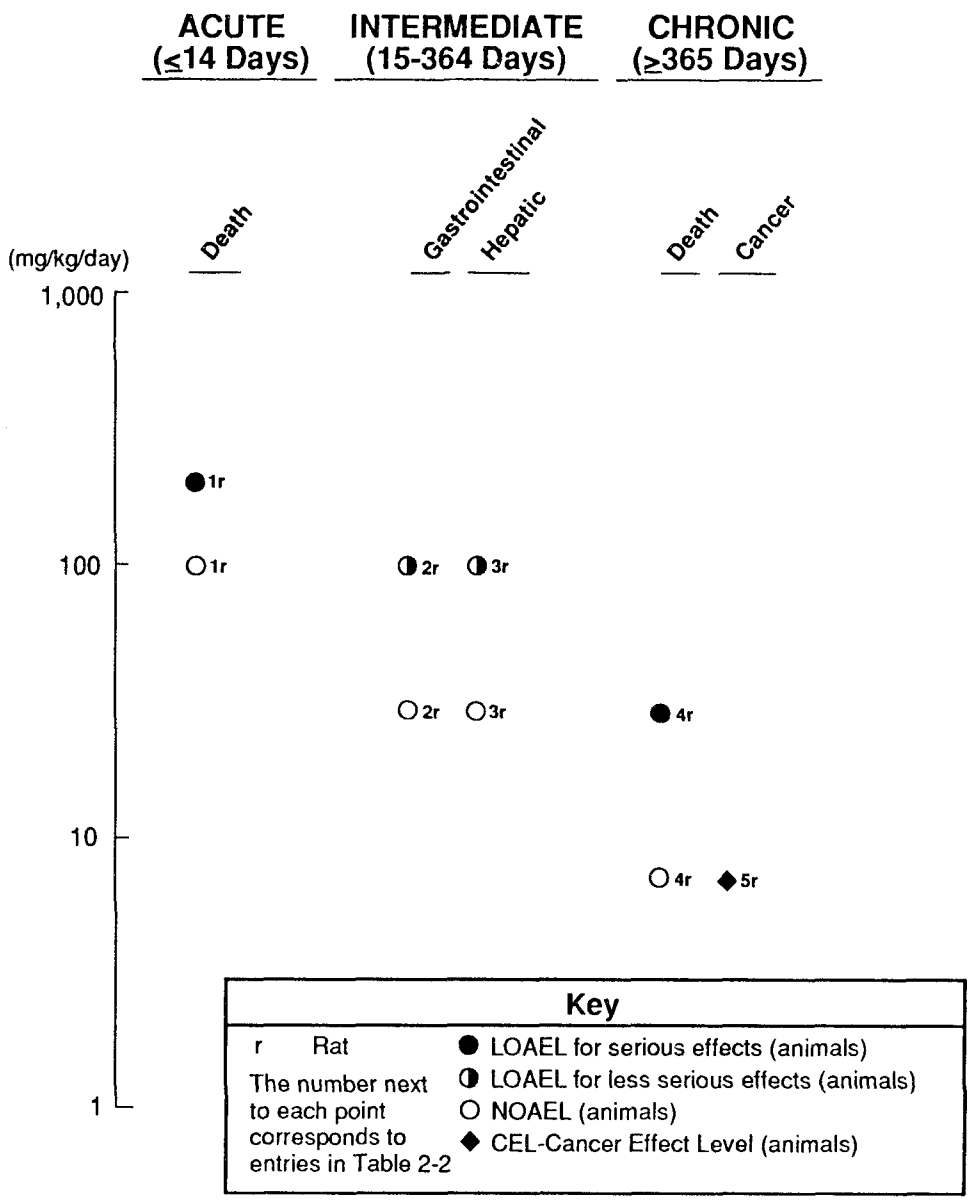



**FIGURE 2-2. Levels of Significant Exposure to Ethylene Oxide – Oral**

These values have been presented in Table 2-2 and plotted in Figure 2-2.

**Hematological Effects**. No studies were located regarding the hematological effects in humans after oral exposure to ethylene oxide.

Hollingsworth et al. (1956) reported that there were no adverse hematological effects in female rats receiving ethylene oxide by gavage at levels up to 100 mg/kg/day at 15 doses in 21 days. No other details were provided.

Based on the limitations of the available data, it is not clear if hematological effects would be an area of potential concern for oral exposure to ethylene oxide.

**Hepatic Effects**. No studies were located regarding hepatic effects in humans after oral exposure to ethylene oxide.

Slight liver damage (no further details) was reported by Hollingsworth et al. (1956) in rats exposed by gavage to ethylene oxide at 100 mg/kg/day for 15 doses in 21 days, but not in animals receiving up to 30 mg/kg/day for 22 doses in 30 days. Because of various limitations in the scope and reporting of this study, it can be viewed only as suggestive evidence that oral exposure to ethylene oxide can result in hepatic effects.

These values have been presented in Table 2-2 and plotted in Figure 2-2.

No studies were located regarding the following health effects in humans or animals after oral exposure to ethylene oxide:

**2.2.2.3 Immunological Effects**

**2.2.2.4 Neurological Effects**

**2.2.2.5 Developmental Effects**

**2.2.2.6 Reproductive Effects**

**2.2.2.7 Genotoxic Effects**

**2.2.2.8 Cancer**

No studies were located regarding carcinogenic effects in humans after oral exposure to ethylene oxide.

In the only animal study available via this route, Dunkelberg (1982) reported that female rats dosed with ethylene oxide at 7.5 or 30 mg/kg/day by gavage for 2 days/week for 3 years developed a d oserelated incidence of local tumors, mainly squamous-cell carcinoma of the forestomach, a tumor commonly seen following long-term gavage administration of irritant chemicals. No tumors were found at sites away from the point of administration.

These levels are presented in Table 2-2, and 7.5 mg/kg/day is plotted as the Cancer Effect Level for ethylene oxide in Figure 2-2.

### 2.2.3 Dermal Exposure

#### 2.2.3.1 Death

No studies were located regarding lethal effects in animals or humans after dermal exposure to ethylene oxide.

#### 2.2.3.2 Systemic Effects

No studies were located regarding the respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic or renal effects in humans or animals after dermal exposure to ethylene oxide. Dermal/Ocular Effects. Data related to human dermal exposure to ethylene oxide are generally associated with case reports of industrial accidents, some of which occurred in the 1930's and 1940's. Concentrated ethylene oxide evaporates rapidly from the skin and produces a freezing effect, often compared to frostbite, leaving burns ranging from first to third-degree severity (Taylor 1977). Workers drenched with a 1% solution developed large vesiculated blisters (Sexton and Henson 1949). Nausea and vomiting were also reported in this case study, but might have resulted from inhalation of the vapors rather than from dermal contact.

A study using human volunteers by Sexton and Henson (1950) showed that the magnitude of skin injury was related to the concentration of ethylene oxide in solution but peaked at about 50%. This was attributed to the rapid evaporation of the more concentrated solutions, which prevented more prolonged skin contact.

Case reports of patients whose intact skin or wounds had contact with gauze or other hospital supplies that had been sterilized with ethylene oxide indicated that the observed skin reactions included erythema, blister formation, scaling, crusted ulcerations and second degree burns (Alomar et al. 1981; Hanifin 1971).

Shupack et al. (1981) demonstrated that human skin reactions to ethylene oxide in patch materials were directly related to the total dose.

Cornea1 burns (McLaughlin 1946; Thiess 1963) and cataracts (Gross et al. 1979; Jay et al. 1982) have been reported in cases of occupational exposure to ethylene oxide. Although the cornea1 burns were due to direct ocular contact with ethylene oxide, it was not clear in the cases of cataracts whether they could be attributed to ocular contact with ethylene oxide vapor or were a systemic effect resulting from inhalation of ethylene oxide.

Dermal application of ethylene oxide on rabbits and guinea pigs has resulted in hyperemia (the presence of an increased amount of blood), edema (Hollingsworth et al. 1956), and skin irritation (Bruch 1973; Woodard and Woodard 1971).

Ocular effects in rabbits after ocular instillation of ethylene oxide solution have been reported as congestion, swelling, discharge, iritis, cornea1 cloudiness, and irritation (McDonald et al. 1977; Woodard and Woodard 1971).

**2.2.3.3 Immunological Effects**

Theiss (1963) did not observe skin sensitization in ethylene oxide plant workers (average exposure: 10.4 years) who were challenged with a single dermal application of 1% ethylene oxide. Dermal application studies using human volunteers by Sexton and Henson (1950) and Shupack et al. (1981) however, have provided some evidence that ethylene oxide is a skin sensitizer. A case study of a hospital patient diagnosed wit1 allergic contact dermatitis in response to ethylene oxide also suggests skin sensitization (Alomar et al. 1981). However, ethylene chlorhydrin may also have contacted the patient's skin.

Skin sensitization studies in guinea pigs by Woodard and Woodard (1971), however, were negative.

No other data on the potential immunologic effects of dermal exposure to ethylene oxide were located, and it is not clear if immunological effects are of concern following dermal exposure to ethylene oxide.

No studies were located regarding the following health effects in humans or animals after dermal exposure to ethylene oxide:

**2.2.3.4 Neurological Effects**

**2.2.3.5 Developmental Effects**

**2.2.3.6 Reproductive Effects**

**2.2.3.7 Genotoxic Effects**

**2.2.3.8 Cancer**

No studies were located regarding carcinogenic effects in humans after dermal exposure to ethylene oxide.

In a lifetime skin painting study, application of a 10% solution of ethylene oxide to the backs of mice did not result in skin tumors or irritation (Van Duuren et al. 1965).

**2.3 TOXICOKINETICS**

**2.3.1 Absorption**

**2.3.1.1 Inhalation Exposure**

In a study of hospital workers by Brugnone et al. (1985), alveolar ethylene oxide concentrations were highly correlated with ambient ethylene oxide concentrations. The average alveolar retention of ethylene oxide was approximately 75% of the ambient concentration. Animal studies have shown that ethylene oxide is rapidly absorbed by the respiratory systems of the rat (Koga et al. 1987; Matsuoka 1988; Nakashima et al. 1987; Tardif et al. 1987), mouse (Cumming et al. 1981; Ehrenberg et al. 1974; Tardif et al. 1987), and rabbit (Tardif et al. 1987).

**2.3.1.2 Oral Exposure**

No studies were located regarding absorption of ethylene oxide after oral exposure.

**2.3.1.3 Dermal Exposure**

No studies were located regarding absorption of ethylene oxide after dermal exposure.

**2.3.2 Distribution .**

2**.3.2.1 Inhalation Exposure**

No studies were located regarding the distribution of ethylene oxide in human tissue after inhalation exposure. Ehrenberg et al. (1974) reported that 75 minutes after exposing mice, the highest concentrations of ethylene oxide were observed in the lungs, liver and kidneys. Lesser amounts were found in the spleen, brain and testes.

Tyler and McKelvey (1982) found that in rats administered $^{14}$C-ethylene oxide, the highest concentrations of $^{14}$C-activity were found in the urinary bladder, liver, packed blood cells, and adrenal glands, with the lowest concentration found in the fat.

Tyler (1983) evaluated the fate of ethylene oxide in pre-exposed rats and their respective controls. Urine, feces and expired air were collected during and 18 hours after exposure to $^{14}$C-ethylene oxide. There were no significant differences in the concentration of radioactivity in either group of animals, except that the radioactivity associated with the red blood cells was 1.3 times greater in animals that were not pre-exposed.

**2.3.2.2 Oral Exposure**

No studies were located regarding distribution of ethylene oxide after oral exposure.

**2.3.2.3 Dermal Exposure**

No studies were located regarding distribution of ethylene oxide after dermal exposure.

**2.3.3 Metabolism**

The metabolism of ethylene oxide is not completely known. Data from animal studies indicate two possible pathways for the metabolism of ethylene oxide: hydrolysis to ethylene glycol and glutathione conjugation to form mercapturic acid and meththio-metabolites. Martis et al. (1982) identified 1,2-ethanediol (ethylene glycol), a hydrolysis product, in the plasma and urine of beagle dogs one hour after intravenous administration of ethylene oxide. Ethylene glycol was the major metabolite of ethylene oxide, with 7 to 24% of the administered dose excreted in the urine within 24 hours. Koga et al. (1987) identified ethylene glycol, 2-hydroxymercapturic acid, 2-methylthioethanol and 2-mercaptoethanol as metabolites in the urine of rats.

Tardi.f et al. (1987) studied the qualitative and quantitative urinary disposition of some metabolites of ethylene oxide in three rodent species: mouse, rat and rabbit. Important differences were observed among the three species in the urinary metabolic disposition of ethylene oxide. After an intravenous injection of ethylene oxide at 20 mg/kg, mice excreted significantly higher quantities of N-acetyl-S-(2-hydroxyethyl)-L-cysteine, S-(2-hydroxyethyl)-L-cysteine, S-carboxymethyl-L-cysteine and ethylene glycol (8.3, 5.8, 1.9 and 3.3% of the administered dose, respectively, in 24 hours), whereas in rats, only N-acetyl-S- (2-hydroxyethyl)-L-cysteine (31%) and ethylene glycol (6%) were apparent. In contrast, the rabbits were found to excrete only

ethylene glycol (2%). This study further revealed species-related differences in the urinary excretion of N-acetyl-S-(2-hydroxyethyl)-L-cysteine and ethylene glycol during the two collection periods. The observed differences among the three species in the metabolic disposition of ethylene oxide were found to be qualitatively independent of the route of exposure, (i.e., inhalation at 200 ppm or intravenous injection of 20 or 60 mg/kg). These results suggest that care should be exercised when using any single animal species as a model for human disposition of ethylene oxide.

Tyler (1983) evaluated the fate of ethylene oxide in pre-exposed rats and their respective controls. Urine, feces and expired air were collected during and 18 hours after exposure to $^{14}$C-ethylene oxide. There were no significant differences between the non-pre-exposed or pre-exposed animals in the metabolic profiles. The data indicate that prolonged exposure of rats to ethylene oxide has little effect on the metabolism of the chemical.

Matsuoka (1988) reported that in rats exposed to ethylene oxide for three months, the cytochrome P-450 enzyme systems in the lung and brain were not affected. However, hepatic cytochrome P-450 and protoheme decreased by 28% and 19%, respectively. Hepatic total microsomal protein, cytochrome b5, NADPH-cytochrome c reductase and NADH-ferricyanide reductase were not affected. The activity of hepatic heme oxygenase showed a two-fold increase. These results suggest that the heme moiety of hepatic cytochrome P-450 was primarily affected by exposure of ethylene oxide and the cellular heme balance in liver was altered.

Nakashima et al. (1987) found that in rats exposed to ethylene oxide for 12 weeks, the concentration of the reduced form of glutathione (GSH) in the liver was not significantly different from that of controls. However, the hepatic GSH levels in rats subjected to a 4 hour exposure to a high concentration of ethylene oxide (2,500 ppm) were markedly decreased. These data suggest the involvement of glutathione in the detoxication of ethylene oxide, at least in the rat.

McKelvey and Zemaitis (1986) exposed rats and mice to different, atmospheric concentrations of ethylene oxide for 4 hours. In mice sacrificed immediately after exposure to ethylene oxide, there was a concentration-related decrease in the GSH levels of all tissues examined. Similar findings were obtained in rats immediately after exposure to ethylene oxide, except that blood GSH levels were not affected at any exposure concentration. In both species, lung and liver GSH levels were depressed at all exposure concentrations. Twenty-four hours after exposure to ethylene oxide, the GSH concentrations of rat bone marrow and testis had not returned to control levels. Only blood GSH levels remained depressed in mice 48 hours after exposure to

ethylene oxide. The results indicate a marked species difference between rats and mice regarding the effects of ethylene oxide exposure on blood GSH levels.

### 2.3.4 Excretion

#### 2.3.4.1 Inhalation Exposure

No studies were located regarding excretion of ethylene oxide in humans after inhalation exposure.

Tyler and McKelvey (1982) found that in the rat, the primary route of $^{14}$C-ethylene oxide elimination was urine (mean value of 59% recovered $^{14}$C-activity), followed by expired CO, (12%), feces (4.5%), and expired ethylene oxide (1%). Cumming et al. (1981) reported that ethylene oxide was rapidly eliminated by mice that had been exposed to radio-labeled ethylene oxide. Ehrenberg et al. (1974) reported that in mice ethylene oxide has a biological half-life of approximately 9 minutes. Seventy-eight percent of the administered dose was eliminated within 48 hours, suggesting rapid urinary excretion. Filser and Bolt (1984) found that ethylene oxide administered in a closed-system inhalation chamber exhibited first-order elimination kinetics.

Tyler (1983) evaluated the fate of ethylene oxide in pre-exposed rats and their respective controls. Urine, feces and expired air were collected during and 18 hours after exposure to $^{14}$C-ethylene oxide. There were no significant differences between the nonpre-exposed or pre-exposed animals in the routes of elimination.

#### 2.3.4.2 Oral Exposure

No studies were located regarding excretion of ethylene oxide after oral exposure.

#### 2.3.4.3 Dermal Exposure

No studies were located regarding excretion of ethylene oxide after dermal exposure.

## 2.4 RELEVANCE TO PUBLIC HEALTH

As discussed previously in Section 2.2, the main route of exposure to ethylene oxide in humans is via inhalation, and the main health effects are central nervous system depression and irritation of the eyes and mucous membranes.

Reproductive effects have been observed in animal studies but there is no clear evidence of these effects in humans. Similarly, ethylene oxide is clearly a carcinogen in animals, and epidemiological studies in humans have shown limited evidence of carcinogenic effects in occupationally exposed populations.

**Death.** The available reports (Gardner et al. 1989; Greenberg et al. 1989) indicate that there is no increased incidence of human death in association with ethylene oxide exposure. In mice, four-hour exposures to 800 ppm resulted in a high rate of mortality (80-100%) whereas 400 ppm exposures for 14 days did not result in death (NTP 1987). A level of 100 ppm for two years did not result in increased lethality of mice (NTP 1987) or monkeys (Lynch et al. 1984a).

Based on the available data, lethality due to inhalation of ethylene oxide may not be a health concern in occupational settings, except with the use of damaged or leaking equipment.

**Systemic Effects**. Bronchitis, pulmonary edema and emphysema have been reported in workers after acute high-level exposure (Theiss 1963), but respiratory problems have not been reported to occur with chronic exposure (Joyner 1964). Evidence of the potential for respiratory irritation resulting from ethylene oxide inhalation comes mainly from animal studies.

Based on data in mice, it appears that exposure level is more important than duration of exposure with respect to respiratory effects. Mice exposed to 200 ppm or more for 14 days suffered from rhinitis, loss of polarity of olfactory and respiratory epithelial cells, epithelial necrosis, loss of cilia and accumulation of purulent exudate. These lesions were not seen by the same investigators in mice exposed to 100 ppm for two years NTP (1987).

Thus it appears that, at least in animals and possibly in humans, there is a critical concentration of ethylene oxide that is necessary to elicit respiratory irritation and the resulting lesions.

Dermal and ocular irritation have been reported in several case studies of individuals occupationally exposed to ethylene oxide. Dermal contact results in skin burns of varying severity depending on the concentration of ethylene oxide and the length of contact (Sexton and Henson 1949; Shupack et al. 1981). Cornea1 burns have been reported in workers whose eyes have been splashed with ethylene oxide in solution or blasted by the vapor (McLaughlin 1946; Thiess 1963).

Cataracts have also been associated with occupational exposure to ethylene oxide when workers were exposed to a leaky sterilizer (Gross et al. 1979; Jay et al. 1982). It is not clear whether the development of cataracts was a response to direct ocular contact with the vapor or was a systemic response to inhaled ethylene oxide.

Dermal application studies in animals have confirmed that ethylene oxide is a dermal irritant (Bruch 1973; Hollingsworth et al. 1956; Woodard and Woodard 1971) and ocular irritant (McDonald et al. 1977; Woodard and Woodard 1971).

**Immunological Effects**. There is no clear evidence in animals or humans that exposure to ethylene oxide via the inhalation, oral, or dermal route is associated with immunological effects.

**Neurological Effects**. Central nervous system effects are frequently associated with human exposure to ethylene oxide in occupational settings. Headache, nausea and vomiting have been reported for more than fifty years (Blackwood and Erskine 1938; von Oettingen 1939; Sexton and Henson 1949). Reliable exposure levels are generally not available in these cases. Peripheral neuropathy, impaired hand-eye coordination and memory loss have been reported in more recent case studies of chronically-exposed workers (Crystal et al. 1988; Estrin et al. 1987; Kuzuhara et al. 1983; Zampollo et al. 1984) at estimated average exposure levels as low as 3 ppm (with possible short-term peaks as high as 700 ppm).

In studies using several animal species at moderately high levels of ethylene oxide (200-375 ppm) for 6 to 7 months, hind leg paralysis and atrophy, abnormal knee and extensor reflexes, and diminished pain perception were reported (Hollingsworth et al. 1956). Even levels of 50 ppm for l0-11 weeks resulted in hunched posture, reduced locomotion, and abnormal righting reflexes in mice (Snellings et al. 1984a). A g-month exposure to 250 ppm resulted in distal axonal degeneration of myelinated fibers in both sural nerves and gracile fascicles in rats (Ohnishi et al. 1986). Chronic exposures to ethylene oxide at 100 ppm resulted in slight demyelination of the brains of monkeys and exposure to 500 ppm resulted in brain lesions in rats (Lynch et al. 1984a). These results raise concerns that similar morphological effects may occur in humans.

Based on the body of available data from both human and animal studies, the neurotoxic effects of ethylene oxide are an occupational health concern for a wide range of exposure levels and durations. Both chronic low level exposure associated with years of normal employment

conditions, as well as the brief or even protracted exposure duration to high ethylene oxide levels due to industrial accidents or faulty equipment, can lead to a broad spectrum of adverse neurological effects.

**Developmental Effects**. No data on the potential human developmental effects of ethylene oxide exposure have been located and the available data in animal studies (Hackett et al. 1982; Snellings et al. 1982a) do not indicate that inhalation exposure to ethylene oxide is associated with teratogenic effects. However, embryo and fetal toxicity were reported in the offspring of rats exposed to 100 ppm during gestation; the neonates were smaller in both length and weight and had reduced ossification of the skull and sternebrae (Snellings et al. 1982a). Intravenous administration of ethylene oxide to pregnant mice resulted in decreased fetal weight and increases in dead and resorbed fetuses and in fetal malformations (La Borde and Kimmel 1980). Therefore, the offspring of humans exposed to ethylene oxide may be at risk for teratogenicity and fetal and embryo toxicity.

**Reproductive Effects**. Based on the available human and animal studies, inhalation exposure to ethylene oxide is associated with numerous adverse reproductive effects in both males and females. In an epidemiological study, Hemminki et al. (1982) reported that the spontaneous abortion rates of ethylene oxide sterilizer operators in Finnish hospitals were significantly higher than those of non-exposed workers. Exposure levels were estimated to be as low as 0.1 to 0.5 ppm. However, there were various limitations to the interpretation of this study, as described in Section 2.2.1.6. Abrahams (1980) reported decreased sperm counts in ethylene oxide workers, but as stated previously, the small number of sperm samples obtained for analysis precluded firm interpretation of the findings.

Decreased numbers of implantation sites have been reported in rats exposed to ethylene oxide at 100 ppm during gestation (Snellings et al. 1982b). Reproductive effects in males have been reported in at least three species of animals. Decreased testicular weights and testicular degeneration have been observed in rats and guinea pigs exposed to ethylene oxide for 6 to 7 months at 204 and 357 ppm, respectively (Hollingsworth et al. 1956). In monkeys exposed at 50 ppm for two years, decreased sperm concentration and drive range and reductions in testicular and epididymal weights have been reported (Lynch et al. 1984a). An autoradiography study in mice by Appelgren et al. (1977) indicates that ethylene oxide or one of its degradation products has access to the male gonads (testes and epididymis) in this species within four hours of intravenous exposure.

The potential for adverse reproductive effects is apparently an area which warrants attention in terms of human exposure to ethylene oxide.

**Genotoxic Effects**. Ethylene oxide has been demonstrated to be genotoxic in a wide variety of prokaryotic and eukaryotic test systems. A summary of the available in vitro genotoxicity studies for ethylene oxide is presented in Table 2-3.

Peripheral blood studies of exposed workers have indicated that ethylene oxide exposure is associated with an elevated incidence of chromosomal aberrations including breaks, gaps, and exchanges and supernumerary chromosomes (Galloway et al. 1986; Pero et al. 1981; Sarto et al. 1984a; Theiss et al. 1981). An increased incidence of sister chromatid exchange (SCE) in the peripheral lymphocytes of ethylene oxide workers has also been reported by Galloway et al. (1986), Garry et al. (1979), Lambert and Lindblad (1980), Sarto et al. (1984 and 1984b) and Yager et al. (1983).

Increased and persistent elevations of SCE have also been observed in the peripheral blood lymphocytes of monkeys, (Kelsey et al. 1988; Lynch et al. 1984a) exposed to ethylene oxide for two years, providing additional concern for the carcinogenic potential of this compound for humans exposed via inhalation.

**Cancer.** There is evidence from both human and animal studies that inhalation exposure to ethylene oxide can result in a wide range of carcinogenic effects. Epidemiological studies in ethylene oxide factory workers and sterilizer operators have indicated that leukemia, stomach cancer (Hogstedt et al. 1979, 1986) pancreatic cancer and Hodgkin's disease (Morgan et al. 1981) were elevated in exposed individuals. As described in Section 2.2.1.8, the Hogstedt data are viewed as having certain limitations. Other studies (Gardner et al. 1989; Greenberg et al. 1990; Kiesselbach et al. 1990) have not found these associations.

Inhalation studies in animals have resulted in mononuclear cell leukemia, peritoneal mesotheliomas, and various brain tumors in rats (Lynch et al. 1984b; Snellings et al. 1984b) at levels as low as 33 ppm. Lung tumors, tumors of the harderian gland, malignant lymphomas and uterine and mammary gland tumors were also found in mice (NTP 1987).

In the only located animal study using the oral route, female rats dosed with ethylene oxide by gavage at 7.5 mg/kg/day developed squamous cell carcinomas of the forestomach (the site of application) only, but not at any distal sites (Dunkelberg 1982). Ethylene oxide is ranked as a Group Bl carcinogen (i.e., a probable human carcinogen) by EPA's

**TABLE 2-3. Genotoxicity of Ethylene Oxide In Vitro**

| End Point | Species (Test System) | Results: With Activation | Results: Without Activation | Reference |
|---|---|---|---|---|
| Prokaryotic organisms: | | | | |
| Gene mutation | Salmonella typhimurium | | | Rannug et al. 1976 |
| | TA1535 | | + | |
| | S. typhimurium | | | |
| | TA98 | | + | Pfeiffer and |
| | TA100 | | + | Dunkelberg 1980 |
| | TA1535 | | + | |
| | TA1537 | | + | |
| | Bacillus subtilis | | | |
| | HA101 | | + | Tanooka 1979 |
| | TKJ 5211 | | + | |
| | TKJ 8201 | | + | |
| Eukaryotic organisms: | Neurospora crassa | | + | Kolmark and Kilbey 1968 |
| Plant: | | | | |
| Gene mutation | Schizosaccharomyces pombe | + | + | Migliore et al. 1982 |
| | Barley | | + | Ehrenberg et al. 1956 |
| | Rice | | + | Jana and Roy 1975 |
| Insects: | | | | |
| Gene mutation | Drosophila melanogaster sex-linked recessive lethal | | + | Bird 1952 |
| | D. melanogaster-sex-linked recessive lethal and heritable translocation | | + | Watson 1966 |
| | D. melanogaster-sex-linked recessive lethal and gonadal | | + | Lee 1980 |
| Mammalian cells: | L5178Y TK Mouse lymphoma | | + | Brown et al. 1979 |
| Gene mutation | gene mutation assay | | | |
| | CHO-K1-BH4 Chinese hamster ovary cell gene mutation assay | + | + | Tan et al. 1981 |

+ = positive result; ND = no data; - = negative result; (+) = positive or marginal result.

Carcinogen Assessment Group (IRIS 1989) and a 2A carcinogen by IARC (1987). These classifications are based on adequate evidence in animal studies but limited or inadequate evidence in humans (EPA 1985a). Ethylene oxide was not found to cause skin tumors in a skin painting study using mice (Van Duuren et al. 1965).

Data from in vitro studies indicate that ethylene oxide is mutagenic in several prokaryotic and eukaryotic systems.

Based on the available data, carcinogenicity is an area of major concern in relation to humans chronically exposed to ethylene oxide via inhalation in occupational settings.

## 2.5 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems *or* samples. They have been classified as markers of exposure, markers of effect, and markers 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 or cell that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the *time* biologic samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as cower, zinc and selenium). Biomarkers of exposure to ethylene oxide are discussed in Section 2.5.1.

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 epithelium cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are

often not substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by ethylene oxide are discussed in Section 2.5.2.

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. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, biologically effective dose, or target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.7, "POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE."

### 2.5.1 Biomarkers Used to Identify or Quantify Exposure to Ethylene Oxide

Ethylene oxide can be measured in blood (Bailey et al. 1987; Brugnone et al. 1986; Farmer et al. 1986) and alveolar air (Brugnone et al. 1986). Because ethylene oxide is very reactive in biological systems, it is usually necessary to measure its addition products (e.g., N-(2-hydroxyethyl)histidine or N-(2-hydroxyethyl)valine) in blood.

However, based on the currently available information, the levels of these substances in biological media cannot be used to calculate or estimate corresponding levels of exposure to ethylene oxide.

### 2.5.2 Biomarkers Used to Characterize Effects Caused by Ethylene Oxide

There are currently no subtle or sensitive biomarkers of effects associated with ethylene oxide.

## 2.6 INTERACTIONS WITH OTHER CHEMICALS

No data have been located that identify the interactions of ethylene oxide with other chemicals in the environment.

## 2.7 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

No population has been identified that is more at risk from ethylene oxide exposure based on biological differences.

## 2.8 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of ethylene oxide is available. Where adequate information is not available, ATSDR, in conjunction with the National

Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of ethylene oxide.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met would reduce or eliminate the uncertainties of human health assessment. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

### 2.8.1 Existing Information on the Health Effects of Ethylene Oxide

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to ethylene oxide are summarized in Figure 2-3. The purpose of this figure is to illustrate the existing information concerning the health effects of ethylene oxide. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not imply anything about the quality of the study or studies. Gaps in this figure should not be interpreted as "data needs" information.

As indicated in Figure 2-3, most of the available information on the health effects of ethylene oxide is related to the inhalation route. Most of the data on humans are related to case studies based on normal or accidental occupational exposure.

Studies in animals have been more comprehensive, but as described in the previous section, much of the information is considered to be limited in its usefulness for a variety of reasons.

### 2.8.2 Identification of Data Needs

**Acute-Duration Exposure**. Information on acute-duration exposure of humans to ethylene oxide indicates that irritation reactions involving the mucous membranes of the respiratory system and the skin are the result of inhalation and dermal exposure, respectively. Available information in animals is limited to lethality data in mice via the inhalation route and in rats via the oral route, as well as information on dermal/ocular effects after local administration. The data were not considered to be adequate to calculate an MRL by any route. Further animal studies using acute-duration inhalation exposure to ethylene oxide may be useful in identifying the mechanism of lethality. This information would be relevant to the safety of workers in industrial or hospital settings. Data on acute-duration exposure via the oral route would also be helpful. Some of the currently available studies were

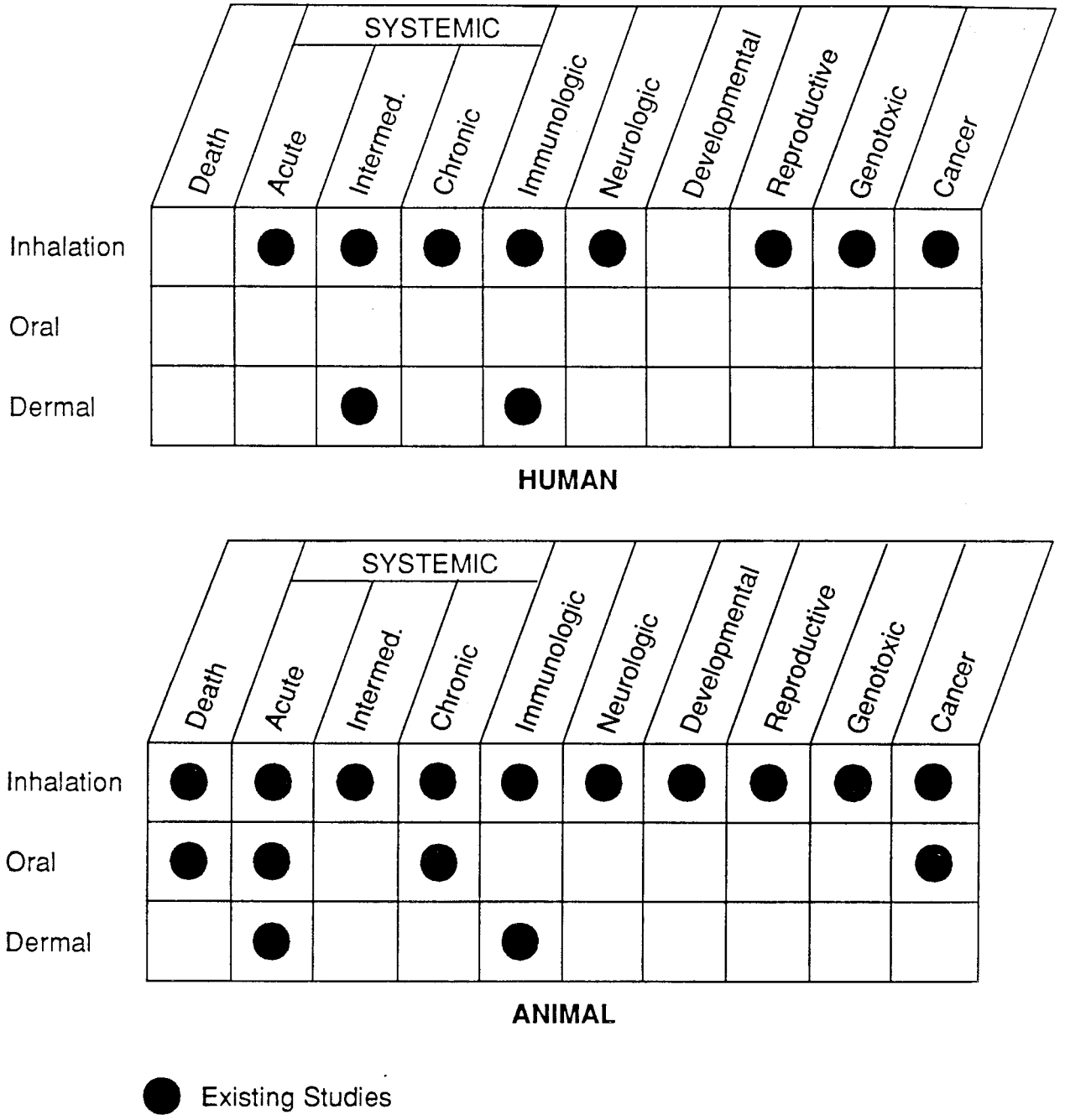



**FIGURE 2-3. Existing Information on Health Effects of Ethylene Oxide**

conducted 30 to 50 years ago, and improvements in experimental technology since then may result in more accurate estimates of exposure levels and analysis of results.

**Intermediate-Duration Exposure**. The currently available data on intermediate-duration exposure to ethylene oxide in humans also indicate that irritation reactions are the major effects resulting from inhalation or dermal exposure. Data in animals via inhalation are useful in assessing its potential effects on a variety of organ systems. An MRL for renal effects in mice exposed via inhalation has been calculated for this duration period. Although intermediate-duration studies via the oral and dermal routes are not currently available, there is no indication that they would be a valuable contribution to the data base for this chemical.

**Chronic-Duration Exposure and Cancer**. Studies are available for this duration period for both humans and animals exposed via inhalation and for animals exposed via the oral route. However, the data were not considered to be adequate to calculate an MRL for any route of exposure.

Data on the carcinogenic potential of ethylene oxide in occupationally exposed humans are inconclusive, with both positive and negative results reported in the available studies. The currently available studies on the chronic exposure of various animal species to ethylene oxide have established that this chemical is clearly carcinogenic via the inhalation route. If it were determined that ethylene oxide residues still remain in or on various agricultural commodities when they are consumed by humans, a chronic feeding study in animals might also be useful. Also, further epidemiologic assessments of the carcinogenic and other health effects in occupationally exposed humans, including dermal effects, would also provide valuable data. Based on the results of such studies, dermal carcinogenicity studies in animals might be relevant to the welfare of occupationally exposed workers.

**Genotoxicity**. The genotoxicity of ethylene oxide has been established in a number of in vitro tests using various prokaryotic and eukaryotic systems as well as in vivo studies of human peripheral blood. Further studies in this area do not currently appear to be necessary.

**Reproductive Toxicity**. Available data on ethylene oxide's reproductive effects on occupationally exposed males are considered inconclusive; further investigation of these individuals would be extremely useful. Further data on occupationally exposed women would also be helpful since the currently available data are limited to a single study of spontaneous abortions in Finnish hospital workers. The currently available reproductive toxicity data from inhalation studies

in animals indicate that this may be an area of concern for inhalation exposure to ethylene oxide. Reproductive toxicity studies in animals via the oral route may also be useful. Studies using the dermal route would probably not be useful unless systemic absorption via skin application is first demonstrated.

**Developmental Toxicity**. There are no data on developmental toxicity in the offspring of humans exposed to ethylene oxide via inhalation, oral, or dermal routes. The currently available data in rats indicate that fetal and embryo toxicity can result from inhalation exposure to ethylene oxide, and fetal abnormalities have been increased in studies using intravenous administration. No studies in this area using oral or dermal exposure have been located. Studies to assess the developmental effects of exposure to ethylene oxide via the inhalation and the oral routes would be useful in assessing the potential risks to offspring of persons exposed to this chemical in the workplace or in the vicinity of hazardous waste sites. Studies using the dermal route would probably not be useful unless systemic absorption can be demonstrated to result from dermal application.

**Immunotoxicity.** The currently available information does not indicate that this is an area of potential concern for ethylene oxide exposure via any route.

**Neurotoxicity**. Ethylene oxide has been established as a neurotoxin in both humans and animals via the inhalation route; therefore, further studies using this route would not appear to be a priority. Studies in animals using the oral route may provide useful information if it is first determined that ethylene oxide residues still remain in or on agricultural commodities when they are consumed by humans. Studies using the dermal route would probably not be useful unless systemic absorption via skin application can first be demonstrated.

**Epidemiological and Human Dosimetry Studies**. Although ethylene oxide has been shown to be toxic to humans in several studies, the related air concentrations have not been sufficiently established. Estimates provided in some studies range from as low as 0.1 ppm for chronic exposure to as high as 700 ppm for intermediate exposure. Dosimetry studies would be valuable in providing retrospective insights into the data reported in human case and epidemiological studies as well as in attempting to determine the most relevant range of exposures at which to conduct any further animal studies. Epidemiological studies of occupationally exposed persons would be useful in determining the risks of cancer, reproductive effects, and neurological effects associated with long-term exposure to ethylene oxide.

**Biomarkers of Exposure and Effect**. Measurement of ethylene oxide or its addition products, N-(Z-hydroxyethyl)histidine or N-(2-hydroxyethyl)valine, in blood may provide an adequate qualitative indication of recent exposure to ethylene oxide. The development of methods that could be used to calculate or estimate levels of exposure to ethylene oxide from the levels of these substances in biological fluids would be extremely useful.

There are currently no subtle or sensitive biomarkers of effects caused by ethylene oxide. It would be useful to have information to correlate levels of ethylene oxide addition products in blood or other biological media with the onset of adverse health effects.

**Absorption, Distribution, Metabolism and Excretion**. The absorption of ethylene oxide administered via inhalation has been extensively studied in humans and several species of animals. Data on its absorption when administered via the oral and dermal routes would also be valuable.

Data are available on the distribution of ethylene oxide after inhalation by rats and mice. Studies that provide information on its distribution after oral and dermal administration would also be helpful. The metabolism of ethylene oxide is not completely known. Studies to further characterize the two possible pathways for the metabolism of ethylene oxide, hydrolysis and glutathione conjugation, and to identify, if possible, the species in which metabolism most resembles that in humans would be useful. It may also be helpful to characterize unidentified urinary metabolites that have been reported in several studies.

Excretion data are available only for rats and mice exposed to ethylene oxide via inhalation. Studies using the oral and dermal routes may also provide useful information.

**Comparative Toxicokinetics**. The available toxicokinetic studies are limited and it is not possible to determine if there are any major differences in the kinetics of ethylene oxide absorption, distribution, metabolism or excretion across species. It would be useful to investigate patterns of distribution, to identify target organs, to measure rates of excretion in several species, and to identify blood metabolites in humans and animals in order to understand what, if any, relationships exist. Studies in this area would also be helpful in putting the results of all available toxicity studies into perspective in terms of their relevance to the potential human health effects of ethylene oxide under similar conditions of exposure.

### 2.8.3 On-going Studies

The NTP Annual Plan for FY 1988 (NTP 1988a) indicated that ethylene oxide testing was scheduled to be ongoing or completed in the following areas:

- In vitro microbial testing for mutagenesis and genetic toxicity
- In vitro Chinese hamster ovary assay to detect chromosomal aberrations and sister chromatid exchange
- Drosophila sex-linked lethality assay
- Neurological and behavioral toxicity testing
- Inhalation testing in mice and rats to study pulmonary and immunologic toxicity

In addition, the Ethylene Oxide Industry Council (EOIC), a panel of the Chemical Manufacturers Association's CHEM STAR Division, has plans to develop, through the Chemical Industry Institute of Toxicology (CIIT) , a Physiologically-Based Pharmacokinetic (PB-PK) model for the metabolism, disposition and macromolecular reactivity of the ethylene oxide. The PB-PK model is intended to permit extrapolation to predict tissue exposures from various ethylene oxide exposure scenarios and in a variety of animal species, including humans. Eventually, a comprehensive risk assessment will combine the PB-PK model for chemical disposition and tissue dosimetry of DNA adducts with biologically-based descriptions of the cancer process. The completed PB-PK model will be used to interpret the rodent bioassay study results, to support a human risk assessment for exposure, and to interpret exposure assessment studies based on the concentration of hemoglobin adducts in exposed persons.

# 3. CHEMICAL AND PHYSICAL INFORMATION

## 3.1 CHEMICAL IDENTITY

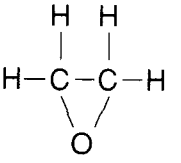
Tables 3-l lists common synonyms, trade names, and other pertinent identification information for ethylene oxide.

## 3.2 PHYSICAL AND CHEMICAL PROPERTIES

Table 3-2 lists important physical and chemical properties of ethylene oxide.

# 3. CHEMICAL AND PHYSICAL INFORMATION

**TABLE 3-1. Chemical Identity of Ethylene Oxide**

| | Value | Reference |
|---|---|---|
| Chemical name | Ethylene oxide | NLM 1988 |
| Synonyms | Oxirane; dihydro-oxirene; dimethylene oxide; epoxyethane; ethene oxide; ETO | NLM 1988 |
| Trade names | Anprolene Oxyfume; T-Gas | NLM 1988 |
| Chemical formula | $C_2H_4O$ | NLM 1988 |
| Chemical structure |  | |
| Identification numbers: | | |
| CAS Registry | 75-21-8 | NLM 1988 |
| NIOSH RTECS | KX2450000 | HSDB 1988 |
| EPA Hazardous Waste | U115 | NLM 1988 |
| OHM/TADS | 7216724 | HSDB 1988 |
| DOT/UN/NA/IMCO | UN 1040 | NLM 1988 |
| Shipping | IMCO. 2.3 | HSDB 1988 |
| HSDB | 170 | NLM 1988 |
| NCI | C50088 | NLM 1988 |

CAS = Chemical Abstracts Service; NIOSH = National Institute for Occupational Safety and Health; RTECS = Registry of Toxic Effects of Chemical Substances; EPA = Environmental Protection Agency; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; HSDB = Hazardous Substances Data Bank; NCI = National Cancer Institute.

**TABLE 3-2. Physical and Chemical Properties of Ethylene Oxide**

| Property | Value | Reference |
|---|---|---|
| Molecular weight | 44.05 | Weast 1985 |
| Color | Colorless | Verschueren 1983 |
| Physical state | Gas | Verschueren 1983 |
| Melting point | -111°C | Weast 1985 |
| Boiling point | 11°C | Verschueren 1983 |
| Density at 10°C | 0.8824 | Weast 1985 |
| Odor | Sweet, olefinic | Verschueren 1983 |
| Odor threshold: | | |
| Water | 140 mg/L | Amoore and Hautala 1983 |
| Air | 787 $mg/m^3$ | Amoore and Hautala 1983 |
| Solubility: | | |
| Water at 20°C | $1 \times 10^6$ mg/L | PHRED 1988 |
| Organic solvents | Soluble in alcohol, ether, acetone, benzene | Weast 1985 |
| Partition coefficients: | | |
| Log octanol/water | -0.22 | PHRED 1988 |
| Log $K_{oc}$ | 0.342 | PHRED 1988 |
| Vapor Pressure at 20°C | $1.095 \times 10^3$ mmHg | Verschueren 1983 |
| Henry's law constant | $7.56 \times 10^{-5}$ atm-$m^3$/mol | PHRED 1988 |
| Autoignition temperature | 429°C | HSDB 1988 |
| Flashpoint | <-18°C | HSDB 1988 |
| Flammability limits | No data | |
| Conversion factors | 1 ppm = 1.83 $mg/m^3$ | Verschueren 1983 |
| | 1 $mg/m^3$ = 0.55 ppm | Verschueren 1983 |

# 4. PRODUCTION, IMPORT, USE AND DISPOSAL

## 4.1 PRODUCTION

Ethylene oxide is a major industrial chemical and is one of the 25 highest production volume chemicals in the United States There was a gradual increase in the production volume of ethylene oxide in recent years from 1,906,800 kkg (metric tons) in 1973 to a peak of 2,610,500 kkg in 1979, and then a gradual decrease to 2,172,530 kkg in 1987.

Ethylene oxide is produced by 12 chemical companies in the United States in four states; one plant is in Illinois, one in Delaware, four in Louisiana, and six in Texas. The manufacturers of ethylene oxide are also the major users and distributors of the compound.

In the United States, all ethylene oxide is produced by the direct oxidation of ethylene by air or oxygen in the presence of a silver oxide catalyst. Another commercial production method, reaction of ethylene chlorohydrin with potassium hydroxide or calcium oxide, was phased out by 1980 (EPA 1985a; SRC 1982; SRI 1984, 1988; USITC 1988; WHO 1985).

## 4.2 IMPORT

Imports of ethylene oxide are relatively small, with amounts increasing from 1982 to 1984 from 4,300 kkg to 5,600 kkg. Exports of ethylene oxide increased substantially over the same period, from 1,500 kkg in 1982 to 11,200 kkg in 1984 (SRI 1984).

## 4.3 USE

Over 99% of the ethylene oxide produced in the United States is used as a chemical intermediate for the production of various chemicals, while less than 1% is used as a sterilant or fumigant. Ethylene oxide is used captively by manufacturers to produce ethylene glycol (64% of ethylene oxide consumption), non-ionic surfactants (11%), glycol ethers (7%), higher glycols (10%), ethanolamines (7%), and miscellaneous chemicals (l%), including choline, polyether polyols, and hydroxyethyl starch. These chemicals are found in antifreeze, textiles, detergents, solvents, polyurethane foam, medicinals, adhesives, and other products.

Relatively small amounts of ethylene oxide are used as a fumigant, a sterilant for food (spices) and cosmetics, and in hospital sterilization of surgical equipment and plastic devices that cannot be sterilized by steam. At one time, ethylene oxide was used in the production of acrylonitrile, but that process was discontinued in 1966 (EPA 1984a, 1985a; NIOSH 1981; SRC 1982; SRI 1984; WHO 1985).

## 4.4 DISPOSAL

Because ethylene oxide is listed as a hazardous substance, disposal of wastes containing this compound is controlled by a number of federal regulations (see Chapter 7). Restrictions are proposed for land disposal of ethylene oxide.

The production processes for ethylene oxide do not generate solid wastes and the waste waters are treated or recycled. The production process is a closed system; however, vent gases and fugitive emissions may contain some ethylene oxide. Waste gases may be removed from the air by scrubbers. Wastes containing ethylene oxide may be incinerated by rotary kiln or fluidized bed incineration methods (EPA 1989; HSDB 1988; SRC 1982; WHO 1985).

# 5. POTENTIAL FOR HUMAN EXPOSURE

## 5.1 OVERVIEW

Ethylene oxide is a gas used in the production of other synthetic chemicals such as ethylene glycol. Gaseous releases of ethylene oxide to the environment are the result of uncontrolled industrial emissions. Less than 1% of the industrial production of ethylene oxide is used as a fumigant and sterilizing agent for a variety of purposes and materials which include hospital equipment and certain food.

Ethylene oxide degrades in both the air and natural water via radical formation and hydrolysis, leading to the formation of glycols, and halogenated alcohols (in the presence of sodium chloride), which in turn degrade into simpler molecules such as carbon dioxide and water. The half-lives of these reactions range from a few hours to less than 15 days, depending on environmental conditions. UV-catalyzed oxidation (in the presence of oxygen and nitrogen dioxide) may also account for some of the ethylene oxide lost in the atmosphere. Ethylene oxide also degrades in wastewater treatment systems with a half-life of about 20 days.

No data are available on the fate of ethylene oxide in soil. Nonetheless, this chemical is expected to either volatilize or be leached due to its high vapor pressure and infinite solubility in water. Soil organisms may also convert it to glycols.

Data on the levels of ethylene oxide in the environment are very limited. There are no data to indicate that ethylene oxide is a common constituent of air or water sources of any type in any geographic location within the United States. Fumigated foods and sterilized hospital equipment may have initially high levels of ethylene oxide, which dissipate and/or degrade into other products within a few days. There are no data on ethylene oxide bioaccumulation in marine organisms.

No data are available to determine the general population's exposure levels to ethylene oxide. Environmental exposures may include ethylene oxide from car exhaust and tobacco smoke. The populations with potentially higher than average risk of exposure to ethylene oxide include sterilization technicians and industrial workers involved in the manufacture and/or use of ethylene oxide.

## 5.2 RELEASES INTO THE ENVIRONMENT

### 5.2.1 Air

Ethylene oxide is a synthetically produced gas used primarily in the production of other chemicals by the chemical industry. As a result, most of the releases of ethylene oxide to the atmosphere occur

during its storage and handling in industrial settings. Industrial emissions of ethylene oxide are due to uncontrolled fugitive emissions or venting with other gases. Estimates of ethylene oxide losses during production range from 1.3 to 3 million pounds (590 to 1,360 kkg) for 1978 and 1980, respectively, as reported in Bogyo et al. (1980). The same report indicated that losses of ethylene oxide during storage might have been about 143,000 pounds (65 kkg) annually.

Other sources of ethylene oxide air emissions include its production from combustion of hydrocarbon fuels and its release from commodity-fumigated materials, estimated to be about 10 million pounds (4,500 kkg) annually (Bogyo et al. 1980), and losses during disinfection of hospital equipment.

Additional nonquantified sources of air emission of ethylene oxide may be bacterial degradation products, photochemical smog, cigarette smoke and hydrocarbon combustion (Bogyo et al. 1980). Barnard and Lee (1972) and Bogyo et al. (1980) reported finding ethylene oxide in the products of n-pentane combustion, but specific concentrations were not given. EPA (1980) concluded that because pentanes are found in gasoline, significant amounts of ethylene oxide are probably released annually into the atmosphere from automobile exhaust.

WHO (1985) reported that the estimated air emissions due *to* agricultural fumigation and disinfection of medical products were about 2% (about 53,000 tons or 48,000 kkg) of the total ethylene oxide production, which was estimated at about 2.4 million tons (2.2 million kkg) in the United States during 1980. The use of ethylene oxide in hospitals was estimated to be less than 0.02% of the total United States production, or about 500 tons (450 kkg) during 1976 (Glaser 1979).

### 5.2.2 Water

Ethylene oxide discharges into water also appear to be mostly industry-related. According to EPA (1982a), industrial producers of ethylene oxide estimated that about 800,000 pounds of this compound were discharged into wastewater treatment systems each year in the United States. EPA (1982a) also reported that ethylene oxide was not detected in treated industrial wastewaters discharged into waterways. WHO (1985) also indicated that biological treatment of wastewaters containing ethylene oxide appears to be successful in the removal of this chemical from reaching waterways. Contract Laboratory Program (CLP) statistical data from November 1988 appear to verify this assertion. A review of this data base indicated that of 5,300 water samples collected from 862 sites, only two sites had samples contaminated with ethylene oxide, including a surface water site with a concentration of 28 µg/L and a groundwater site with 21 µg/L (mean of two samples) (CLPSD 1988).

### 5.2.3 Soil

No discharges of ethylene oxide into the soil are reported in the literature. Although ethylene oxide is a potent fumigant and will kill fungi, viruses, and insects, it is not approved as a soil fumigant. However, since ethylene oxide is infinitely soluble in water, it is likely that the soil environment is exposed to this chemical as a result of the atmospheric scrubdown of rainfall and some uncontrolled discharges of liquid wastes containing this chemical. The Contract Laboratory Program Statistical Database (CLPSD 1988) reported that only six soil samples collected from four different sites, out of 862 total sites, had quantifiable amounts of ethylene oxide (mean: 22 µg/kg) (CLPSD 1988).

### 5.2.4 Other Sources

Solid or liquid wastes containing measurable amounts of ethylene oxide, as defined in Part 261 of CFR 40 (1984), can be classified as hazardous with ignitable and toxic properties. However, according to Bogyo et al. (1980), no specific wastes containing large amounts of ethylene oxide associated with the manufacture of ethylene oxide have been identified.

## 5.3 ENVIRONMENTAL FATE

### 5.3.1 Transport and Partitioning

The primary mode of transport of ethylene oxide is via air emissions into the atmosphere. At atmospheric pressure and room temperature, ethylene oxide exists as a gas due to its very high vapor pressure (1,095 mm Hg at 20°C) and low boiling point (10.4° C) (WHO 1985).

The reported log of the octanol/water partition coefficient ($K_{ow}$) for ethylene oxide is -0.30 (Hansch and Leo 1979), indicating that ethylene oxide is a very polar chemical. From its chemical and physical properties, it can be inferred that ethylene oxide in soil will volatilize as water evaporates, leach through the soil, or be removed by runoff during rainstorms. It is, therefore, unlikely that ethylene oxide will accumulate in soils or sediments. No data on the accumulation and/or fate of ethylene oxide in the soil environment are available.

EPA (1984b) indicated that there are no data on the bioaccumulation of ethylene oxide in animal tissue.

# 5. POTENTIAL FOR HUMAN EXPOSURE

Although ethylene oxide dissolves in water in any proportion, it also has the tendency to escape (volatilize) due in part to its high vapor pressure. Conway et al. (1983) reported that about 95% of ethylene oxide mixed with water volatilizes within 4 hours (its half-life is about 1 hour).

Ethylene oxide is used as a fumigant for some food commodities. The Environmental Protection Agency (198413) reported the use of ethylene oxide to fumigate cocoa, flour, dried fruits, dehydrated vegetables, fish, and bone meal. However, Meister (1988) listed ethylene oxide as a fumigant and sterilizing agent for only three food products: spices, black walnuts and copra. Currently, EPA has set tolerances for residues on these three items (see Table 7-l).

### 5.3.2 Transformation and Degradation

#### 5.3.2.1 Air

There is limited information on the fate of ethylene oxide in the atmosphere. EPA (1984b) reported that the most probable path of atmospheric degradation of ethylene oxide is oxidation via free-radical formation, and estimated its half-life in air at 25°C to range from 69 to 149 days, based on data (rate constants and the concentration of OH radicals) obtained by Fritz et al. (1982).

Ethylene oxide also reacts with atmospheric oxygen in the presence of nitrogen dioxide and W light. Studies by Gomer and Noyes (1950) indicated that photocatalyzed chemical decomposition of ethylene oxide would result in the formation of methane, ethane, hydrogen, carbon dioxide, and some smaller amounts of simple aldehydes. Jaffe (1971) examined ethylene oxide decomposition products and postulated that ethylene oxide reacts with W-excited nitrogen dioxide molecules, eventually leading to the formation of acetaldehyde, methane, and carbon dioxide. According to EPA (1984b), measurements of the absolute rate constant, determined to be about 6 x $l0^{-l6}$ $cm^3$/mole/sec by Bogan and Hand (1978) for the reaction between oxygen and ethylene oxide at 27° C, indicate an ethylene oxide half-life of about 1,400 years, assuming an atmospheric oxygen concentration of 25,000 molecules/$cm^3$. Bogan and Hand (1978) determined the final products of oxygen-W catalyzed ethylene oxide oxidation to be hydrogen, water, carbon monoxide, carbon dioxide, and formaldehyde. Joshi et al. (1982) determined ethylene oxide to have a low reactivity with atmospheric nitrogen dioxide under W radiation and at 25° C. Using ethylene oxide:nitrogen dioxide ratios similar to those found in urban and rural air, these researchers reported the ethylene oxide half-life to be more than 53 hours.

In summary, the few available studies on the photodecomposition of ethylene oxide in the atmosphere suggest that it undergoes measurable rates of degradation into simpler products. However, laboratory estimates of the half-life of ethylene oxide in the atmosphere vary widely.

**5.3.2.2 Water**

Ethylene oxide hydrolyzes in water to form glycols (Long and Pritchard 1956). Bogyo et al. (1980) reported the hydrolysis rate constant (acid catalyzed) to be about 19.9 x $l0^{-3}$ L/mol-sec at 30° C. According to the same report, all epoxides, including ethylene oxide, can react with anions such as chloride and bromide in aqueous solutions, forming halogenated alcohols. Conway et al. (1983) determined the half-life of ethylene oxide to range from 12 to 14 days in sterile, deionized and natural river water. They also reported that increased water salinity (up to 3% sodium chloride) decreased the half-life of ethylene oxide to 9 days (Conway et al. 1983), and produced ethanediol and chloroethanol.

According to Anbar and Neta (1967), the degradation of ethylene oxide in water via hydroxyl radicals is very slow, with a computed half-life of about 50 years.

Conway et al. (1983) reported that the half-life measurements for ethylene oxide in sterile and natural river water were not appreciably different. This may be because hydrolytic degradation of ethylene oxide is more rapid than biodegradation of this compound in aqueous media.

**5.3.2.3 Soil**

No studies on the degradation of ethylene oxide in the soil environment have been located. However, it is likely that ethylene oxide would be found in both the water and vapor phases of the soil environment due to its high vapor pressure and very low octanol/water partition coefficient. Thus, ethylene oxide in the soil is likely to undergo at least some degradation via the same types of mechanisms as those that predominate in aquatic environments.

**5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT**

**5.4.1 Air**

There is very little information on ethylene oxide levels in air, but the data available indicate that ethylene oxide does not seem to be a contaminant in ambient air. Hunt et al. (1986) conducted an air quality survey in Texas during 1985 and 1986. Quarterly state and local air quality measurements indicated that ethylene oxide was not detected

at concentrations above the detection limit of 0.194 ng/$m^3$. These authors also reported that ethylene oxide was not detected in a comprehensive air quality survey in the state of California.

### 5.4.2 Water

There are very limited data on the presence or absence of ethylene oxide in water (drinking water supplies, groundwater, etc.) on a national scale. EPA (1984b) reported a survey showing ethylene oxide at a concentration of 2 mg/L in the effluent of a chemical plant in Bandenburg, Kentucky.

### 5.4.3 Soil

No data are available on the presence or absence of any significant levels of ethylene oxide in soil. However, DeBont and Albers (1976) reported that ethylene oxide is produced by the metabolism of ethylene by an ethylene-oxidizing bacterium. Also, ethylene is a relatively common volatile hydrocarbon in wet soil, where it can be produced by several species of fungi, bacteria, and actinomycetes (Alexander 1977). Therefore, small but constant levels of ethylene oxide may be present in soils under wet conditions. No data are available on ethylene oxide in soils resulting from uncontrolled releases of ethylene oxide liquid waste or from atmospheric depositions of any kind.

### 5.4.4 Other Media

Ethylene oxide may be found in tobacco and some food as a result of its use as a fumigant and a sterilizing agent. The Farm Chemicals Handbook (Meister 1988) lists ethylene oxide for use only as a fumigant on three food products: spices, black walnuts and copra. However, ethylene oxide may have been used (and may still be used) as a fumigant for tobacco and some cosmetics. Measurable amounts of ethylene oxide were detected in both fumigated and unfumigated tobacco and its smoke; the ethylene oxide concentration in smoke from unfumigated tobacco was 1 μg/g (Bogyo et al. 1980).

Residual ethylene oxide may be found in foods temporarily, following fumigation. Scudamore and Heuser (1971) reported that ethylene oxide may react with water and inorganic halides (chloride and bromide) from foods and produce glycols and halohydrins. The same researchers concluded that the persistence or disappearance of ethylene oxide and its byproducts in fumigated commodities depends on the grain size, type of foods, aeration procedures, temperature, and storage and cooking conditions. According to Scudamore and Heuser (1971), most experimentally fumigated commodities had levels of ethylene oxide below 1 ppm after 14 days in normal storage conditions. No residues of ethylene oxide were found in commercially fumigated flour or tobacco.

Rajendran and Muthu (1981) reported that concentrations of ethylene oxide in 24-hour aerated foods (wheat, rice, spices, dates and peas) (following a 24-hour fumigation period) ranged from 0 to 3.5 ppm. IARC (1976) indicated that food fumigated with ethylene oxide generally had negligible levels of ethylene oxide within a few hours after fumigation, due primarily to loss by volatilization. However, in spices, ethylene oxide levels ranging from 53 to 116 mg/kg (ppm) and about 25 mg/kg (ppm) at 2 days and 26 days after fumigation, respectively have been reported (WHO 1985).

**5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE**

The general population's exposure to ethylene oxide may occur via inhalation and food ingestion. There is no information to indicate that ethylene oxide is a common contaminant of drinking water supplies.

Since ethylene oxide is used as a sterilant and fumigant, the potential locations of contaminated air include hospitals (ethylene oxide is commonly used to sterilize medical equipment), libraries, museums, and laboratories. Sources include vapors from certain foods, clothing, cosmetics, and beekeeping equipment (NIOSH 1981).

Sources of exposure of the general population to ethylene oxide may be the by-products of gasoline combustion and cigarette smoke. There is also some evidence that some foods such as flour and spices retain measurable ethylene oxide and by-products several months after fumigation. Ethylene oxide exposure levels of the general population via air, water, or foods have not been found in the available literature or from national surveys and have not been estimated.

Occupational groups exposed to ethylene oxide include workers in ethylene oxide manufacturing or processing plants, sterilization technicians, workers involved in the fumigation of foods, clothing, and cosmetics, and indoor fumigators. OSHA (1988b) estimates that 67,728 workers were exposed to ethylene oxide in 1988. OSHA and ACGIH have established an 8-hour workshift exposure limit of 1 ppm (ACGIH 1986; OSHA 1988b). However, NIOSH (1985b) recommends the exposure level to be 0.1 ppm or less over 8 hours, not to exceed 5 ppm for more than 10 minutes. The odor threshold of ethylene oxide in air is 430 ppm (Amoore and Hautala 1983), which is well above the OSHA PEL (1 ppm). Thus, worker exposure to ethylene oxide can be determined only through routine air monitoring.

Hospital workers and patients may be exposed to residual levels of ethylene oxide from the sterilization of hospital equipment. Some sterilized plastics may retain concentrations of ethylene oxide ranging from 3 to 443 mg/kg (ppm) even after seven days of aeration (WHO 1985).

Other medical equipment such as adhesive dressings and cotton wool pads may also retain ethylene oxide at 2 mg/kg (ppm) or less for 7 to 8 days after sterilization (Dauvois et al. 1982).

## 5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Technicians involved in routine disinfection of medical equipment in hospitals may be exposed to relatively high levels of ethylene oxide. Studies of worker exposures in five hospital sterilization rooms in the United States indicate that the time-averaged exposures range from less than 0.1 to 4.3 ppm, with peaks as high as 795 ppm (Hansen et al. 1984). Brugnone et al. (1985) have reported alveolar concentrations of ethylene oxide to be about 75% of the environmental concentrations of ethylene oxide in a hospital sterilizing unit (0.1 to 7.8 ppm); the OSHA timeweighted-average limit is 1 ppm and the 15-minute excursion limit is 5 mm. Occupational exposure levels estimated by OSHA (1988b) range from 0.08 to 3.97 ppm (8-hour TWA) and 0.24 to 32.2 ppm (15-minute) (see Table 7-l).

According to Flores (1983), workers in chemical manufacturing plants in the United States may also be exposed to high levels of ethylene oxide in air; typical average daily exposure levels ranging from 0.2 to 2.2 ppm were measured during 1979. Some isolated incidents of very high (peak) worker exposures have also occurred as a result of plant breakdowns (Flores 1983; Thiess et al. 1981). It is expected that occupational exposures will be reduced because of recent OSHA regulations (OSHA 1988b).

## 5.7 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of ethylene oxide is available. Where adequate information is not available, ATSDR, in conjunction with the NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of ethylene oxide.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met would reduce or eliminate the uncertainties of human health assessment. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

### 5.7.1 Identification of Data Needs

**Physical and Chemical Properties**. Ethylene oxide is commonly used in the synthesis of many other products, and its basic physical and chemical properties are well known and documented (see Chapter 3). However, data on the properties related to its fate in the environment are less reliable or are totally lacking. For example, there are no recent studies that verify the degradation rates of ethylene oxide in air. Also, there is only one study, Conway et al. (1983), that provides data on the rates of degradation and on water to air transfer of ethylene oxide during the 1980s. There are no data on the fate and transport of ethylene oxide in the soil environment. Since ethylene oxide is a gas and a polar solute in water, these types of data are particularly important for media with water-saturated or near saturated conditions, such as landfills. Data on the rates of microbial degradation and toxicity of ethylene oxide in soils are needed.

**Production, Use, Release, and Disposal**. Available production, use, release, and disposal data indicate that most ethylene oxide manufactured in the United states is consumed in the synthesis of other chemicals. However, current quantitative data on the amounts of ethylene oxide released to the environment during ethylene oxide production and use are sparse. This information would be helpful in evaluating the effect of industrial practices on environmental levels of ethylene oxide.

According to the Emergency Planning and Community Right to Know Act of 1986 (EPCRTKA), (§313), (Pub. L. 99-499, Title III, §313), industries are required to submit release information to the EPA. The Toxics Release Inventory (TRI), which contains release information for 1987, became available in May of 1989. This database will be updated yearly and should provide a more reliable estimate of industrial production and emission.

**Environmental Fate**. Data on the fate of ethylene oxide in the atmosphere are limited. The half-life estimates of this chemical should be refined and include measurements in the stratosphere. Since ethylene oxide has been shown to slowly react with oxygen, stratospheric measurements should also include data on the potential impact of ethylene oxide on the ozone layer. Data on the fate of ethylene oxide in the water environment are available but are very limited. More information is needed on the rates of transport of ethylene oxide between water and air. Also, more data on the rates of biodegradation of ethylene oxide in natural environments such as lakes, rivers, groundwater, and soil are needed. Data on the fate of ethylene oxide in

the soil environment would be useful. Because all of the ethylene oxide that does not degrade in the atmosphere eventually returns to the soil and water, data on transport and degradation of ethylene oxide would be helpful in determining its potential contamination of water supplies.

**Bioavailability from Environmental Media**. Ethylene oxide has been shown to be absorbed following inhalation of contaminated air. However, there are no data on absorption after oral or dermal administration of this compound. No information was located on the bioavailability of ethylene oxide from contaminated water, soil, or plant material. These data would be useful in determining potential exposure levels for organisms (humans, animals, and plants) that may have contact with ethylene oxide in these media.

**Food Chain Bioaccumulation**. WHO (1985) has concluded that ethylene oxide will not bioaccumulate in animals since it is readily metabolized via hydrolysis and glutathione conjugation and excretion. This conclusion was based on the review of several studies in both humans and animals (terrestrial and marine species). No data are available in the literature that indicate that ethylene oxide bioaccumulates in plants. Research on the possible mechanisms of plant uptake, absorption and assimilation of ethylene oxide would be useful since it may be a common and natural constituent in the soil environment, as discussed in Section 5.4.3, and because it is also an atmospheric pollutant.

**Exposure Levels in Environmental Media**. Neither environmental monitoring nor background data are available for ethylene oxide in soil, air, or water. Ambient concentrations of ethylene oxide are not known in high density urban and industrial areas which have potentially large sources of ethylene oxide such as car exhaust or point sources (industrial). These data would be helpful in determining the ambient concentrations of ethylene oxide so that exposure estimates can be made for the general population.

**Exposure Levels in Humans**. Available data indicate that some work environments provide continuous exposure to ethylene oxide at levels that may exceed OSHA regulations. Data on other industrial workers such as building and agricultural fumigators and construction workers would be useful.

Estimates of the exposure levels of the general population would also be helpful.

**Exposure Registries**. No exposure registries for ethylene oxide were located. This compound is not currently one of the compounds for which a subregistry has been established in the National Exposure Registry. The compound will be considered in the future when chemical

selection is made for subregistries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to the exposure to this compound.

### 5.7.2 On-going Studies

No on-going studies related to the potential for human exposure to ethylene oxide were located in the available literature.

# 6. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting and/or measuring and monitoring ethylene oxide in environmental media and in biological samples. The intent is not to provide an exhaustive list of analytical methods that could be used to detect and quantify ethylene oxide. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used to detect ethylene oxide in environmental samples are the methods approved by federal agencies such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by a trade association such as the Association of Official Analytical Chemists (AOAC) and by the American Public Health Association (APHA). Additionally, analytical methods are included that refine previously used methods to obtain lower detection limits, and/or to improve accuracy and precision.

## 6.1 BIOLOGICAL MATERIALS

Ethylene oxide is relatively reactive in biological systems and undergoes chemisorption to biological materials to form addition products with compounds that contain hydroxyl, phenolic, carbonyl, amino, or sulfhydryl groups. Therefore, it is usually necessary in biological samples to determine these addition products. Examples of such products that are determined to measure in vivo exposure to ethylene oxide are N-(2-hydroxyethyl)histidine and N-(2-hydroxyethyl)valine (Bailey et al. 1987; Farmer et al. 1986). Methods have been published for the determination of ethylene oxide in blood and alveolar air (Brugnone et al. 1986).

As with other materials in biological samples, samples containing ethylene oxide, its reaction products, and its metabolites must undergo some form of sample cleanup prior to analysis. Cleanup is a separation procedure that ideally isolates the analyte in a mixture, concentrates it, and eliminates most of the sample matrix. The chemical and biochemical reactivity of ethylene oxide complicates the cleanup of the biological samples in which it is contained.

Methods for the determination of ethylene oxide and its reaction products in biological samples are summarized in Table 6-l.

## 6.2 ENVIRONMENTAL SAMPLES

Ethylene oxide in environmental samples is most commonly determined after derivatization to stable, volatile halogenated species, particularly 2-bromoethanol (Cummins et al. 1987), followed by gas chromatography with an electron capture detector (GC/ECD) for

halogenated derivatives, or by gas chromatography/mass spectrometry (GC/MS) (Farmer et al. 1986). Infrared spectrometry may also be used (APHA 1985). A sensitive method for ethylene oxide determination has been published in which the brominated compound is formed in a standard solution of propylene oxide and the chromatographic peak ratios for the brominated ethylene oxide and propylene oxide derivatives are compared (Kikuchi et al. 1988).

The most straightforward means of determining ethylene oxide in air is direct analysis of air samples without analyte collection. This has been done with a portable gas chromatograph using clean air as a carrier gas and a photoionization detector (PID) for detection (Bond and Dumas 1982; Collins and Barker 1983). Ethylene oxide can be concentrated from air samples with a solid sorbent, desorbed with carbon disulfide, and measured by gas chromatography (NIOSH 1977). A major problem with this approach is the reaction of ethylene oxide with moisture or with halides, resulting in loss of the analyte. However, this reaction tendency can be used to advantage by derivatization of ethylene oxide to 2-bromoethanol on a collection column treated with hydrobromic acid, followed by elution of the product with benzene/carbon disulfide and measurement by GC/ECD. In the analysis of ethylene oxide in air by direct GC/ECD determination of 2-bromoethanol formed by reaction of ethylene oxide with HBr on HBr-coated charcoal, reproducibility problems have been encountered as a consequence of interference by unreacted HBr (Cummins et al. 1987). This interference has been overcome by forming a derivative of 2-bromoethanol by reaction with heptafluorobutyrylimidazole and measuring the product with GC/ECD (Cummins et al. 1987).

A method for the determination of ethylene oxide in water and in soil by partition infrared spectrophotometry has been reported (APHA 1985; Environment Canada 1985).

Methods for the determination of ethylene oxide in environmental samples are summarized in Table 6-2.

## 6.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of ethylene oxide is available. Where adequate information is not available, ATSDR, in conjunction with the NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of ethylene oxide.

**TABLE 6-1. Analytical Methods for Determining Ethylene Oxide in Biological Materials**

| Sample Matrix | Sample Preparation | Analytical Method | Sample Detection Limit | Accuracy | Reference |
|---|---|---|---|---|---|
| Blood | No data | GC | No data | No data | Brugnone et al. 1986 |
| Alveolar air | No data | GC | No data | No data | Brugnone et al. 1986 |
| Hemoglobin adducts from blood | Separation of erythrocytes, derivatization of N-(2-hydroxy ethyl)histidine or N-(2-hydroxyethyl)valine | GC/MS | 2 ng/mL | No data | Farmer et al. 1986 |
| Hemoglobin | Separation of erythrocytes, derivatization of N-(2-hydroxy-ethyl)histidine | HRGC/MS | No data | No Data | Bailey et al. 1987 |

GC = gas chromatography; MS = mass spectrometry; HRGC = High Resolution Gas Chromatography.

**TABLE 6-2. Analytical Methods for Determining Ethylene Oxide in Environmental Samples**

| Sample Matrix | Sample Preparation | Analytical Method | Sample Detection Limit | Accuracy | Reference |
|---|---|---|---|---|---|
| Air | Direct injection of air sample | GC/FID | <1 ppb by volume | No data | Bond and Dumas 1982 |
| Air | Direct injection of air sample | GC/FID | No data | No data | Collins and Barker 1983 |
| Air | Collect on HBr-coated charcoal tube forming 2-bromoethanol, desorb with dimethylformamide to produce volatile derivative | GC/ECD | 0.1 ppm (volume) | 97% Rec. of 2 ppm | Cummins et al. 1987 |
| Air | Collect on charcoal, desorb with carbon disulfide | GC | No data | No data | NIOSH 1977 |
| Air | Derivatize to 2-bromoethanol | GC/ECD | 0.45 μg/ sample | No data | NIOSH 1987 |
| Soil | No data | Partition infrared | >40 ppm | No data | APHA 1985 |
| Water | No data | Partition infrared | 40-400 ppm | NR | APHA 1985 |

GC = gas chromatography; FID = flame ionization detector; ECD = electron captive detector; Rec. = recovery; NR = not reported.

# 6. ANALYTICAL METHODS

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met would reduce or eliminate the uncertainties of human health assessment. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

### 6.3.1 Identification of Data Needs

**Methods for Determining Biomarkers of Exposure and Effect**. Ethylene oxide is rapidly metabolized in biological systems and tends to form addition products such as N-(2-hydroxyethyl)histidine and N-(2-hydroxyethyl)valine. Although existing methodology is adequate to provide qualitative evidence of exposure, it would be useful to have the means to determine corresponding levels of exposure to ethylene oxide from the levels of these substances in biological media.

There are currently no available methods that can be used to associate the levels of ethylene oxide in biological media with the onset of adverse health effects. Further information in this area would be useful. It is not known if existing methods are sensitive enough to measure background levels of these compounds in the blood, urine or other biological media of the general population.

Supercritical fluid extraction coupled with supercritical fluid chromatography and immunoassay analysis are two areas of intense current activity from which substantial advances in the determination of ethylene oxide metabolites in biological samples can be anticipated. The two techniques are complementary in that supercritical fluid extraction is especially promising for the removal of analytes from sample materials and immunoassay analysis is very analyte selective and sensitive (Vanderlaan 1988). This combination has been described for the determination of sulfonylurea herbicides and their metabolites in complex media including soil, plant materials, and a cell culture medium (McNally and Wheeler 1988). This technique should be applicable to many other toxicologically and environmentally significant analytes including ethylene oxide metabolites.

**Methods for Determining Parent Compounds and Degradation Products in Environmental Media.** Methods are available for the determination of ethylene oxide in a clean, dry, gas-phase matrix. However, because of ethylene oxide's reactivity, its determination in air, water and soil matrices is difficult. The development of methods for analysis of ethylene oxide that have improved sensitivity and selectivity would be useful.

# 6. ANALYTICAL METHODS

There is an ongoing effort to develop a "Master Analytical Scheme" for organic compounds in water (Michael et al. 1988). The overall goal is the development of technology capable of detecting and measuring organic compounds present at levels of 0.1 µg/L in drinking water, 1 µg/L in surface water, and 10 µg/L in effluent waters. In addition to volatile compounds (bp < 150° C), analytes are to include numerous semivolatile compounds and some compounds that are sparingly soluble in water.

Determination of the degradation products of ethylene oxide in environmental media is difficult, not because of analytical problems, but because the fundamental environmental chemistry of these compounds in water, soil, air, and biological systems is not known.

The development of analytical methods to measure ethylene oxide in situ in water and other environmental media could contribute to environmental studies of this compound.

### 6.3.2 On-going Studies

Studies designed to improve methods for the determination of environmental contaminants may provide refinements and improvements in the determination of ethylene oxide. The current high level of activity in supercritical fluid extraction of solid and semisolid samples should yield improved recoveries and sensitivities for the determination of ethylene oxide and its environmental degradation products in solid wastes, and these compounds should be amenable to supercritical fluid chromatographic analysis. Immunoassay analysis (Vanderlaan 1988) is an area of intense current activity from which substantial advances in the determination of ethylene oxide in environmental samples can be anticipated.

# 7. REGULATIONS AND ADVISORIES

Because of its potential to cause adverse health effects in exposed persons, a number of regulations and advisories have been established for ethylene oxide by various international, national, and state agencies. These regulations and advisories are summarized in Table 7-l.

# 7. REGULATIONS AND ADVISORIES

**TABLE 7-1. Regulations and Guidelines Applicable to Ethylene Oxide**

| Agency | Description | Value | Reference |
|---|---|---|---|
| IARC | Carcinogenic classification | Group 2A[a] | IARC 1987 |
| | **National** | | |
| Regulations: | | | |
| a. Air: | | | |
| EPA OAQPS | Hazardous air pollutant notice of intent to list | No data | EPA 1985b |
| OSHA | PEL | | |
| | TWA | 1 ppm | OSHA 1988b |
| | Excursion limit (15 min) | 5 ppm | 29 CFR 1910.1047 |
| b. Nonspecific media: | | | |
| EPA OERR | Reportable quantity | 1 lb | EPA 1985c (40 CFR 302.4) |
| | Reportable quantity (proposed) | 10 lb | EPA 1987a |
| | Extremely hazardous substance threshold planning quantity | 1000 lb | EPA 1987b (40 CFR 355) |
| EPA OPP | Tolerances for residues on raw agricultural commodities | 50 ppm | 40 CFR 180.151 |
| EPA OSW | Hazardous waste constituent (Appendix VIII) | No data | EPA 1980 (40 CFR 261) |
| | Land disposal restrictions | No data | EPA 1989 |
| EPA OTS | Health and safety data reporting rule | No data | EPA 1988a (40 CFR 716.120) |
| | Preliminary assessment information rule | No data | EPA 1982b (40 CFR 712.30) |
| | Toxic chemical release reporting | No data | EPA 1988b (40 CFR 372) |
| FDA | Fumigant for spices permitted | | 21 CFR 193.200 |
| | Tolerance for residue in ground spices | 50 ppm | |
| | Maximum residue limits in medical devices (proposed) | 5-250 ppm | FDA 1978 |
| | Maximum residue limits in drug products (proposed) | 5-35 ppm | FDA 1978 |
| | Maximum daily exposure level to residues in drug products (proposed) | 30 μg/kg/day 30 days | FDA 1978 |
| Guidelines: | | | |
| a. Air: | | | |
| ACGIH | TLV TWA | | ACGIH 1986 |
| | Suspected human carcinogen | 1 ppm ($2\ mg/m^3$) | |
| NIOSH | IDLH | 800 ppm | NIOSH 1985b |
| | Recommended exposure limits | | |
| | TWA | <0.1 ppm | NIOSH 1988 |
| | Ceiling (10 min/day) | 5 ppm | |
| b. Other: | | | |
| EPA | Carcinogenic classification group B1[b] | | EPA 1985a |

# 7. REGULATIONS AND ADVISORIES

**TABLE 7-1 (Continued)**

| Agency | Description | Value | Reference |
|---|---|---|---|
| | **State** | | |
| Regulations: | | | |
| a. Air: | Acceptable ambient air concentration | | NATICH 1988 |
| Connecticut | | 20 $\mu g/m^3$ (8 hr) | |
| Indiana | | 450 $\mu g/m^3$ (8 hr) | |
| Nevada | | 0.048 $mg/m^3$ (8 hr) | |
| New York | | 6.67 $\mu g/m^3$ (1 yr) | |
| North Carolina | | 0.10 $\mu g/m^3$ (annual) | |
| North Dakota | | 0.0 (bact) | |
| Pennsylvania (Philadelphia) | | 4.87 $\mu g/m^3$ (1 yr) | |
| Rhode Island | | 0.01 $\mu g/m^3$ (annual) | |
| South Carolina | | 10 $\mu g/m^3$ (24 hr) | |
| South Dakota | | 20 $\mu g/m^3$ (8 hr) | |
| Virginia | | 20 $\mu g/m^3$ (24 hr) | |

[a] Group 2A: Probably carcinogenic to humans.
[b] Group B1: Probable human carcinogen.

IARC = International Agency for Research on Cancer; EPA = Environmental Protection Agency; OAQPS = Office of Air Quality, Planning and Standards; OSHA = Occupational Safety and Health Administration; PEL = Permissible Exposure Limit; TWA = Time-Weighted Average; OAQPS = Office of Air Quality Planning and Standards; OERR = Office of Emergency and Remedial Response; OPP = Office of Pesticide Programs; OSW = Office of Solid Wastes; OTS = Office of Toxic Substances; FDA = Food and Drug Administration; ACGIH = American Conference of Governmental Industrial Hygienists; TLV = Threshold Limit Value; NIOSH = National Institute for Occupational Safety and Health; IDLH = Immediately Dangerous to Life or Health Level.

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# 9. GLOSSARY

**Acute Exposure** -- Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

**Adsorption Coefficient ($K_{oc}$)** -- The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

**Adsorption Ratio ($K_d$)** -- The amount of a chemical adsorbed by a sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

**Bioconcentration Factor (BCF)** -- The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same time period.

**Cancer Effect Level (CEL)** -- The lowest dose of chemical in a study or group of studies which produces significant increases in incidence of cancer (or tumors) between the exposed population and its appropriate control.

**Carcinogen** -- A chemical capable of inducing cancer.

**Ceiling value (CL)** -- A concentration of a substance that should not be exceeded, even instantaneously.

**Chronic Exposure** -- Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

**Developmental Toxicity** -- The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

# 9. GLOSSARY

**Embryotoxicity and Fetotoxicity** -- Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurred. The terms, as used here, include malformations and variations, altered growth, and in utero death.

**EPA Health Advisory** -- An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

**Immediately Dangerous to Life or Health (IDLH)** -- The maximum environmental concentration of a contaminant from which one could escape within 30 min without any escape-impairing symptoms or irreversible health effects.

**Intermediate Exposure** -- Exposure to a chemical for a duration of 15-364 days, as specified in the Toxicological Profiles.

**Immunologic Toxicity** -- The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

**In Vitro** -- Isolated from the living organism and artificially maintained, as in a test tube.

**In Vivo** -- Occurring within the living organism.

**Lethal Concentration($_{LO}$) ($LC_{LO}$)** -- The lowest concentration of a chemical in air which has been reported to have caused death in humans or animals.

**Lethal Concentration($_{50}$) ($LC_{50}$)** -- A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

**Lethal Dose ($_{LO}$) ($LD_{LO}$)** -- The lowest dose of a chemical introduced by a route other than inhalation that is expected to have caused death in humans or animals.

**Lethal Dose($_{50}$) ($LD_{50}$)** -- The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

# 9. GLOSSARY

**Lethal Time($_{50}$) ($LT_{50}$)** -- A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

**Lowest-Observed-Adverse-Effect Level (LOAEL)** -- The lowest dose of chemical in a study or group of studies which produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

**Malformations** -- Permanent structural changes that may adversely affect survival, development, or function.

**Minimal Risk Level (MRL)** -- An estimate of daily human exposure to a chemical that is likely to be without an appreciable risk of deleterious effects (noncancerous) over a specified duration of exposure.

**Mutagen** -- A substance that causes mutations. A mutation is a change in the genetic material in a body cell. Mutations can lead to birth defects, miscarriages, or cancer.

**Neurotoxicity** -- The occurrence of adverse effects on the nervous system following exposure to a chemical.

**No-Observed-Adverse-Effect Level (NOAEL)** -- That dose of chemical at which there are no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

**Octanol-Water Partition Coefficient ($K_{ow}$)** -- The equilibrium ratio of the concentrations of a chemical in n-octanol and water, in dilute solution.

**Permissible Exposure Limit (PEL)** -- An allowable exposure level in workplace air averaged over an 8-hour shift.

**$q_1$*** -- The upper-bound estimate of the low-dose slope of the dose response curve as determined by the multistage procedure. The $q_1$* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually µg/L for water, mg/kg/day for food, and µg/$m^3$ for air).

# 9. GLOSSARY

**Reference Dose (RfD)** -- An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the NOAEL (from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

**Reportable Quantity (RQ)** -- The quantity of a hazardous substance that is considered reportable under CERCLA. Reportable quantities are: (1) 1 lb or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Sect. 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

**Reproductive Toxicity** -- The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

**Short-Term Exposure Limit (STEL)** -- The maximum concentration to which workers can be exposed for up to 15 min continually. No more than four excursions are allowed per day, and there must be at least 60 min between exposure periods. The daily TLV-TWA may not be exceeded.

**Target Organ Toxicity** -- This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

**Teratogen** -- A chemical that causes structural defects that affect the development of an organism.

**Threshold Limit Value (TLV)** -- A concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a TWA, as a STEL, or as a CL.

**Time-weighted Average (TWA**) -- An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

**Toxic Dose ($TD_{50}$)** -- A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

# 9. GLOSSARY

**Uncertainty Factor (UF)** -- A factor used in operationally deriving the RfD from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of humans, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using LOAEL data rather than NOAEL data. Usually each of these factors is set equal to 10.

# APPENDIX

APPENDIX

## PEER REVIEW

A peer review panel was assembled for ethylene oxide. The panel consisted of the following members: DK. Martin Alexander, Professor, Department of Agronomy, Cornell University; Dr. Richard Thomas, Consulting Toxicologist, Thomas and Thomas Technologies, Inc.; and Dr. Mohammed Mustafa, School of Public Health, University of California. These experts collectively have knowledge of ethylene oxide's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in the Superfund Amendments and Reauthorization Act of 1986, Section 110.

A joint panel of scientists from ATSDR and EPA has reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply their approval of the profile's final content. The responsibility for the content of this profile lies with the Agency for Toxic Substances and Disease Registry.