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) 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) 50 CEL (F:mammary) 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

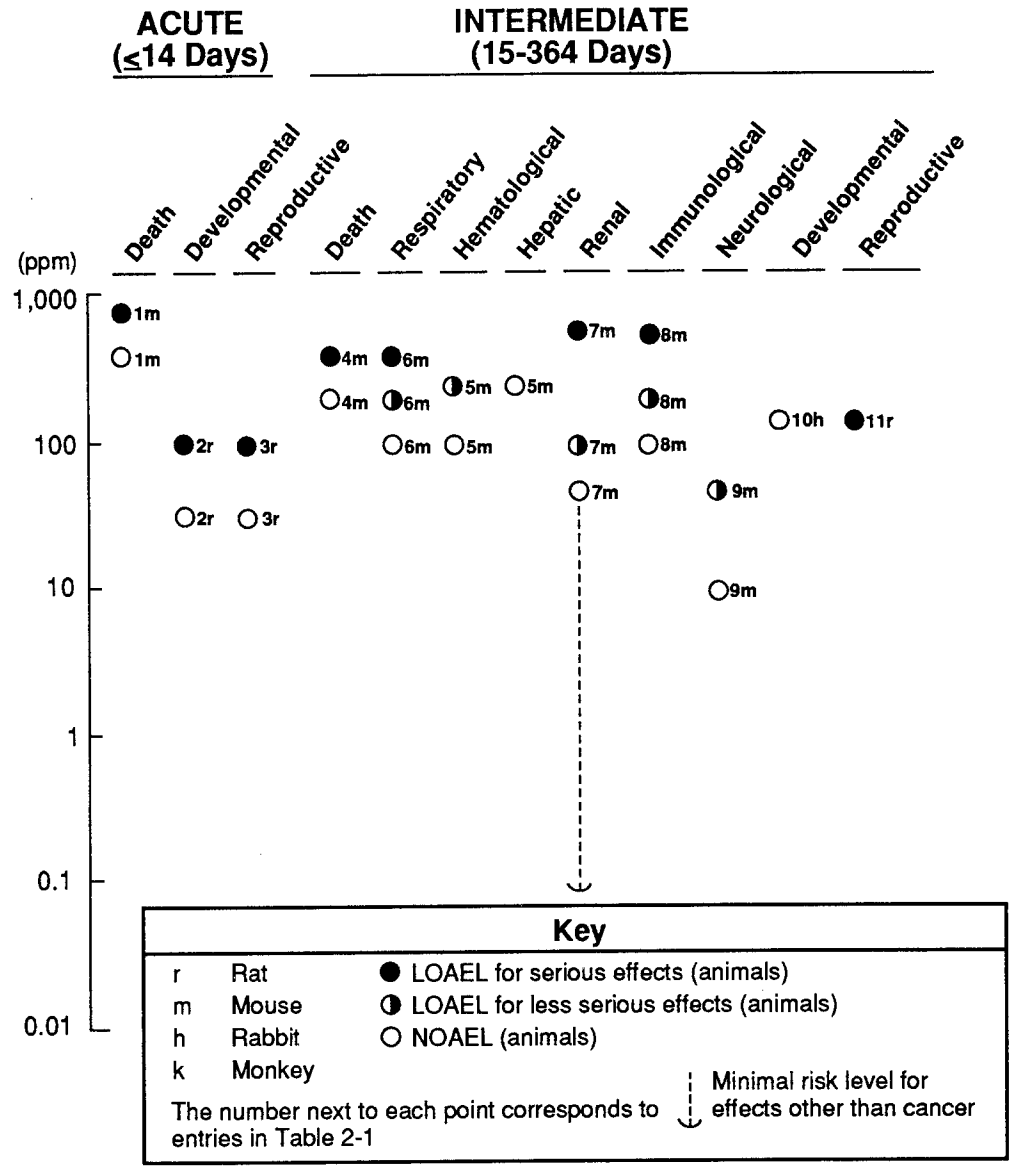

FIGURE 2-1. Levels of Significant Exposure to Ethylene Oxide – Inhalation

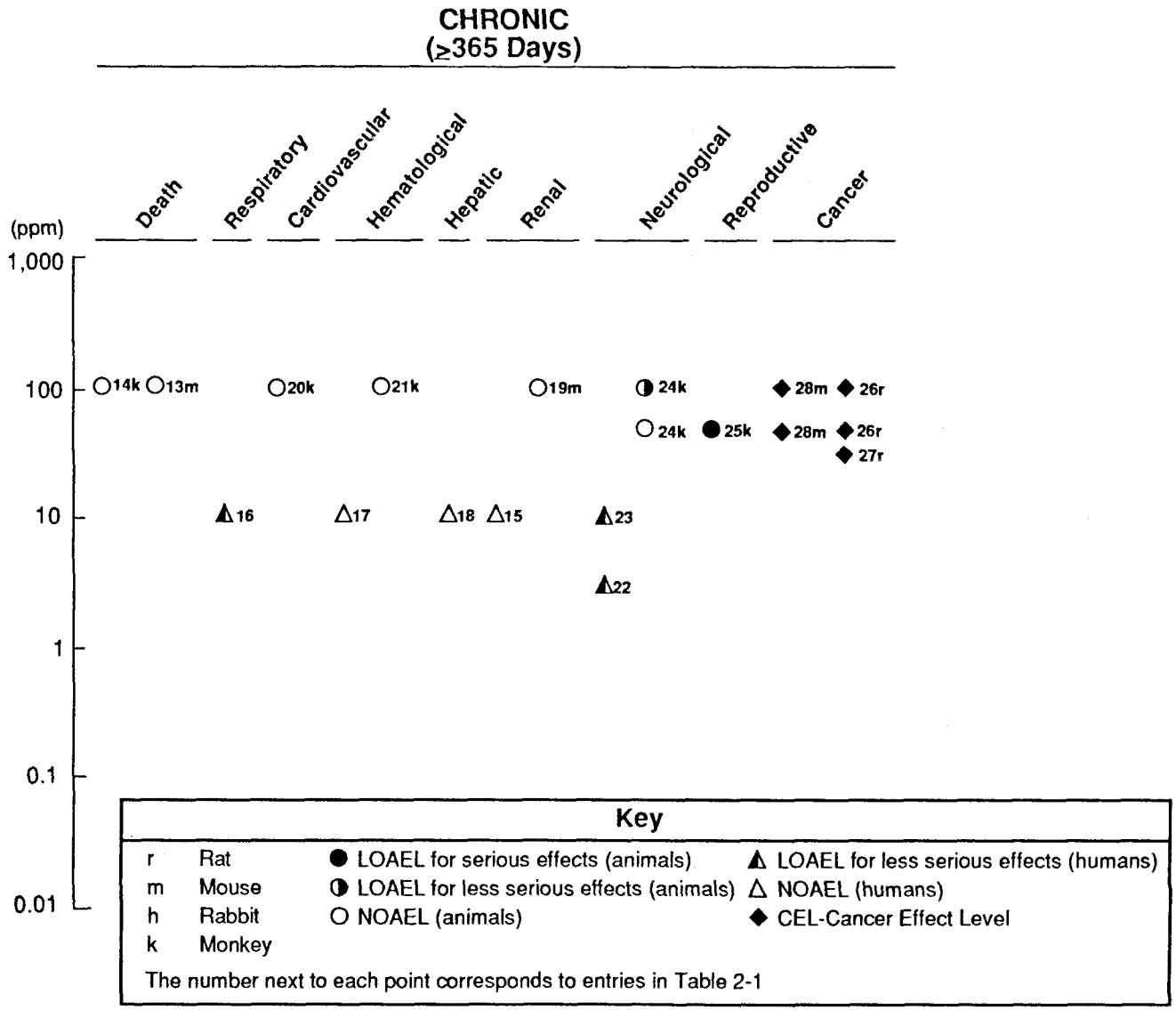

FIGURE 2-1 (Continued)

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 3.5×10^{-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.

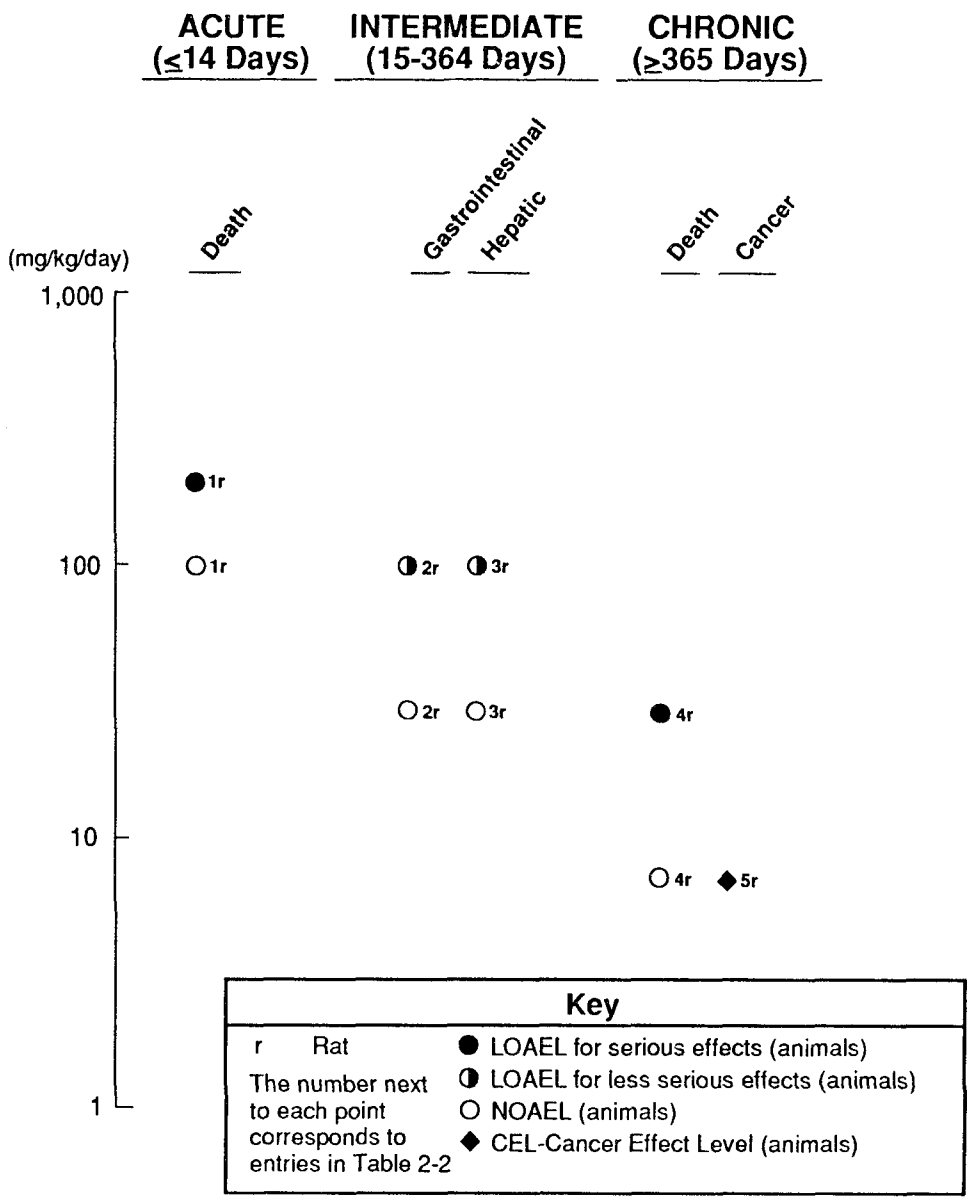

FIGURE 2-2. Levels of Significant Exposure to Ethylene Oxide – Oral

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

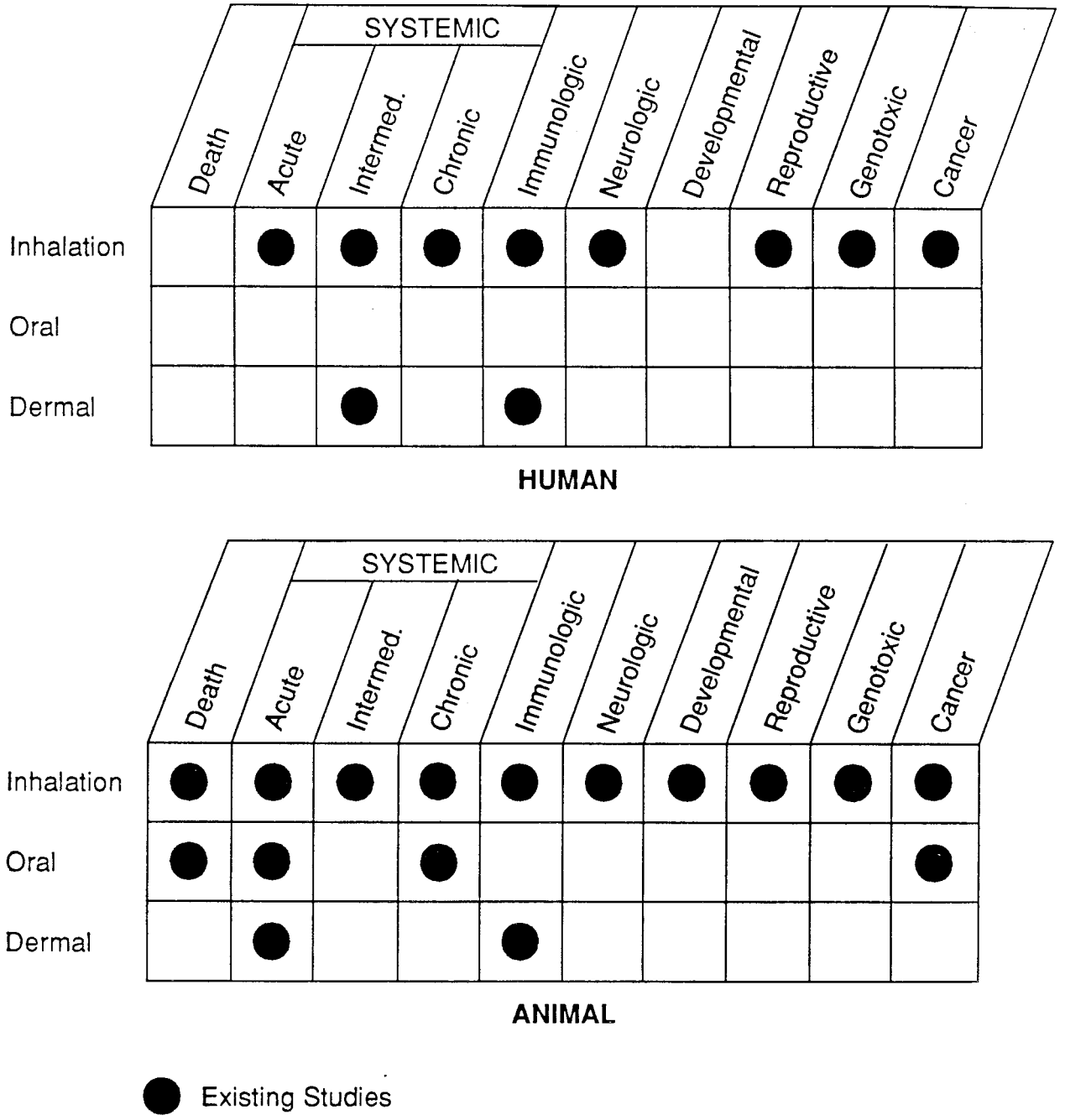

FIGURE 2-3. Existing Information on Health Effects of Ethylene Oxide

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.