NIOSH

Current Intelligence Bulletin 35

MAY 22, 1981

ETHYLENE OXIDE (EtO)

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Centers for Disease Control
National Institute for Occupational Safety and Health

The National Institute for Occupational Safety and Health (NIOSH) Current Intelligence Bulletin is the primary product of the Current Intelligence System. The purpose of the Current Intelligence System is to promptly review, evaluate, and disseminate new information received by NIOSH that may indicate either the existence of an occupational hazard not previously recognized or a greater hazard than generally known. The Current Intelligence System staff within the Division of Criteria Documentation and Standards Development was responsible for the preparation of this Bulletin.

Current Intelligence Bulletins are disseminated to NIOSH staff, other government agencies, and the occupational health community, including labor, industry, academia, and public interest groups. The Bulletins are intended to disseminate new data that may affect prevailing perceptions of occupational hazards. They convey important public health information and recommend voluntary protective measures. Current Intelligence Bulletins do not recommend occupational standards, nor are they intended to have any regulatory significance.

DHHS (NIOSH) Publication No. 81-130

NIOSH CURRENT INTELLIGENCE BULLETIN: #35

ETHYLENE OXIDE (EtO): *Evidence of Carcinogenicity*

May 22, 1981

The National Institute for Occupational Safety and Health (NIOSH) recommends that ethylene oxide be regarded in the workplace as a potential occupational carcinogen, and that appropriate controls be used to reduce worker exposure. These recommendations are based primarily on an industry-sponsored study demonstrating that ethylene oxide is carcinogenic in experimental animals. In this study, ethylene oxide was associated with increases in leukemia in female rats and peritoneal mesotheliomas (malignant tumors) in male rats. There has been widespread recognition of the mutagenic potential of ethylene oxide, and recent evidence demonstrates adverse reproductive effects in mammals, which also are of public health concern. In addition, limited epidemiologic investigations at two worksites provide evidence that excess risk of cancer mortality may exist for the ethylene oxide workers studied. Some workers are on occasion exposed to relatively high concentrations of ethylene oxide, particularly where it is used for fumigation and sterilization. On the basis of this information, NIOSH requests that producers, distributors, and users of ethylene oxide, and of substances and materials containing ethylene oxide, give this information to their workers and customers, and that professional and trade associations and unions inform their members.

BACKGROUND

Purpose of Bulletin

The purpose of this bulletin is to disseminate recent information concerning the potential carcinogenic hazard of ethylene oxide (EtO) to workers, and to update the assessment made in the 1977 NIOSH Special Occupational Hazard Review on EtO.[1] This bulletin conveys public health information and recommends voluntary protective measures.

In the 1977 review, NIOSH concluded that occupational exposure to EtO may increase the frequency of mutations in human populations. This conclusion was based on observations of (1) changes in the genetic material of cells in at least 13 biological species following exposure to EtO, and (2) covalent chemical bonding between EtO and deoxyribonucleic acid (DNA), a major constituent of genetic material. While these observations raised concern about the potential carcinogenicity of EtO, there were no epidemiologic studies or long-term carcinogenesis assays available at the time to assess carcinogenic potential for humans.

Additional evidence is now available that suggests the current Occupational Safety and Health Administration (OSHA) standard of 50 parts per million (ppm)

as a time-weighted average (TWA) concentration needs to be reexamined for its adequacy in safeguarding worker health. A recent study demonstrates that EtO induces cancer in experimental animals.[2] A dose-related increase in mononuclear cell leukemia was established in that study; exposures as low as 10 ppm increased the proportion of female rats with the leukemia. Peritoneal mesothelioma was treatment-related in male rats exposed to EtO at 33 and 100 ppm. Also, experiments indicate that EtO exposure to either male or female animals results in adverse effects on reproduction.[3,4]

Other work supports these findings. Epidemiologic investigations of cancer mortality among Swedish workers exposed to EtO suggest an increased risk of leukemia and other cancers.[5,6] Recent information also suggests that EtO is associated with chromosomal abnormalities in peripheral lymphocytes of exposed workers.[7] The environmental measurements reported indicate that these workers were exposed to 8-hour TWA concentrations below the current OSHA standard.

Although this bulletin focuses on new evidence of carcinogenic, mutagenic, and reproductive hazards, EtO has other adverse effects on health. The acute toxic effects of EtO in humans and animals include acute skin, respiratory, and eye irritation; skin sensitization; nausea, vomiting, and diarrhea; and nervous system effects. Nonmalignant chronic effects in humans include anemia and respiratory irritation, with susceptability to secondary respiratory infection. The literature reporting these effects was reviewed in the 1977 NIOSH document.[1] More recently, cases of peripheral neuropathy among exposed workers have been reported.[8]

Production and Use

At room temperature and atmospheric pressure, EtO is a colorless gas; at higher pressures it may be a volatile liquid. Synonyms and identifiers are listed in Appendix III. It has a characteristic ether-like odor with a widely variable threshold of detection in humans; the mean detectable concentration is about 700 ppm (1260 mg/m^3).[9] It is completely miscible with water, alcohol, acetone, benzene, ether, carbon tetrachloride, and most organic solvents. Ethylene oxide is highly reactive and potentially explosive in the presence of alkali metal hydroxides and highly active catalytic surfaces, or when heated. However, it is relatively stable in aqueous solutions, or when diluted with carbon dioxide (CO_2) or halocarbons. In order to reduce explosion hazards, when EtO is used as a fumigant or sterilant it is often in mixtures, such as 10% EtO and 90% CO_2, or 12% EtO and 88% halocarbon.

Ethylene oxide is a major industrial chemical and is one of the 25 chemicals of highest production volume in the United States. Current production capacity in the United States is about 6.1 billion pounds (2.8 Tg) per year. In 1978, the industrial consumption of EtO was about 4.9 billion pounds (2.2 Tg), and the projected consumption for 1983 is about 6.2 billion pounds (2.8 Tg). The chemical is used extensively worldwide, and U.S. production capacity is about 43% of the world capacity.[10]

On a volume basis, EtO is primarily used as an intermediate in the production of several industrial products. The largest consumption of EtO is in the production of ethylene glycol for automotive antifreeze and as an intermediate for polyester fibers, films, and bottles. The second largest consumption is in production of nonionic surface-active agents for industrial applications and for heavy-duty home laundry detergents and dishwashing formulations. Production of glycol ethers (e.g., solvents for surface coatings) and ethanolamines (used in production of soaps, detergents, and textile chemicals) constitute the third and fourth largest uses, respectively.

Many smaller uses account for the remainder of EtO consumption. Ethylene oxide is used as a pesticide fumigant (including antimicrobial sterilant). Industries and work settings where it is used as a sterilant or fumigant include: health care, diagnosis, and treatment facilities; medical products manufacturing; libraries; museums; research laboratories; beekeeping; spices, seasonings, and black walnut meats fumigation; dairy packaging; cosmetics manufacturing; animal and plant quarantine service at ports of entry; transportation vehicles (e.g., aircraft, buses, and railroad cars) fumigation; and clothing, furs, and furniture fumigation.

Potential for Occupational Exposure

The vast majority of EtO is found in chemical plants where it is produced and used for intermediates. Because EtO is highly explosive and reactive, the process equipment containing it in these plants generally consists of tightly closed and highly automated systems. The equipment is often located outdoors, and workers spend most of their work shift inside or around control rooms, away from the equipment. Samples collected in general process areas of six plants indicated that EtO concentrations were, with few exceptions, less than 1 ppm.[11] The greatest potential for worker exposure probably occurs during the loading or unloading of transport tanks, product sampling procedures, and equipment maintenance and repair.

In contrast to the chemical-manufacturing plants, other industries and activities may use only a very small portion of the total EtO produced, but are responsible for high occupational exposures to many workers. For example, less than 0.24% of the annual U.S. production of EtO is consumed in the health care and medical products industries,[12] and only about 0.02% of the production is used for sterilization in hospitals.[1] Yet, in 1977 NIOSH estimated that approximately 75,000 health care workers employed in sterilization areas were potentially exposed to EtO and that 25,000 others may have been incidentally exposed due to improper engineering and administrative controls.[1] In a limited field survey of hospitals, NIOSH found that EtO concentrations near malfunctioning or improperly-designed equipment may reach transitory levels of hundreds or even a few thousand ppm. Time-weighted average ambient and breathing zone concentrations were generally below the OSHA standard of 50 ppm.

EPIDEMIOLOGIC EVIDENCE FOR CANCER IN HUMANS

In 1979, Hogstedt et al. reported the results of a historical prospective mortality study of workers employed in a Swedish EtO production facility.[5] Individuals in

this investigation were employed as of 1961 and exposed or employed for more than 1 year. These individuals were followed through 1977. The authors required an interval of at least 10 years between initial employment and the beginning of the observation period. Three separate cohorts were studied: 89 persons who worked full time in the EtO production area, with 1,234 person-years of observation; 86 maintenance workers who intermittently worked in the EtO area, with 1,211 person-years of observation; and 66 workers who had never worked in EtO production, with 955 person-years of observation. The followup was complete for each cohort. Diagnoses for malignancies were provided by the Swedish Cancer Registry. The expected numbers of deaths were calculated from Swedish national mortality rates adjusted for age and calendar time-period.

Among the full-time production workers, 23 deaths were observed, compared with 13.5 expected ($p<0.05$). Of the 23 deaths, 9 cancer deaths were observed, compared with 3.4 expected ($p<0.01$). With regard to cause-specific mortality, 2 leukemia deaths were observed, compared with 0.14 expected ($p<0.01$), and 3 stomach cancer deaths were observed, compared with 0.4 expected ($p<0.01$). Twelve circulatory system deaths were observed, compared with 6.3 expected ($p<0.05$). Of the two leukemia cases in the cohort of full-time production workers, one died from chronic lymphatic leukemia and the other from acute myeloid leukemia. In contrast, the cohorts of maintenance workers with intermittent exposure and the workers never exposed to EtO did not demonstrate any statistically significant excess cause of death. However, one leukemia death was observed among the maintenance workers, compared with 0.13 expected deaths. This case was reported to be chronic lymphatic leukemia.

The complex exposure patterns and production changes in the chemical industry make it difficult to assess exposure in this study. However, the authors estimated that concentrations of airborne EtO in the facility during the 1940's were probably below 25 mg/m^3 (14 ppm), with occasional exposures up to the odor threshold of 1,300 mg/m^3 (730 ppm). Concentrations of 10-50 mg/m^3 (6-28 ppm) were estimated for the 1950's and early 1960's, although peaks above the odor threshold still occurred. Random samples in the 1970's showed a range of 1-10 mg/m^3 (0.6-6 ppm), and occasional higher values.

Other potential chemical exposures in the production area included ethylene dichloride, ethylene chlorohydrin, ethylene, and bis-chloromethyl ether, as well as traces of other unspecified chemicals. Although the authors could not attribute the excess cancer to any particular substance, EtO and ethylene dichloride were thought to be suspect because of the amounts of exposure and toxicological reports.

Also in 1979, Hogstedt et al. reported an investigation of leukemia among workers potentially exposed to EtO in a Swedish factory.[6] In this factory, a mixture of 50% EtO and 50% methyl formate had been used since 1968 to sterilize hospital equipment. Between 1972 and 1977, 3 cases of leukemia (2 women, 1 man) occurred among the workforce of 230 persons. It was determined that only 0.2 cases would have been expected for men and women combined, based on the sex-specific Swedish national leukemia incidence rates for 1972. The cases of leukemia were categorized as chronic myeloid leukemia and acute myelogenic leukemia for the women, and as primary macroglobulinemia for the man.

The authors calculated the 8-hour TWA concentration of EtO in the breathing zone of the two women who developed leukemia to be 20 $\pm$ 10 ppm. The EtO exposure was not reported for the man who developed leukemia, but it was estimated that, as plant manager, he was exposed to EtO 3 hours per week. This individual also had some occasional contact with benzene in laboratory work.

The significance of these epidemiologic findings is limited by the small number of observed deaths, the uncertainty of worker exposure information, and the inability to attribute the observed mortality to a particular chemical. These epidemiologic investigations cannot be cited as definitive evidence of an excess risk of cancer resulting from EtO exposure, but they should be considered evidence that excess risk of cancer may exist for the EtO workers studied.

EVIDENCE OF CARCINOGENICITY IN EXPERIMENTAL ANIMALS

The final report of an inhalation toxicology study of EtO sponsored by a group of EtO manufacturers was released January 28, 1981.[2] In this chronic inhalation study, male and female rats of the Fischer 344 strain were exposed to EtO vapor at test concentrations of 10, 33, or 100 ppm for 6 hours per day, 5 days per week, for about 2 years. Two other groups of animals served as untreated controls. Initially there were 120 animals of each sex in each of the experimental and control groups.

Postmortem examinations were made of all animals that died or were killed when moribund, and at scheduled intervals at 6, 12, 18, 24, and 25 months. Based on histologic evaluation, the researchers concluded that the incidences of mononuclear cell leukemia and peritoneal mesothelioma were significantly increased because of exposure to EtO. At the end of the experiment, the incidence of mononuclear cell leukemia in female rats was dose-related, increasing linearly with increasing exposure concentrations. A statistically significant increase in mononuclear cell leukemia was observed only in the group of females exposed at 100 ppm. For females exposed at 33 ppm, the cumulative percentage incidence of leukemia was significantly higher than that for one control group and for a combination of both control groups, but not for the second control group. However, the incidence for the females exposed at 33 and 10 ppm did indicate a dose response. The regression analysis of leukemia incidence versus exposure concentration was significant with a correlation coefficient of +0.99, indicating that induction of the leukemia was highly correlated to exposure at each concentration.

Peritoneal mesothelioma was reported to be treatment-related in the male rats exposed at 33 and 100 ppm. Among the males expsoed at 100 ppm, the cummulative percentage developing this tumor was statistically higher than controls beginning with the 21st month of exposure, whereas the incidence of the tumors in males exposed at 33 ppm was not appreciably higher than in controls until the last month of the study. These peritoneal tumors originated on the testicular mesothelium and were confined to the abdominal cavity.

In addition, the researchers reported that analysis (mortality-adjusted trend) indicated EtO exposure was associated with a higher frequency and/or earlier

observation of mononuclear cell leukemia in male rats. The researchers also reported that a significant, positive, mortality-adjusted trend analysis indicated that the normal occurrence of pituitary adenoma in male and female rats was accelerated by exposure to EtO.

Government scientists representing NIOSH, OSHA, and the National Toxicology Program reviewed this study with the investigators and concluded that EtO induced mononuclear cell leukemia in the female rats and peritoneal mesothelioma in male rats.

In 1979, Dunkelberg reported preliminary results of a long-term carcinogenicity assay in mice.[13] Ethylene oxide was administered to female NMRI mice by subcutaneous injection in weekly dosages of 0.1, 0.3, or 1.0 mg per animal. Two control groups were used: one received the vehicle (tricaprylin) only, and the other group received no treatment. The animals had been treated for 91 weeks at the time the results were reported. Dunkelberg reported that tumors (sarcomas) appeared at the injection site in the treated groups, but not in the control groups. The first tumor appeared in the 50th week of treatment. The number of subcutaneous tumors at the injection site appeared to increase with the size of the dose; the number of tumors at sites distant from the injection sites was not significantly greater in the treatment groups than in control groups. Such findings may indicate a chemical's carcinogenic potential, although the relevance of subcutaneous tumors at injection sites to carcinogenicity is often questioned. Dunkelberg has apparently not published a final report.

EVIDENCE OF MUTAGENIC AND REPRODUCTIVE EFFECTS

The ability of a chemical to serve as an alkylating agent and to cause mutations in a variety of biological test systems is widely accepted as an indicator that the chemical may have carcinogenic potential. Both alkylation and mutagenicity have been demonstrated for EtO. Further, effects of a chemical on basic genetic material within the cells of living mammals are relevant for assessing mutagenic and carcinogenic hazards for humans. Evidence of this nature is available for EtO.

Results in Sub-Mammalian Test Systems

EtO is effective as both an alkylating agent and as a mutagen in a wide variety of biological systems. It will bind covalently and irreversibly to mammalian protein,[14] human protein,[15] and mammalian DNA.[16] Several investigators have reported the mutagenic properties of EtO in microbial and plant systems including: viruses,[17,18] Salmonella typhimurium,[19] Escherichia coli,[20] Neurospora crassa,[21] barley,[22,23,24,25] rice,[26] wheat,[27] and Tradescantia paludosa.[28] Studies in Drosophila melanogaster exposed to EtO have revealed an increase in both sex-linked recessive lethal,[29,30] and autosomal deletion mutations[30] in a dose-response relationship. In D. melanogaster, lethal mutations and translocations have been induced in all stages of spermatogenesis.[31]

Results in Humans and Experimental Animals

The capability of EtO to cause gene mutations and transmissible genetic damage in mammalian systems also has been reported. Appelgren et al. demonstrated the ability of EtO to reach the testes of mice following intravenous injection.[32] A whole-body autoradiographic study using ^{14}C-labelled EtO indicated that ^{14}C concentrations in the testicle, epididymis, and other organs were higher than those in the blood when measured 20 minutes to 4 hours after EtO exposure. This radioactivity was still present in the epididymis 24 hours after exposure had ended. Two investigators reported dominant lethal mutations: in mice following intraperitoneal administration of a single dose of EtO at 150 mg/kg of body weight,[33] and in rats following a single inhalation exposure of 1,000 ppm for 4 hours.[34] An unpublished study by Cumming et al.[35] reports a dose-response relationship for unscheduled DNA synthesis (UDS) in the testes of mice exposed to EtO by inhalation. UDS reflects the repair of damaged DNA catalyzed by enzymes. Normally, there should be no DNA synthesis in the testes during sperm maturation. At both 600 and 800 ppm a maximum response indicating DNA damage was observed after 4 hours of exposure. Generoso et al. also studied the effects of EtO on heritable translocations (HT) in the mouse.[33] Male mice were injected intraperitoneally with EtO at doses of 30 or 60 mg/kg of body weight per day. Each male mouse was then allowed to mate with three female mice. The male progeny were studied for sperm translocation heterozygosity. A dose-response relationship was observed; 9.36% (38/406) of the animals had HT in the high dose group, while 1.32% (6/456) had HT in the low dose group. None of the animals (0/822) in the control group had HT.

Appelgren et al., in 1978, reported significantly increased numbers of polychromatic erythrocytes containing micronuclei in mice and rats following intravenous injection of EtO.[36] Fomenko and Strekalova[37] and Strekalova et al.[38] reported increased numbers of chromosomal aberrations in bone marrow cells of rats exposed to EtO by inhalation at concentrations ranging from 1 to 112 mg/m^3 (0.6 to 63 ppm). Tests of statistical significance were not reported in either study. Significant excesses of chromosomal abnormalities in bone marrow cells have been reported in rats exposed to EtO by oral doses of 9 mg/kg of body weight (in aqueous solution),[39] or by inhalation of EtO at 250 ppm for 7 hours per day for 3 days.[19] Chromosomal aberrations have been reported in humans accidentally exposed to high concentrations of EtO.[40] More detailed reviews of the mutagenicity of EtO are available.[1,41,42]

In 1978, a company that uses EtO in manufacturing and distributing health care products began to investigate possible adverse effects of EtO on its workers. The investigation entailed monitoring the work environment for concentrations of EtO at its nine facilities, and medical evaluation of 75 workers who had potential EtO exposure. The medical evaluation included analysis of chromosomal aberrations in lymphocytes for all exposed workers and sperm analysis for the men. Workers were exposed for an average of 2.9 years (range: 0.5-10 years). A group of 37 workers who had no known prior exposure to EtO served as controls for the chromosomal analysis.

The company submitted data from this study to NIOSH in April to September 1980; most of the data have since been published.[7] The submitted data revealed that (1) all nine facilities complied with the OSHA standard of 50 ppm for an 8-hour TWA, but there were instances when the extant NIOSH recommendation[1] for a maximum short-term (15-minute) exposure of 75 ppm had been exceeded; (2) physical examinations showed no unusual findings in exposed persons; (3) there was a statistically significant increase in the number of chromosomal aberrations in peripheral lymphocytes obtained from the blood of workers exposed to EtO, when compared with those not exposed; (4) there were statistically significant increased numbers of sister chromatid exchanges (SCE's) in the peripheral lymphocytes of some workers exposed to EtO, and that this increase was statistically significant for workers who had chromosomal abnormalities characterized by quadriradial and triradial exchanges; and (5) data from sperm analysis were inconclusive.

The incidences of chromosome aberration and sister chromatid exchange were higher among the workers exposed to EtO than in workers who had no known EtO exposure. However, it is difficult to evaluate the significance of the findings because of the manner in which the data were presented and the design of the investigation. A major concern is the failure to select matched control individuals for concurrent cytogenetic testing. Cigarette smoking which may affect the incidence of sister chromatid exchange and chromosome aberration, was not accounted for in this investigation. However, quadriradial chromosomes are rare, and while their significance is not well understood, their occurrence should be viewed with concern.

Systematic field investigations are needed to confirm these findings. However, based on these data and in light of the additional evidence of EtO causing chromosomal breakage in workers and experimental animals, it is probable that cytogenetic effects did occur in the workers exposed at TWA concentrations below the OSHA standard of 50 ppm.

Results of a one-generation reproductive study in rats also have been reported.[3] This study involved exposing male and female rats to EtO vapor for 12 weeks prior to mating. Animals were exposed at concentrations of 10, 33, or 100 ppm for 6 hours per day. Before mating, animals were exposed 5 days per week; during and after mating they were exposed 7 days per week. Two control groups of animals were exposed to room air.

The major treatment-related adverse effect observed was a significant reduction in the number of pups born per litter in the group of highest exposure (100 ppm). There were fewer implantation sites per pregnant female, and the average ratio of the number of fetuses born to the number of implantation sites was smaller in the highest exposure group than any other group. Fewer females in the 100-ppm exposure group than in the control groups became pregnant after two mating periods.

The potential for EtO to cause adverse transplacental effects also has been reported.[4] Female mice were administered EtO intravenously at daily doses of 0, 75, or 150 mg/kg of body weight during one of four periods of gestation (days 4-6,

6-8, 8-10, or 10-12). Maternal animals showed signs of toxicity at the higher dose level when administered in the first, third, and fourth periods, but not in the second period (days 6-8 of gestation). A significant reduction in mean fetal body weight compared with controls was reported for all four treatment periods at the 150-mg/kg level. There was a significant increase in the percentage of malformed fetuses/litter from dams administered EtO at the high dose level during the second and fourth gestational periods. Approximately 19% of the fetuses in each litter from maternal animals that showed no signs of toxicity when given 150 mg/kg in the second period had some type of malformation, mostly in the cervical and thoracic regions of the skeleton.

Chemicals may be considered to be teratogenic if they produce certain malformations in the offspring in the absence of maternal toxicity. In this experiment, EtO administered intravenously to pregnant mice at 150 mg/kg on days 6-8 of gestation caused such a response. However, the investigators cautioned that the case of teratogenicity of EtO is weakened somewhat by the high incidence of maternal mortality they observed with the same dose at other gestational periods.

EXPOSURE STANDARDS AND GUIDES

OSHA's standard for occupational exposure to EtO is 50 ppm (90 mg/m^3) as a time-weighted average (TWA) concentration for an 8-hour work shift.[43] Studies of carcinogenicity were not available when this standard was developed.

In its 1977 review of EtO, NIOSH recommended that occupational exposure be limited to a ceiling concentration of 75 ppm (135 mg/m^3), determined during a 15-minute sampling period. Additionally, NIOSH recommended that the OSHA standard of 50 ppm (90 mg/m^3) as a TWA be observed. NIOSH emphasized that its document did not attempt to address the adequacy of the OSHA standard.[1]

The values recommended by NIOSH in 1977 were the same as the Threshold Limit Values (TLV's) then recommended by the American Conference of Governmental Industrial Hygienists (ACGIH) for Time Weighted Average (TWA) and Short Term Exposure Level (STEL) concentrations, respectively.[44] In 1979, ACGIH published its intent to change its TLV to 10 ppm (20 mg/cu m^3) as a TWA concentration.[45,46]

Reflecting increased concern over the mutagenic and carcinogenic potential of EtO, some manufacturers and commercial users of the chemical are adopting occupational exposure guidelines lower than the OSHA standard. Self-imposed guidelines adopted by companies have been reported to range from 1 to 10 ppm as 8-hour TWA concentrations, with two companies also adopting peak limits of 5 and 15 ppm.[47]

RECOMMENDATIONS

Ethylene oxide has caused statistically significant increases in mononuclear cell leukemia in female Fischer 344 rats. The incidence of this disease in the exposed females increased linearly with dose. Among male Fischer 344 rats in the same

experiment, EtO induced peritoneal mesothelioma which originated in the testicular mesothelium. Although humans and animals may differ in their susceptibility to specific chemical compounds, any substance that produces cancer in experimental animals should also be considered to have carcinogenic potential in humans. The mutagenicity of EtO has been extensively demonstrated in lower biological species and in mammals. Recent experiments in mammals have demonstrated adverse reproductive effects, which are also of public health concern. The widespread recognition of EtO as an effective alkylating agent and mutagen reinforces concern over the carcinogenic potential of EtO. Also, epidemiologic investigators reported excess cancer mortality at two worksites where workers were exposed to EtO. These epidemiologic findings are not by themselves proof of an excess risk of cancer resulting from EtO exposure. However, the causal inference from animal experimental evidence is compatible with the observed excess of cancer among workers exposed to EtO in two separate operations.

Based on these recent findings, NIOSH recommends that EtO be regarded in the workplace as a potential occupational carcinogen. Safe levels of carcinogens have not been demonstrated, but the probability of developing cancer should be reduced by decreasing exposure. The excess cancer risks to workers exposed to EtO at or below the present OSHA standard of 50 ppm as a TWA concentration have not yet been estimated. However, NIOSH believes the present standard needs to be reexamined because its adoption preceded the recognition of the carcinogenic potential of EtO and was established to protect against only acute and nonmalignant chronic effects. As prudent public health policy, NIOSH urges employers, in the interim, to voluntarily assess the conditions under which their workers may be exposed to EtO and take all reasonable steps to reduce exposure to the extent possible. The actions taken by some companies to voluntarily adopt exposure guidelines lower than the present standard are commendable moves in the right direction, however, these exposure guidelines have not been evaluated by NIOSH. The "Guidelines for Minimizing Worker Exposure to Ethylene Oxide," Appendix I, should be adapted to specific work situations.

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APPENDIX I

GUIDELINES FOR MINIMIZING WORKER EXPOSURE TO ETHYLENE OXIDE

NIOSH recommends that ethylene oxide (EtO) be regarded in the workplace as a potential occupational carcinogen. Exposure should be limited to as few workers as possible, and workplace exposure levels should be minimized. Substitutes of lesser hazards should be used where practicable. The area in which EtO is used should be restricted to only those workers essential to the process or operation.

NIOSH recognizes that it may be harder to reduce exposure in the industries and work settings where EtO is used as a sterilant or fumigant than in industrial plants where systems are generally closed and automated. Considerable attention has been directed toward developing control methods for sterilizing and fumigating operations. The recommendations of NIOSH's 1977 Special Occupational Hazard Review with Control Recommendations: Use of Ethylene Oxide as a Sterilant in Medical Facilities are still appropriate and should be implemented whenever applicable.[1] Consult the end of this appendix for the availability of Government publications.

More recent work in this area was presented at a seminar sponsored by the Health Industry Manufacturers Association (HIMA). The proceedings from this seminar contain useful information on monitoring and controlling emissions of EtO from sterilizing systems. This publication discusses in detail work practices and engineering controls that can be incorporated into existing and new sterilizer systems and areas. Engineering controls include installing exhaust ventilation at the sterilizer door, providing a purge or airflush cycle to precede the full opening of the sterilizer door, ensuring that all equipment and piping are leak-free, venting water drains and exhausted air outside the work area and occupied spaces, and providing capture and removal of EtO off-gasing from sterilized items. The proceedings can be obtained by writing to HIMA, 1030 15th Street, N.W., Suite 1100, Washington, D.C. 20005, and requesting information on HIMA Report No. 80-4, The Safe Use of Ethylene Oxide: Proceedings of the Educational Seminar. A companion document, HIMA Report No. 81-1, Monitoring Airborne Ethylene Oxide: Proceedings of the Ethylene Oxide Monitoring Workshop, is in preparation.

The latest in a series of EtO-related activities undertaken by the American Hospital Association is the development of a personnel training manual. The manual, to be published in the summer of 1981, is intended to be used by central service supervisors in the routine training of their staff in the safe use of ethylene oxide as a gas sterilant in health care facilities. The manual will be entitled Ethylene Oxide Use in Hospitals: A Manual for Health Care Personnel. For

information on its availability contact: American Hospital Association, 840 North Lake Shore, Chicago, Illinois 60611.

The U.S. Environmental Protection Agency (EPA) has been supporting an extensive study to identify engineering controls, monitoring devices, and personnel procedures that would reduce exposure to EtO in industries that use it as a pesticide (e.g., as a sterilant or fumigant). This work, performed by the MITRE Corporation under EPA Contract No. 68-01-5944, is nearing completion; and a final report with recommendations should be available in the spring of 1981. For information on the availability of this report contact:

U.S. Environmental Protection Agency
Special Pesticide Review Division (TS-791)
Branch #1
Crystal Mall #2, Room 711-H
1921 Jefferson Davis Highway
Arlington, Virginia 22202

Telephone: (703) 557-7401

The guidelines listed below are more general and have greatest application in industrial settings. However, they should be given consideration for all settings and be adapted to specific work situations as required.

EXPOSURE MONITORING

Initial and routine worker exposure surveys should be made by competent industrial hygiene and engineering personnel. These surveys are necessary to determine the extent of worker exposure and to ensure that controls are operational and effective.

The NIOSH Occupational Exposure Sampling Strategy Manual may be helpful in developing efficient programs to monitor worker exposure to EtO.[48] The manual discusses determination of the need for exposure measurements and selection of sampling times.

Worker exposure measurements should be 8-hour TWA and short-term (15-minute) exposure estimates calculated from personal or breathing zone samples (air most like that inhaled by the workers). Short-term samples should be taken during periods of maximum expected exposure by using all available knowledge of the area, work procedures, and processes. Area and source measurements may be useful to identify problem areas, processes, and operations.

CONTROLLING WORKER EXPOSURE

There are four basic methods of limiting worker exposure to EtO, none of which is a simple industrial hygiene or management decision. Careful planning and thought should be used prior to implementation.

o Product Substitution

The substitution of an alternative material with a lower potential health risk is an important method for reducing exposure. However, extreme care must be used when selecting possible substitutes. Possible health effects and exposure potentials of alternatives to EtO should be fully evaluated prior to selection.

o Contaminant Controls

Airborne concentrations of EtO can be most effectively controlled at the source of contamination by enclosure of the operation and/or use of local exhaust ventilation. Guidelines for selected processes and operations can be found in NIOSH's Recommended Industrial Ventilation Guidelines.[49]

When enclosing a process or operation, a slight vacuum should be used to create negative pressure so that leakage will result in the flow of external air into the enclosure and minimize contamination of the workplace. This can be accomplished with a well-designed local exhaust ventilation system that physically encloses the process as much as possible, with sufficient capture velocity to keep the contaminant from entering the workplace atmosphere. The design of ventilation systems should take into account the flammable, explosive, and reactive characteristics of EtO.

Ventilation equipment should be checked at least every 3 months to ensure adequate performance. System effectiveness should also be checked soon after any change in production, process, or control that might result in significant increases in airborne exposure to EtO.

o Worker Isolation

If feasible, workers may be isolated from direct contact with the work environment by the use of automated equipment operated by personnel observing from a closed control booth or room. The control room is maintained at a greater air pressure than that surrounding the process equipment so that air flow is out of, rather than into, the room. This type of control will not protect those workers that must perform process checks, adjustments, maintenance, and related operations. Special precautions are often necessary to prevent or limit exposure in these situations and frequently involve the use of personal protective equipment.

o Personal Protective Equipment

Personal protective equipment, which may include respirators, goggles, and gloves, should not be used as the only means to prevent or minimize exposure during routine operations. Ethylene oxide can penetrate many materials; care should be exercised in selecting personal protective equipment to insure that the equipment is relatively impermeable to EtO.

However, exposure to EtO can be controlled with the use of this equipment:

-- During the time necessary to install or implement engineering or work practice controls; or

-- In work situations in which engineering and work practice controls have proven ineffective; or

-- For maintenance; or

-- For operations that require entry into tanks or closed vessels; or

-- In emergencies.

Proper maintenance procedures, good housekeeping in the work area, and worker education are all vital aspects of a good control program. Workers should be informed as to the nature of the hazard, its control, and appropriate personal hygiene procedures.

MEDICAL SURVEILLANCE

A medical surveillance program should, as noted in the 1977 NIOSH review,[1] be made available that can evaluate both the acute and chronic effects of EtO exposure. Effects such as upper respiratory irritation, dermatitis, or other forms of sensitization and irritation should alert management that unacceptable acute exposure to EtO may be occurring. A careful history with emphasis on the reproductive history should be done initially and updated yearly. In addition, an evaluation of chronic effects would require that an examination give particular attention to the hematological, neurological, and reproductive systems. Unusual findings for a worker should prompt medical personnel to consider specific tests (e.g., cytogenetic analysis) for the individual.

AVAILABILITY OF GOVERNMENT PUBLICATIONS

Government publications referenced in this appendix are available from the Government Printing Office (GPO).

Reference 1: From GPO as #017-033-00262-2 for $2.30.
Reference 48: From GPO as #017-033-00247-9 for $2.75.
Reference 49: From GPO as #017-033-00136-7 for $3.90

GPO publications can be ordered from:

Superintendent of Documents
U.S. Government Printing Office
Washington, D.C. 20402

APPENDIX I I

MAJOR MANUFACTURERS OF ETHYLENE OXIDE

BASF - Wyandotte Corporation
Calcasieu Chemical Company
Celanese Corporation
Dow Chemical U.S.A.
Northern Petrochemical Company
Olin Corporation
PPG Industries, Inc.
Shell Chemical
Sun-Olin Corporation
Texaco Chemical Company
Union Carbide Corporation

APPENDIX III

IDENTIFIERS AND SYNONYMS FOR ETHYLENE OXIDE AND ETHYLENE OXIDE MIXTURES USED IN GASEOUS STERILIZATION

Chemical Abstracts Service Registry Number: 75-21-8

NIOSH RTECS Number: KX2450000

Chemical Formula: C_2H_4O

Anprolene
Benvicide
Carboxide
Cry-Oxide
Dihydrooxirene
Dimethylene oxide
Epoxyethane
1,2-Epoxyethane
Ethylene oxide
EO
ETO
EtO
Oxacyclopropane
Oxane
Oxidoethane
Oxiran
Oxirane
Oxirene, dihyro-
Oxyfume
Oxyfume 12
Oxyfume Sterilant -20
Pennoxide
Steroxide -12
Steroxide -20
T-gas

The above information was obtained from the NIOSH's computerized Registry of Toxic Effects of Chemical Substances (RTECS), and from the National Library of Medicine's computerized chemical dictionary file CHEMLINE. Registered trademark information is not included in these files. Therefore, some of the above synonyms and identifiers may be trademarked but are not so indicated above.

CUMULATIVE LIST OF NIOSH CURRENT INTELLIGENCE BULLETINS

1.	Chloroprene	- January 20, 1975
2.	Trichloroethylene (TCE)	- June 6, 1975
3.	Ethylene Dibromide (EDB)	- July 7, 1975
4.	Chrome Pigment	- June 24, 1975 - October 7, 1975 - October 8, 1976
5.	Asbestos - Asbestos Exposure during Servicing of Motor Vehicle Brake and Clutch Assemblies	- August 8, 1975
6.	Hexamethylphosphoric Triamide (HMPA)	- October 24, 1975
7.	Polychlorinated Biphenyls (PCBs)	- November 3, 1975 - August 20, 1976
8.	4,4'-Diaminodiphenylmethane (DDM)	- January 30, 1976
9.	Chloroform	- March 15, 1976
10.	Radon Daughters	- May 11, 1976
11.	Dimethylcarbamoyl Chloride (DMCC) Revised	- July 7, 1976
12.	Diethylcarbamoyl Chloride (DECC)	- July 7, 1976
13.	Explosive Azide Hazard	- August 16, 1976
14.	Inorganic Arsenic - Respiratory Protection	- September 27,1976
15.	Nitrosamines in Cutting Fluids	- October 6, 1976
16.	Metabolic Precursors of a Known Human Carcinogen, Beta-Naphthylamine	- December 17,1976
17.	2-Nitropropane	- April 25, 1977
18.	Acrylonitrile	- July 1, 1977
19.	2,4-Diaminoanisole in Hair and Fur Dyes	- January 13, 1978
20.	Tetrachloroethylene (Perchloroethylene)	- January 20, 1978
21.	Trimellitic Anhydride (TMA)	- February 3, 1978
22.	Ethylene Thiourea (ETU)	- April 11, 1978
23.	Ethylene Dibromide and Disulfiram Toxic Interaction	- April 11, 1978
24.	Direct Black 38, Direct Blue 6, and Direct Brown 95 Benzidine Derived Dyes	- April 17, 1978
25.	Ethylene Dichloride (1,2-Dichloroethane)	- April 19, 1978
26.	NIAX® Catalyst ESN	- May 22, 1978
27.	Chloroethanes - Review of Toxicity	- August 21, 1978
28.	Vinyl Halides - Carcinogenicity	- September 21,1978
29.	Glycidyl Ethers	- October 12, 1978
30.	Epichlorohydrin	- October 12, 1978
31.	Adverse Health Effects of Smoking and the Occupational Environment	- February 5, 1979
32.	Arsine (Arsenic Hydride) Poisoning in the Workplace	- August 3, 1979
33.	Radiofrequency (RF) Sealers and Heaters: Potential Health Hazards and Their Prevention	- December 4, 1979
34.	Formaldehyde: Evidence of Carcinogenicity	- April 15, 1981
35.	Ethylene Oxide (EtO): Evidence of Carcinogenicity	- May 22, 1981

NOTE: Bulletins #1 through #18 and #19 through #30 have been reprinted as NIOSH publications, #78-127 and #79-146 respectively, for the convenience of those that desire a complete series of Current Intelligence Bulletins. Distribution of these publications and single copies of Bulletins #31 and later are available from NIOSH Publications Dissemination, Division of Technical Services, 4676 Columbia Parkway, Cincinnati, Ohio 45226.

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