INDUSTRYWIDE STUDIES REPORT:
WALK THROUGH SURVEY OF

AMERICAN PHARMASEAL
American Hospital Corporation
4401 Foxdale Avenue
Irwindale, California 91706

PROJECT NO: P:84:12

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DATE OF SURVEY:
August 21-22, 1984

DATE OF REPORT:
October 29, 1985

REPORT NUMBER: 67.32

Industrial Hygiene Section
Industrywide Studies Branch
Division of Surveillance, Hazard Evaluations and Field Studies
National Institute for Occupational Safety and Health
Centers for Disease Control
Cincinnati, Ohio

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PURPOSE:	To evaluate the industrial hygiene records, production processes, and personnel records to determine the suitability of including this facility in the NIOSH Industrywide Studies Branch mortality/industrial hygiene study of ethylene oxide (ETO).
EMPLOYER REPRESENTATIVES:	American Hospital Supply Ronald Abrahams-Director, Regulatory/Environmental Division. American Pharmaseal John Budd-Vice President, Regulatory Affairs and Quality Assurance Alan Eaton-Manager, Divisional Chemical Laboratories)hen Thorton, Jr-Division Manager, St ;rilization Engineering Rodney Wein-Project Engineer, Divisional Sterilization Engineering
EMPLOYEE REPRESENTATIVES:	No union.
STANDARD INDUSTRIAL CLASSIFICATION:	3841 - Surgical and Medical Instruments and Apparatus

ABSTRACT

On August 21-22, 1984, a walk-through survey was conducted at American Pharmaseal (AP), a division of American Hospital Supply Corporation, Irwindale, California, to evaluate industrial hygiene and personnel records, production processes, and document historic use of ethylene oxide (ETO). This survey was conducted as part of an industrywide study of mortality associated with an occupational exposure to ETO. AP produces single-use medical devices such as diagnostic trays and syringes with and without needles. AP has used 100% ETO since 1962 to sterilize its product.

This facility has collected extensive industrial hygiene data on ETO exposures since 1978. The first two years (1978-79) charcoal tubes were used. These tubes were replaced with 3M passive ETO monitors in 1981. The data is discussed in this report.

This plant meets the three eligibility requirements as defined in the protocol and therefore, should be included in the study. These requirements are 1) the plant must contribute at least 200 person-years to the high exposure group, or 400 person-years total, 2) the plant must have adequate personnel records or other records that can be used for identifying past and present workers exposed to ETO, and 3) the plant must not have any serious confounding exposure to a known leukemogen.

INTRODUCTION

Ethylene oxide (ETO) is one of the 25 chemicals of highest production volume in the United States.[1] The major portion of ETO produced is used in the production of ethylene glycol (antifreeze) and as a chemical intermediate for polyester films, fibers, and bottles. A small fraction of ETO, less than 0.24%, has been used by the health care and medical supply industries over the past 35-40 years to sterilize heat-sensitive medical supplies.[1]

ETO, a colorless gas at standard temperature and pressure or a liquid at higher pressures, is miscible with water, ethanol, ether, and most common organic solvents. In addition, it is highly explosive when in concentrations of 3 to 100% (ETO) in air.[2] The biological warning properties are essentially useless since the (ether-like) odor threshold among individuals ranges from 300 to 1,500 parts per million (ppm) and adverse health effects may be elicited at levels much less than this.[3]

Due to the toxicity and possible carcinogenicity of ETO (see section on Toxicity), NIOSH researchers initiated an investigation in 1982 to assess the feasibility of conducting a cohort mortality study and industrial hygiene evaluation of workers exposed to ETO. Based on the data gathered during the feasibility study, it was concluded that the cohort of workers in the health care and medical supply industry, specifically those workers exposed to ETO in industrial sterilization processes, was the most adequate group to support a cohort mortality study.[4] This decision was supported by the findings of a 1977 survey conducted by National Institute for Occupational Safety and Health (NIOSH) researchers which showed that it is in this industry most of the employee exposures occur.[5,6] This survey estimated that approximately 75,000 health care workers were employed in ETO sterilization operations, with an additional 25,000 employees which may have incidental exposure resulting from inadequate engineering controls.[5,6]

This walk-through survey was conducted to determine the suitability of including American Pharmaseal in the industrywide mortality and industrial hygiene study of workers potentially exposed to ETO in industrial sterilization processes. The suitability of including this facility was based on data gathered in this walk-through and is discussed in the Conclusion and Recommendation section.

The authority and responsibility for conducting and reporting on field studies in industry was given to NIOSH under the Occupational Safety and Health Act of 1970 (set forth by the 91st Congress, S.9123, Public Law 91-596). Section 20(a)7 states that NIOSH shall conduct and publish industrywide studies of the effects of chronic low level exposure to industrial materials, processes, and stresses on the potential for illness, disease, or loss of functional capacity in the aging adult.

DESCRIPTION OF FACILITY

AP, a division of American Hospital Supply Corporation, produces single use medical devices such as diagnostic trays and syringes with and without needles. AP began using 100% ETO in 1962 to sterilize its product in three

vessels (6 pallet, 850 ft^3 each). These vessels were located outside the building. In 1968, one (1) 2800 ft^3 (20 pallet) vessel was added, and all four vessels were moved to their present location. This new location, which was on the opposite side of the facility, had walls on 2 sides and a roof. The ETO tanks, which supply the vessels with an underground line and were located near the sterilizers, were moved 200 ft. to the north. In 1970, an additional 2800 ft^3 vessel replaced two of the 850 ft^3 vessels. In 1973, one more 2800 ft^3 vessel was added, so that Pharmaseal had three 2800 ft^3 vessels and one 850 ft^3 vessel. The ETO tanks were moved an additional 200 ft. to the north. In 1976, the sterilization area was completely enclosed. There is an on-site cafeteria where most the employees eat. The rest of the employees leave the site.

The company estimates that the amount of ETO used over the last several years has declined, primarily because the ETO concentration per sterilizer load has decreased.

DESCRIPTION OF WORKFORCE

According to the plant management, workers at this plant were relatively young. Prior to 1979, the age of the workforce ranged between 25 and 40, and after 1979 it was under 25. The workers are primarily males and Mexican-Americans. Prior to 1979, the employment turnover rate at the plant was approximately 1%, while after 1979 the turnover rate increased to between 50 and 150 percent. This increase in turnover rate was supposedly related to the introduction of the medical surveillance and respirator program.

DESCRIPTION OF THE PROCESS

AP produces single use medical devices such as diagnostic trays and syringes with and without needles (see Figure I). The raw plastics are delivered to the plant, and sent to the molding department where the various products are formed. These products are transfered to various assembly and printing departments. The assemblied components are packaged and palletized. Quality control samples (QC) are placed on the pallets before they are sent to the preconditioning area. The pallets are preconditioned before they are loaded into a vessel. The vessel is loaded on one end (the entry side), and the vessel is placed under a vaccum. Steam is introduced into the vessel, followed by ETO, which has been previously vaporized. The ETO exposure time and concentration are dependent on the type of product to be sterilized. The total cycle time from load to unload however, is generally about 8 hours. After the appropriate ETO exposure time, the vessel is returned to atmospheric pressure. The vessel is unloaded from the opposite end, and the QC samples are collected from the pallets. The QC samples are placed in aeration ovens for twenty-four (24) hours before they are taken to the QC area. The pallets are transfered to the quarantine area where they room aerate. Following a ten (10) day quarantine period, the product is sent directly to shipping.

DESCRIPTION AND REVIEW OF PERSONNEL AND OTHER RECORD SYSTEMS

Personnel

Personnel files for active employees, and for workers who terminated employment since 1980 are on file in the personnel office. Files for workers who terminated employment between 1975 and 1979 are stored in a warehouse. Personnel records for employees who terminated employment prior to 1975 have been destroyed. Separate filing systems are maintained for active hourly and salaried employees, whereas these records are mixed together for former employees.

The personnel files contain application forms, personnel change notices (PCN) and other records which are not relevant for this study. The application forms could be used for obtaining demographic information (e.g., date of birth, sex). The PCNs, which are filed each time an employee has a change in salary or position, could be used for creating detailed work histories. For workers terminated since 1975 there are a total of 3,895 records on file. Hourly and salaried files for terminated workers have been interfiled.

For hourly workers an index card system is maintained. These cards contain the necessary demographic and detailed work history information needed for the study. For active hourly workers these cards are filed separately from the personnel file; whereas, for former hourly workers, these records have been placed in the personnel file.

Since 1976, a computerized personnel record system has been used. Employee profiles can be generated from this system, which contain basic demographic information (e.g., sex, date of birth) and for salaried workers (not hourly) a detailed work history going back to 1976.

Payroll Department

The payroll department has payroll registers for about the last 5 years. These are weekly reports which have salary information listed by department, and name. Social security numbers are also listed in these reports. These reports are only for hourly, and salaried non-exempt workers. Payroll records for salaried exempt workers are maintained at another facility.

Additional payroll registers were located in a warehouse. These registers cover the time between 1970 and 1982, although it appears that not every weekly report is present in these registers.

Finally, the payroll department has annual reports from 1970 to the present. These reports list the names and social security numbers of all workers who were on the payroll for that year. They also are organized by department number.

Other Record Systems

Union records, which list names by department, were located in the warehouse. These records cover the time period between 1970-1974 and 1976-1978. Most likely these records are limited to hourly workers, and it is likely that only certain departments were organized.

Some of the individual departments maintain their own records. In the sterilizer department attendance records have been maintained since 1970. These records lists individuals by name (sometimes only the first name is used), and indicate the first and last date of employment. The shipping department has also maintained attendance records for the last 5 years. The Chemical Department has on file personnel change notices going back to about 1976. Finally, the Maintenance Department has, stored in the warehouse, work logs going back to 1978, which indicate daily departmental job assignments.

Summary

Personnel records are only available at this facility back to 1975. Payroll and union records are probably not complete enough to reliably determine exposure histories prior to this time. The sterilizer department records may be used for identifying workers exposed to ETO in this department between 1970 and 1975.

Thus, based on these constraints with the exception of sterilizer workers it may only be possible to include workers employed after 1975 in the mortality study.

Definition of Exposure

Based upon a review of the processes using ETO, and discussions with plant personnel, a list of job and department titles with potential for ETO exposure was developed. Workers involved in any of these activities for at least 3 months would be included in the mortality study. Following is a list of these jobs (or departments); Quarantine/sterilization (Dept. 31), Shipping (Dept. 73), Raw Material Stores (Dept. 29), Mechanics or Electricians in Maintenance (Dept. 26/99), Biology Lab (Dept. 88), Chemistry (Dept. 87) and Sterility Engineers (Dept. 86).

Sampling and Review of Personnel Record System

A random sample of approximately 10% of the personnel files was selected and reviewed. An attempt was made based on the records alone to determine whether an individual was exposed according to the criteria described above. In order to be considered potentially exposed, the individual had to have been first exposed prior to 1978, since this is a requirement in the retrospective cohort mortality study. In all cases it was possible using the work histories presented in the personnel records to judge whether individuals were potentially exposed to ETO, according to the criteria described above. For workers judged to be potentially exposed to ETO, information was recorded on year of birth, sex, year first employed and year last employed. A summary of this information is presented in Table 2. Overall 74% of the sample was male, the average year of birth was 1948, the average year first employed was 1977, and the average duration of employment was 3.8 years. It is estimated that this facility would contribute 256 potentially exposed workers, and 1,691 person-years to the mortality study.

TABLE 2

SUMMARY OF PERSONNEL RECORDS REVIEW[a,b,c]

RECORD SYSTEM	RECORDS (# SAMPLED)	EST % EXP	EST # EXP	% MALE	YR BIRTH	DUR EXP	EST[d] P-YRS
Inactive[c]	3695 (368)	4.3	167	75	1950	2.0	1281
Active-Hourly	NA	7.5	49	100	1948	8.8	378
Active-Salaried	NA	13.3	40	25	1945	11.5	32
Overall	3895 (368)	5.3	256	72	1949	4.9	1691

a) The following abbreviations were used in this table; EST for estimated, YR for year, EXP for exposed, DUR for duration, NA for not available and P-YRS for person-years.

b) Statistics presented are based on data abstracted from the workers classified as being potentially exposed to ETO in this review.

c) In order to be considered exposed a worker must have been first exposed prior to 1978 for at least 3 months.

d) Person-years were estimated by calculating the number of person-years for workers in the sample first exposed prior to 1978, and extrapolating to the entire group. For example, among the sample inactive workers exposed prior to 1978, the estimated number of person-years contributed was 121 person-years. Multiplying 12 person-years by the sample fraction (3895/368) yields an estimate of 1281 person-years for the entire group.

DESCRIPTION OF MEDICAL, INDUSTRIAL HYGIENE AND SAFETY PROGRAMS

Medical

AP has an in-house medical department which is equipped to handle minor emergencies. In 1978, an annual medical surveillance program was instituted to monitor all ETO exposed persons. In addition, all newly hired employees, into an ETO area or ETO exposed employees who left the area (reassignment, retirement, or termination) were included in the program. Exposure to ETO was determined by industrial hygiene measurements. The surveillance program, which was part of a company-wide ETO abatement policy, and includes an internal control group (employees who have never been exposed to ETO), collected family, work, and reproductive histories; urine and blood profiles; physical examinations (including chest x-rays and pulmonary function tests); and cytogenetic assays (sister chromatid exchange and abberations). In addition, from 1979 to 1982, sperm counts were also examined on all ETO exposed male workers. The results of this study (sperm

counts) were considered to be negative by the company therefore, the study was discontinued.

Industrial Hygiene and Safety

AP has an industrial hygiene program which is managed and conducted by on-site personnel. Monitoring with charcoal tubes for ETO began in late 1978, to establish baseline levels in those areas where exposure to ETO may occur. Sample analysis was done by the Chemistry Quality Assurance lab, which is on-site. In 1981, the company conducted side-by-side field and laboratory tests to compare 3M passive monitors with the charcoal tubes. The tests, which according to the company showed very good correlation between the two methods, resulted in a gradual increase in the use of the badges. At the time of this survey, all personnel monitoring, to establish an 8-hour time weighted average (TWA) exposure to ETO, is conducted with these badges. The company has also conducted some general area sampling with direct reading instruments to document leaks or areas of particular concern. The company uses the data it collects to augment its ETO abatement program.

The industrial hygiene data indicate that, in general, those employees working in the sterilizer area have the highest potential exposure to ETO. Employees working in the quarantine area have the next highest potential for ETO exposure. The actual employee exposure, in either one of these areas, however, is probably very small because of the enforced use of an self contained breathing apparatus (SCBA) respirator in these areas. Other areas such as raw material stores, shipping, chemistry and biology labs do have a small potential for exposure. The personal TWA (8 hr) exposures in the quarantine, sterilizer and shipping areas also appeared to fall over time and then rise. The rise was very small in shipping, however. The personal TWA (8 hr) exposures in raw material stores, chemistry and biology labs have, in general, decreased over time (since 1979).

The company also conducts extensive employee training programs in the hazards associated with and the safe use of ETO. Part of this training program involves the proper use and fit of a respirator. The company instituted an ETO respirator program in 1979. Anyone entering a restricted area (sterilization or quarantine) was required to have a qualitative fit test and wear an air purifying (cannister type) respirator. In 1981, the required mask was changed to a SCBA with positive pressure. In 1983, the requirement was again changed to a SCBA with a dual regulator. Respirators were permanently mounted on all fork lift trucks, which entered the quarantine area, to ensure compliance with the respirator program. A detailed use and maintenance log is kept by each department where the use of a respirator is required.

The company requires the use of protective polypropylene gloves in most of the production areas. This is because the products produced require such a high degree of sterility. The company also requires safety shoes in some areas.

DESCRIPTION OF PAST EXPOSURES

The company has instituted several changes in work practices (requiring the use of a respirator), sterilization procedures or vessels, and the quarantine area as efforts to reduce employee exposure to ETO. Many of these changes were part of the ETO abatement program instituted by the company in 1979.

Work Practices-Use of Respirators

The company instituted an ETO respirator program in 1979 as part of its ETO abatement program. Anyone entering a restricted area (sterilization or quarantine) was required to have a qualitative fit test and wear a air purifying type respirator. In 1981, the required mask was changed to a SCBA with positive pressure. In 1983, the requirement was again changed to a SCBA with a dual regulator. Respirators were permanently mounted on all fork lift trucks, which entered the quarantine area, to ensure compliance with the respirator program.

Sterilization Procedures or Vessels

There have been many changes in the sterilization procedures or vessels over the last several years. AP began using 100% ETO in 1962 to sterilize its product in three vessels (6 pallet, 850 ft^3 each). These vessels were located outside the building. In 1968, one (1) 2800 ft^3 (20 pallet) vessel was added, and all four vessels were moved to their present location. This new location, which was on the opposite side of the facility, had walls on two (2) sides and a roof. A control room was also built. The vessels were equipped with a semi-automatic steam system to aid in ejection of ETO. The ETO tanks, which supply the vessels with a underground line and were located near the sterilizers, were moved 200 ft. to the north. In 1970, an additional 2800 ft^3 vessel replaced two of the 850 ft^3 vessels. In 1973, one more 2800 ft^3 vessel was added, so that Pharmaseal had three 2800 ft^3 vessels and one 850 ft^3 vessel. The ETO tanks were moved an additional 200 ft. to the north.

In 1976, the sterilization area was completely enclosed. There were also changes in the final evacuation pressures of the vessel, as well as, a trend to decrease the final ETO concentration in the vessels. A fully automatic vessel control system was added. This system allowed the operator to control the amount of ETO delivered to the vessel from a central control panel, instead of opening the tank and physically weighing out the ETO to be delivered to the vessel. This should serve to reduce the possibility of accidental exposure to ETO due to poor connections at the tank or operator error. In 1979, the semi-automatic steam ejection system was replaced with a water sealed vaccum pump. Also during 1979, the use of a respirator was instituted as part of the ETO abatement program.

In 1980, the vessels were redesigned. A fan was installed on the unloading side of the vessel, so that before the door could be opened, air was swept through the vessel toward the loading side. The air was exhausted through a butterfly valve. This should reduce the concentration of ETO remaining in the vessel following the last vacuum. In 1984, the exhaust from the vessels was then divereted to an incinerator. In addition, the employees which unloaded the vessels were required to wear full-face SCBA respirators. An exhaust system was also installed vertically along the wall nearest to the unloading end of the vessels. These ducts, which had openings about six feet from the floor, helped to remove the ETO that would areate from the freshly sterilized product as it was being unloaded. In addition, there were guards placed on the floor approximately two (2) feet in front of these ducts to ensure proper movement of air.

An aeration oven for freshly sterilized QC samples was installed in the sterilization area in 1981. The QC samples, which have been pulled from the freshly sterilized pallets, are placed in these ovens for 24 hours before they are taken back to the QC department. These ovens are exhausted into the incinerator.

Quarantine

The quarantine area shared a common floor space with shipping and raw material storage until 1979. At that time, quarantine was isolated by a cement block floor to roof wall. There was always a wall separating the sterilizer area from quarantine, however, the doorway is always open. The doorway between quarantine and shipping is also open, just during the first shift, to allow movement of goods into shipping. Access to quarantine was restricted in 1979, so that anyone entering the area must wear a respirator. Over the next couple of years (from 1980-1982), a dedicated exhaust ventilation system was installed in the area so that air was blown down from the ceiling and pulled toward the sides of the area.

TOXICITY

Evidence from animal studies suggests that ETO may have carcinogenic properties.[7,8] A group of ETO manufacturers sponsored a study at the Bushy Run Research Center in which male and female Fischer 344 rats were exposed to ETO at airborne concentrations of 10, 33, or 100 parts per million (ppm) for 6 hours per day, 5 days per week for two years.[7] Two other groups of animals served as controls. Initially, there were 120 animals of each sex, in each exposure group. The researchers observed a statistically significant increase in the incidence of mononuclear cell leukemia among the female rats, and peritoneal mesothelioma among the male rats exposed to ETO. The increase in leukemia incidence was found to increase linearly as a function of ETO exposure. An elevation in mortality from brain cancers (glial type) was also observed in the rats exposed to ETO.

NIOSH researchers have recently reported on the results from an animal experiment which corroborated the findings of the Bushy Run Study.[8] Male Fischer 344 rats were exposed to ETO for 7 hours/day, 5 days/week for 2

years at airborne concentrations of 0, 50, or 100 ppm. There were 80 rats in each exposure group. Increases in the incidence of mononuclear leukemia, peritoneal mesothelioma, and cerebral gliomas were observed among the ETO exposed rats, relative to nonexposed controls.

Only a few epidemiologic studies have examined the potential human carcinogenicity of ETO.[9-11] Hogstedt, et al, conducted a retrospective cohort mortality study of a group of workers in a Swedish chemical factory that had previously been included in a hematologic investigation.[9] This facility produced ETO via the chlorohydrin process in which, in addition to ETO, there was potential exposure to ethylene, ethylene chlorohydrin, ethylene dichloride, and small amounts of bis(2-chloro-ethyl) ether. Among 89 "full-time" exposed workers, a statistically significant (p less than .01) excess of leukemia mortality was observed (2 observed versus 0.14 expected). In addition, a statistically significant (p less than .01) excess of stomach cancer was observed (3 observed versus 0.4 expected). Because of the mixed exposures, these findings could not be attributed to ETO; however, ethylene oxide and ethylene dichloride were the prime suspects.

Morgan, et al, conducted a retrospective cohort mortality study of workers involved in the production of ETO at a Texaco Facility.[10] A total of 850 workers were included in the study, of which 767 were potentially exposed to ETO. No ETO was detected in most samples taken in the production area, and all measurements in this area were below 10 ppm. No cases of leukemia were observed in this study; however, the authors estimated that the lowest relative risk that they had a high probability of detecting (80% power) was 10.5.

Hogstedt also reported on three cases of leukemia that occurred in a small group of workers at a Swedish company.[11] The company used a mixture of 50% ETO and 50% methyl formate to sterilize hospital equipment. The 8-hour TWA exposure for ETO at this facility was estimated at 20 ppm. According to national statistics, only 0.2 deaths due to leukemia were expected in this cohort. One of the cases was exposed to benzene, a known leukemogen, and it was speculated that the combined exposure of ETO and methyl formate might produce a special risk.

ETO is also a potent alkylating agent capable of causing irreversible changes or mutations in cellular proteins and DNA in animals.[12,13] ETO is also a positive mutagen in several *in vitro* systems such as *Salmonella typhimurium*, viruses, and *Tradescantia poludosa*.[6]

Chromosomal aberrations related to ETO exposure have been observed in a number of animal studies and epidemiologic investigations.[8,13-20] Yager and Benz observed a dose related increase in sister chromatid exchanges (SCEs) among New Zealand white rabbits that were exposed via inhalation to 50 to 250 ppm of ETO.[14] NIOSH (Lynch, et al) recently reported preliminary findings in which cynomolgus monkeys were exposed to 0, 50, or 100 ppm of ETO for 7 hours per day, 5 days per week.[8] After 24 months of exposure, statistically significant increases were observed in the frequency of chromosomal aberrations (including quadriradial chromosomes) and SCEs in

the peripheral lymphocytes of the 50 and 100 ppm exposed groups versus the controls.

Garry, et al, examined the occurrence of SCE in the peripheral lymphocytes of 12 ETO exposed workers and 12 nonexposed controls in a hospital sterilization facility.[15] The exposed group showed statistically significant elevations in the number of SCEs compared to the controls. Particularly high SCE frequencies were observed among 4 workers that had reported either neurologic or respiratory symptoms. The maximum peak exposure level of ETO measured at this facility was 36 ppm.

Cytogenetic abnormalities have also been observed in several studies of workers exposed to ETO. Ehrenberg, in a study of workers at a factory manufacturing and using ETO, observed a high frequency of chromosomal aberrations in 8 workers who were accidentally exposed to high concentrations of ETO. One case of leukemia was also observed among the 37 workers studied.[16]

American Hospital Supply initiated a cytogenetic survey of workers that were exposed to ETO in the sterilization of medical devices in 1978.[17,18] Seventy-five exposed workers at 9 facilities were studied, as well as 37 nonexposed workers who served as controls. Compared to controls, exposed workers were found to have statistically significant increased frequencies of SCEs and chromosomal aberrations.

In response to the findings from the American Hospital Supply study, Johnson and Johnson initiated a cytogenetic study of workers that were also exposed to ETO in the sterilization of medical products.[19,20] Approximately 50 workers not exposed to ETO were compared to 50 exposed workers at three facilities with 8-hour Time-Weighted Average (TWA) exposures to ETO of less than 1 ppm, 1-10 ppm, and 25-200 ppm, respectively. Statistically significant elevations in SCE frequency were observed in the latter two facilities, and these changes have persisted after one year. The frequency of SCEs appeared to increase in a dose response manner. Chromosomal aberrations were also elevated in the high exposure groups; however, these findings were not statistically significant.

APPLICABLE STANDARDS AND RECOMMENDED LEVELS

Prior to June 22, 1984, the Occupational Safety and Health Administration (OSHA) Permissible Exposure Limit (PEL) for ETO was 50 ppm as a TWA concentration for an 8-hour workshift.[21] OSHA established a new PEL of 1 ppm as an 8-hour TWA on August 21, 1984.[22] In addition, an "action level" of 0.5 ppm as an 8-hour TWA was established (by OSHA) as the level above which employers must initiate periodic employee exposure monitoring and medical surveillance. The Environmental Protection Agency (EPA) supported the OSHA PEL of 1 ppm in the Federal Register (June 22, 1984).[23]

In 1977, NIOSH recommended a ceiling level of 75 ppm as determined during a 15 minute sampling period.[6] This level, however, was set prior to the recognition of the carcinogenic potential of ETO. Based on recent findings, NIOSH recommends that ETO exposures not exceed 5 ppm for a maximum of 10

minutes per day and that exposures be controlled to less than 0.1 ppm determined as an 8-hour TWA (NIOSH Policy Statement, July 20, 1983). The American Conference of Governmental Industrial Hygienists (ACGIH) recommends a Threshold Limit Value (TLV) of 10 ppm for an 8-hour TWA based on data available prior to 1982.[24] However, in 1982, the ACGIH issued a notice of intended change in which it was proposed that the TWA concentration be lowered to 1 ppm. This recommendation was reviewed and adopted in 1984. ACGIH has also designated ETO as an A2 carcinogen.[24] An A2 carcinogen is defined as an industrial substance suspected of having carcinogenic potential for man. This designation is based on either (1) limited epidemiologic evidence, exclusive of clinical reports of single cases, or (2) demonstration of carcinogenesis in one or more animal species by appropriate methods.

CONCLUSIONS AND RECOMMENDATIONS

AP produces single-use medical devices such as diagnostic trays and syringes with and without needles and has sterilized its product with 100% ETO since 1962. This facility has collected extensive industrial hygiene data on ETO exposures since 1978. The first two years (1978-79) charcoal tubes were used. These tubes were replaced with 3M passive ETO monitors in 1981.

This plant meets the three eligibility requirements as defined in the protocol and therefore, should be included in the study. These requirements are 1) the plant must contribute at least 200 person-years to the high exposure group, or 400 person-years total, 2) the plant must have adequate personnel records or other records that can be used for identifying past and present workers exposed to ETO, and 3) the plant must not have any serious confounding exposure to a known leukemogen.

REFERENCES

1. NIOSH. Current Intelligence Bulletin 35 - Ethylene Oxide (ETO). DHHS (NIOSH) Publication No. 81-130, May 22, 1981.

2. Chemical Economics Handbook, SRI International, Ethylene Oxide, January, 1980.

3. Clayton, G.D.; Clayton, F.E.; eds, Patty's Industrial Hygiene and Toxicology, 3rd Revised ed., Vol. 2A, John Wiley and Sons, New York, 1978.

4. NIOSH. Draft Feasibility Study for a Cohort Mortality Study of Workers Exposed to Ethylene Oxide. Internal report from the Industrywide Studies Branch, June, 1983.

5. National Occupational Hazard Survey, National Institute for Occupational Safety and Health, 1977.

6. Glazer, Z.R., Special occupational hazard review with control recommendations for the use of ethylene oxide as a sterilant in medical facilities. National Institute for Occupational Safety and Health, DHEW (NIOSH) Publication No. 77-200, 1977.

7. Snelling, W.M.; Weill, C.S.; and Maronport, R.R., Final report on ethylene oxide two-year inhalation study on rats. Project Report 44-20, Bushy Run Research Center, January 28, 1981. Submitted by Union Carbide Corporation to the U.S. Environmental Protection Agency under section 8(e) of the Toxic Substances Control Act, on behalf of co-sponsors of the study (February, 1981).

8. Lynch, D.W.; Lewis, T.R.; Moorman, W.J.; Sabharwal, P.S.; and Burg, J.R., Chronic inhalation toxicity of ethylene oxide and propylene oxide in rats and monkeys -- a preliminary report. Presented at the 21st Annual Society of Toxicology Meeting, Boston, Massachusetts, February 22-26, 1982.

9. Hogstedt, C.; Rohlen, O.; Berndtsson, B.S.; Axelson, O.; and Ehrenberg, L., A cohort study of mortality and cancer incidence in ethylene oxide production workers. Br. J. Ind. Med., 39:276-280, 1979.

10. Morgan, R.W.; Claxton, K.W.; Divine, B.J.; Kaplan, S.D.; and Harris, V.B, Mortality Among Ethylene Oxide Exposed Workers. J. Occ. Med., 23:767-770, 1981.

11. Hogstedt, C.; Malmqvist, N.; and Wadman, B., Leukemia in workers exposed to ethylene oxide. JAMA, 241:1132-1133, 1979.

12. Calleman, C.J.; Ehrenberg, L.; Jansson, B.; Osterman-Golkar, S.; Segerback, K.; and Wachtmeister, C.A., Monitoring and risk assessment by means of alkyl groups in hemoglobin in persons occupationally exposed to ethylene oxide. J. Environ. Pathol. Toxicol., 2:427-442, 1978.

13. Ehrenberg, L.; Heische, K.D.; Osterman-Golkar, S; and Wennberg, I., Evaluation of genetic risks of alkylating agents: Tissue doses in the mouse from air contaminants with Ethylene Oxide. Mutat. Res., 24:83-103, 1974.

14. Yager, J.W., and Benz, R.D., Sister chromatid exchanges induced in rabbit lymphocytes by ethylene oxide after inhalation exposure. Environ. Mutagen., 4:121-134, 1982.

15. Garry, V.E.; Hozier, J.; Jacobs, D.; Wade, R.; and Gray, D., Ethylene Oxide: evidence of human chromosomal effects. Env. Mutag., 1:375-382, 1979.

16. Ehrenberg, L., and Hallstrom, T., Haematologic studies on persons occupationally exposed to ethylene oxide. In: International Atomic Energy Agency Report, SM 92/26, pp. 327-334, 1967.

17. Abrahams, R.H., Recent studies with workers exposed to ethylene oxide, in The Safe Use of Ethylene Oxide. J.F. Jorkasky, ed. Health Industry Manufacturers Association, Washington, D.C., HIMA Report No. 80-4: 211-220, 1980.

18. Abrahams, R.H., Chromosomal changes in workers exposed to ethylene oxide -- an update. Ethylene Oxide Worker Safety Issues. J.F. Jorkasky, ed., Washington, D.C., HIMA Report No. 82-2:27-38, 1982.

19. Herman, A.A., (Johnson and Johnson Corporate Submittal to OSHA). Pilot research chromosome study of workers at sites where ethylene oxide gas is utilized as a sterilant. Submitted to OSHA, March 30, 1982.

20. Jones, J.P., Chromosomal changes in employees exposed to ethylene oxide. Ethylene Oxide Worker Safety Issues. J.F. Jorkasky, ed., Washington, D.C., HIMA Report No. 82-2, 5-25, 1982.

21. Occupational Safety and Health Administration (OSHA), Safety and Health Standards 29 CFR 1910, General Industry Standards, OSHA 2206, Revised, June, 1981.

22. Federal Register, Department of Labor, Occupational Safety and Health Administration, 29 CFR Part 1910, Occupational Exposure to Ethylene Oxide. 49(122):25734-25809, June 22, 1984.

23. Federal Register, Ethylene Oxide; Certain Pesticide Products Registered for the Sterilization of Equipment and Supplies in Hospitals and Health Care Facilities. 49(122):25675-25676, June 14, 1984.

24. Threshold Limit Values for Chemical Substances and Physical Agents in the Work Environment with Intended Changes for 1983-84, American Conference of Governmental Industrial Hygienists, 1983.

FIGURE I

AMERICAN PHARMASEAL
IRWINDALE, CALIFORNIA
AUGUST 21-22, 1984

PROCESS FLOW DIAGRAM