INDUSTRYWIDE STUDIES REPORT:
A WALK THROUGH SURVEY

OF

BECTON DICKINSON COMPANY
West Highway 6
P.O. Box 435
Holdredge, Nebraska 68949

SURVEY CONDUCTED BY:
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DATE OF SURVEY:
August 21-22, 1985

REPORT WRITTEN BY:
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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

DISCLAIMER

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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 CONTACTED:	Moe Milliken, Industrial Relations Manager (308) 995-6501 Gary Sims, Human Resources Representative (308) 995-6501 Anthony Piniat, Senior Program Manager, Corporate Safety, Paramus, New Jersey
EMPLOYEE REPRESENTATIVES CONTACTED:	No union.
STANDARD INDUSTRIAL CLASSIFICATION:	3841 - Surgical and Medical Instruments and Apparatus

ABSTRACT

On August 21-22, 1985, a walk-through survey was conducted at Becton Dickinson Consumer Products, Holdredge, Nebraska. This division of Becton Dickinson and Company produces single use insulin syringes. The company has sterilized these products in sterilizers with 100% EtO since 1968. This survey was conducted to evaluate the industrial hygiene records, production processes, and personnel records to determine the suitability of including this facility in the mortality/industrial hygiene study of EtO being conducted by NIOSH researchers.

During the visit, personnel records were evaluated and a walk through survey of the facility and production processes was conducted. Industrial hygiene records were reviewed and the EtO exposure data submitted by the company is summarized. EtO has been used by this company since 1968; five, 1000 ft^3 sterilizers are currently used to sterilize product. EtO exposure data has been collected since 1981 and range from non-detectable to 7.9 ppm.

Results of the survey indicated that this facility meets all the eligibility requirements as defined in the protocol of EtO mortality study and will be included. These requirements are: 1) the plant must contribute at least 400 person years, 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.

Recommendations were offered to reduce the EtO exposure potential in this facility. NIOSH has no immediate plans to conduct on industrial hygiene sampling survey at this plant as a part of the EtO study.

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 Becton Dickinson Company 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. In addition, the data gathered during the walk-through survey will be used to develop, to the extent possible, estimates of exposure to EtO by department and/or job category, level and duration of continuous and peak exposures, and calendar year within this plant. These exposure estimates will then be compiled into an exposure matrix which will be used to determine the existence of a dose response relationship with any positive association observed in the mortality study.

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

Becton Dickinson and Company is composed of six operating groups which include a total of 25 divisions. Each division operates from one to six plants with a total of 68 plants worldwide. Fifty of these are domestic with other facilities located in Ireland, Spain, France, Brazil, Mexico, and Canada. This facility in Holdredge has always been operated by Becton Dickinson and Company. This plant is composed of two single story buildings.

The Holdredge, Becton Dickinson plant produces and EtO sterilizes hypodermic needles and syringes. This EtO sterilization process has been conducted in 1000 ft^3 sterilizers using 100% EtO since 1968. This plant opened in 1966 and two, 1000 ft^3 AMSCO® sterilizers were installed in 1968. A 1000 ft^3 Vacudyne® sterilizer was added each year in 1974, 1980, and 1981. Diagram 1 shows the locations of the sterilizers in relation to the manufacturing, shipping and quarantine areas. There are two designated cafeteria areas within the facility where all workers are required to spend lunch and break periods.

DESCRIPTION OF THE WORKFORCE

Approximately 65% of the workforce is female and about 2.5% are minority workers. Workers in the sterilization department, however, are primarily males. This is a stable workforce with an annual turnover rate of less than 2%. There is no union representing the workers at this facility.

DESCRIPTION OF THE PROCESS

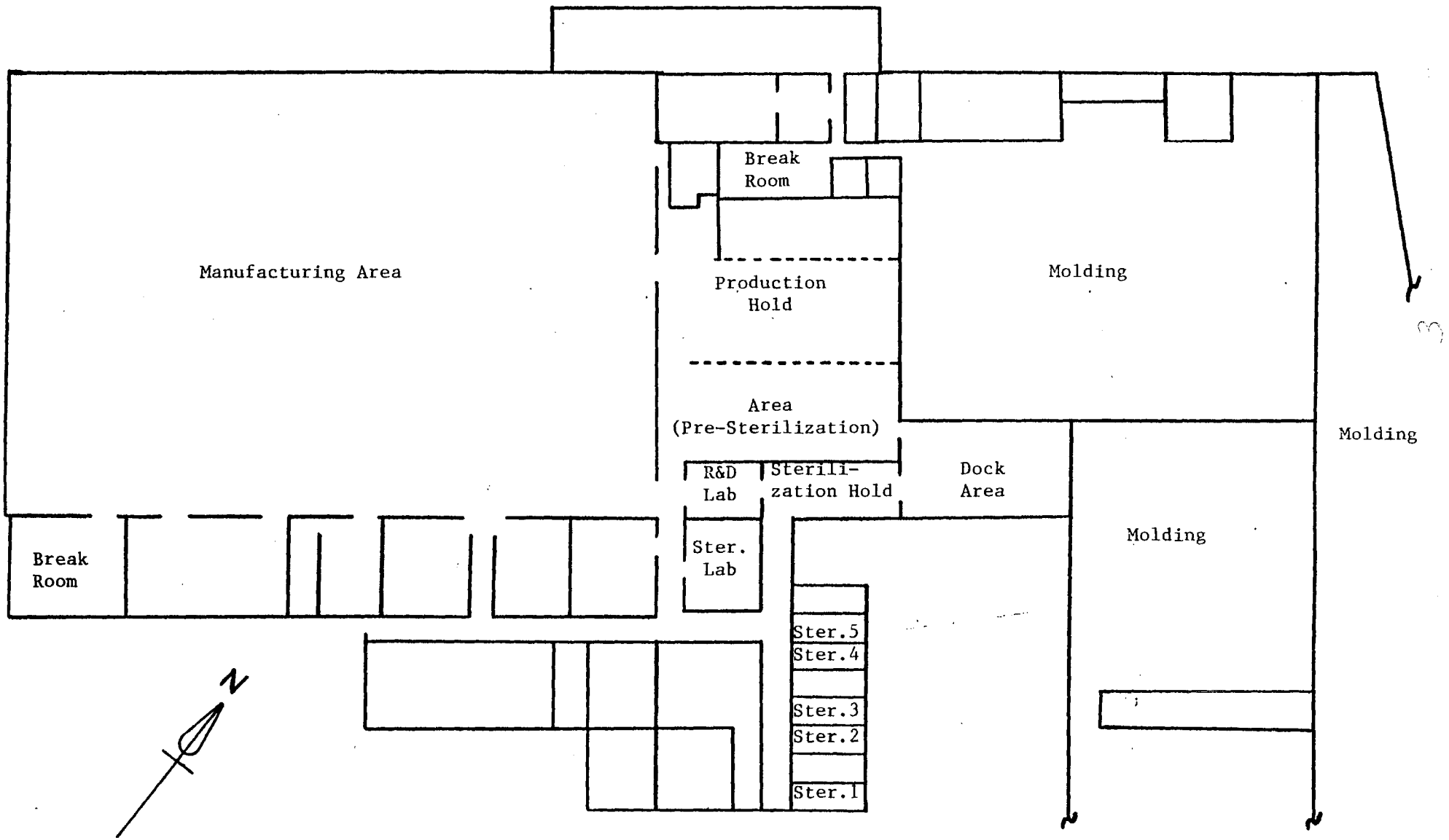
The Becton Dickinson, Holdredge plant, currently produces sterile single use medical devices such as hypodermic insulin syringes and allergist syringe trays. EtO sterilization of products from other Becton Dickinson production plants is also conducted at the Holdredge plant.

Plastic components, used in the assembly of the syringes, are manufactured (molded) within this facility using polypropylene extrusion processing. The needle portion of the syringe is produced and supplied to the Holdredge facility by another plant. Individuals components are assembled and packaged at the Holdredge plant. Cases of the product are placed on pallets and remain on the pallets for sterilization.

A typical sterilization process in this plant consisted of the following cycle.

- The sterilization chamber is loaded with product and closed,
- a pre-conditioning phase for a specific time interval at increased humidity and temperature is conducted,
- an initial vacuum is achieved,
- a second conditioning (humidification) is conducted,

DIAGRAM 1
MANUFACTURING/STERILIZATION BUILDING
BECTON DICKINSON CONSUMER PRODUCTS PLANT
HOLDREDGE, NEBRASKA



- 100% EtO is introduced into the chamber over various time intervals to effect sterilization,
- a post sterilization vacuum with carbon dioxide (CO_2) introduced into the chamber,
- a second post sterilization vacuum without CO_2,
- filtered air is introduced to bring chamber back to atmospheric pressure,
- the chamber is unloaded and product is placed in the holding room (8-10 hours) prior to quarantine.

The sterilizer operators use a fork truck to load and unload the pallets of product. Sterilized product was warehoused and quarantined in a building separate from the manufacturing and sterilization areas shown in Diagram 1.

The sterilization process was operated on a three shift basis, five days per week.

DESCRIPTION OF PAST EXPOSURES

This plant has used 100% EtO to sterilize products since 1968. In that year, two 1000 ft^3 AMSCO® sterilizers were installed to use 100% EtO. Additional Vacudyne® 1000 ft^3 sterilizers were installed in 1974, 1980, and 1981 for a total of five sterilizers. From 1968 to 1972 the product was sterilized wrapped in paper packages which were hand packed prior to sterilization. During the years 1972 to 1974, the product was bulk sterilized in plastic bags. After sterilization (1968-1974), the product was thereby individually packed and cased (EtO emitted from the product) in the production hold area before it was placed in quarantine. During the years 1975 to 1982, the sterilized product was individually packaged and cased in the warehouse (separate from the manufacturing building). In 1985, the procedure was revised and all packaging and casing of the product is currently conducted prior to sterilization. This revised procedure reduced the number of personnel exposed to EtO. From 1968 to January 1985, it is difficult to fully identify and quantify EtO exposure because of the different product packaging schemes. Workers who handled sterilized product would have been exposed to EtO emitted from that product. EtO is expected to have migrated from the sterilizer area into that area of the building adjacent to the sterilizers. Sterilized product packaged in the production hold area certainly contributed EtO to the ambient levels in that area. Aeration prior to handling of the sterilized product was not performed during this time period.

The sterilizer area was equipped with a through the wall exhaust fan from 1968 to 1982. The sterilizers were vacuum purged using water sealed vacuum pumps into recessed open drains inside fully enclosed mechanical access rooms during the years 1968 to 1985. These rooms also contained the drums of 100% EtO. The sterilizers were equipped with rear exhaust ventilation systems and local exhaust ventilation hoods above the doors in 1982. These systems are dedicated and exhaust through six foot high stacks above the sterilizer area. Also in 1982, the sterilizer area, and the quarantine area were equipped with single pass air handling units; prior to that time the

air handling units operated on approximately 30% recirculation. An overhead (garage style) door, located at the front of each sterilizer, further separates the sterilizers from the rest of the facility.

The quarantine air handling unit during prior to 1982 was not part of the warehouse system.

Becton Dickinson began monitoring EtO exposure at the Holdredge plant in 1981 using Qazi Ketchem charcoal tubes. The samples were analyzed by a Becton, Dickinson and Company laboratory in North Carolina. This laboratory is accredited by the American Industrial Hygiene Association. It is unclear whether the 1981 samples were personal or area measurements. In 1983, Becton Dickinson began using DuPont passive dosimeters, but discontinued use of this sampling method because of questionable accuracy and sensitivity. 3M passive monitors have been used since 1984 to monitor EtO exposure. In 1985, this company began using AMSCO passive monitors in conjunction (side-by-side sampling) with the 3M passive monitors. These samplers are analyzed at the Becton, Dickinson and Company laboratory in North Carolina.

Table 1 presents summarized 8-hour time weighted average EtO exposure data by job title for 1984 and 1985 using the 3M and AMSCO passive monitors. The highest mean exposure level for a job was 3.5 ppm in July, 1984 for employees working in the self contained packaging operation. This reflects exposure potential during packaging/casing sterilized product while EtO is being emitted from the product. The exposure potential appears lower (mean of $\leq$ 0.6 ppm), after the revised production procedure, for the employees in the case pack operation in 1985.

The sterilizer operators and sterilizer repair technician's exposure potential is about 2.0 ppm. Exposure to EtO for the microbiologist and laboratory technicians is on the average 1.3 and 1.0 ppm respectively. Apparently EtO exposure for quality control testers has decreased (from 3.1 to 0.3) because of the revised production process.

Two small (< 3 ft^3) AMSCO® EtO sterilizers are located in the laboratory and are used for research and development purposes. These units use a mixture of 12% EtO and 88% dichlorodifluromethane. The laboratory technicians' and microbiologists' exposure is primarily from the use of these two sterilizers.

DESCRIPTION OF PERSONNEL RECORDS AND DEFINITION OF EXPOSED GROUP

Personnel files are available for all workers who have ever been employed at this facility, except for salaried workers who have transferred to another Becton Dickinson plant. The number of workers who have transferred is believed to be small, and since the majority of the workers that would be included in this study are hourly workers this would not be a major problem for this study.

TABLE I
EtO EXPOSURE LEVELS (PPM)*
BECTON, DICKINSON CONSUMER PRODUCTS PLANT
HOLDREDGE, NEBRASKA

DATE	JOB TITLE	SAMPLES	RANGE	MEAN
June/July, 1984	Sterilizer Operator	13	0.7-4.5	2.0
May, 1985	Sterilizer Operator	6	0.8-1.6	1.3
July, 1985	Sterilizer Operator	6	1.0-2.9	1.9
June/July, 1984	Sterilizer Repair Tech.	3	1.1-3.1	2.0
May, 1985	Sterilizer Repair Tech.	2	0.6-0.7	
July, 1985	Sterilizer Repair Tech.	2	1.3-1.7	
June/July, 1984	Microbiologist	9	0.6-3.3	1.3
August, 1985	Microbiologist	2	0.3-0.5	
June/July, 1984	Lab. Technician	9	0.7-2.1	1.0
July, 1984	Quality Control Testers	21	0.3-7.2	3.1
February, 1985	Quality Control Testers	75	N.D.-1.0	0.3
July, 1984	Self Contained Packaging	94	0.1-8.0	3.5
February, 1985	Case Pack (Self Contained Pack.)	14	N.D.-1.1	0.6

*PPM - Parts per million-8-hour time weighted average exposure information submitted by company.
N.D. - Non-detected.

Personnel files for current employees and for employees who have terminated employment within the last 3 years are on file in the personnel office. Personnel files for workers who have terminated employment more than 3 years ago are on file in a warehouse in Holdredge. These files contain application forms, attendance record cards, and employee status notices. The employee status notices are filed each time a person makes a change in job or department, and could be used for constructing detailed work histories.

The personnel department also maintains a system of employee record cards. These cards are maintained separately from the personnel files, except for workers who have terminated employment within the last 3 years (their cards are in the personnel files). This record contains information essential to this study including address, date of birth, sex, social security number, and a detailed work history. Department numbers have not been consistently entered onto this record, but they are available from the employee status notices described above.

Personnel files and employee record cards for active employees are filed separately for hourly and salaried workers. Salaried workers files are further subdivided by overtime exempt and nonexempt categories. There are a total of approximately 460 files for active hourly employees and 100 files for active salaried employees. Personnel files for former hourly and salaried workers have been interfiled and there are a approximately 2700 of these files.

Based upon a review of the plant's processes which utilize EtO and extensive discussions with the plant's management a list of jobs and departments involving potential exposure to EtO was developed. Workers who have been employed for at least 3 months in one of these activities would be considered exposed to EtO and included in this study. Table II contains a list of these jobs and departments and descriptions of the activities involving EtO exposure.

The company had prepared a list of individuals that they believed were potentially exposed to EtO. This list was prepared by reviewing the personnel records. All of the exposed job categories listed in Table II were included on this list, except for jobs in the warehouse department. The personnel records of two individuals from each job category on the company's list were pulled and reviewed in the presence of a company representative. The purpose of this review was to evaluate the feasibility of using the personnel record keeping system as the basis for identifying exposed workers in the cohort study.

Overall, the records appeared adequate for the purposes of the cohort study, although there were some problem areas. First, workers in the packaging department were part of, and had the same department number as, the production department (either 485 or 486) from approximately 1968 to 1974. During this time period it is not possible to tell whether a 'Utility' worker or a 'Setup instruct and repair' worker were working in the production (nonexposed) or the packaging (exposed) area. Other job titles in the packaging department (see Table II) are unique to this department and

TABLE II
DEPARTMENTS AND POSITIONS INVOLVING POTENTIAL EtO EXPOSURE
AND DESCRIPTIONS OF ACTIVITIES INVOLVING EtO EXPOSURE
BECTON DICKINSON CONSUMER PRODUCTS PLANT
HOLDREDGE, NEBRASKA

DEPARTMENT	POSITION	EtO RELATED ACTIVITY
Self Contained Packaging (489, 485, 486)	Utility Operator	Opened boxes of freshly sterilized goods and unloaded the product for packaging
Self Contained Packaging (489, 485, 486)	Bodolay Loader Oper.	Work in the same area as the utility operators and were incidentally exposed to EtO
Self Contained Packaging (489, 485, 486)	Syringe Putup	Work in the same area as the utility operators and were incidentally exposed to EtO
Self Contained Packaging (489, 485, 486)	Case-Pack	Work in the same area as the utility operators and were incidentally exposed to EtO
Self Contained Packaging (489, 485, 486)	Autobag Operator	Work in the same area as the utility operators and were incidentally exposed to EtO
Self Contained Packaging (489, 485, 486)	Packaging Operator	Work in the same area as the utility operators and were incidentally exposed to EtO
Self Contained Packaging (489, 485, 486)	Floating Operator Setup, Instruct and Repair	Work in the same area as the utility operators and were incidentally exposed to EtO
Self Contained Packaging (489, 485, 486)	Salvage Operator	Work in the same area as the utility operators and were incidentally exposed to EtO
Quality Control (413 or 414)	Intermediate Inspectors	Some but not all of the workers in this job/department worked in the packaging department and were incidentally exposed.
Quality Control (413 or 414)	Test After Sterilization or Stat. Sample	Tested the product for its physical integrity after it was sterilized. Also worked in the packaging department and were incidentally exposed.
Sterilization (487)	Microbiologist Bacteriologist	Involved in the testing of biologic indicators in the sterilization lab. Also operate the R&D sterilizer units.

TABLE II (continued)
DEPARTMENTS AND POSITIONS INVOLVING POTENTIAL EtO EXPOSURE
AND DESCRIPTIONS OF ACTIVITIES INVOLVING EtO EXPOSURE
BECTON DICKINSON CONSUMER PRODUCTS PLANT
HOLDREDGE, NEBRASKA

Sterilization (487)	Lab Assistant	Involved in the testing of biologic indicators in the sterilization lab. Also operate the R&D sterilizer units.
Sterilization (487)	Lab Technician	Involved in the testing of biologic indicators in the sterilization lab. Also operate the R&D sterilizer units.
Sterilization (487)	Senior Lab Technician Sterility Tester	Involved in the testing of biologic indicators in the sterilization lab. Also operate the R&D sterilizer units.
Sterilization (487)	Sterilizer Operator	Operate the production EtO sterilizers.
Sterilization (487)	Sterilizer Technician	Operate the production EtO sterilizers.
Sterilization (487)	Repair Tech	In addition to the duties of a sterilizer operator, this job involves maintenance and repair of the sterilizers.
Sterilization (487)	Record Clerk	Works in the sterilization lab and is incidentally exposed.
Warehouse (483)	Warehouser	Works in the warehouse in which EtO sterilized goods are stored. Also workers on the 2nd and 3rd shift pick up freshly sterilized goods from the sterilization area and move it to the quarantine area in the warehouse.
Warehouse (483)	Incoming Mater. Handler	Works in warehouse in which EtO sterilized goods are stored. Does not work directly with EtO sterilized goods.
Warehouse (483)	Receiving Clerk	Works in warehouse in which EtO sterilized goods are stored. Does not work directly with EtO sterilized goods.
Warehouse (483)	Shipping and Receiving Clerk	Works in warehouse in which EtO sterilized goods are stored. Does not work directly with EtO sterilized goods.

thus do not present a problem. Second, 'Intermediate Inspectors' from the Quality Control Department may have worked in either the production or the packaging department. Finally, several of the 'Microbiologists' have transferred to other BD facilities and their personnel files were also transferred to these facilities. All of these problems may be worked out through discussions with plant personnel who are familiar with where individuals have actually worked.

Approximately 5% of the personnel records were randomly selected and reviewed. This review served the following purposes; as an additional test of the adequacy of the personnel records, as a means of estimating the number of person-years that this plant would contribute to the study, and for describing the demographic characteristics of the cohort. The findings from this review are summarized in Table III. Overall, the sample of the exposed population was primarily female and middle age with a mean year of birth of 1945. Based on this review it is estimated that this cohort would contribute 279 persons and 3463 person-years to this study.

TABLE III
PERSON YEARS AND DEMOGRAPHIC CHARACTERISTICS OF
A 5% SAMPLE OF THE PERSONNEL FILES[a,b]
BECTON DICKINSON CONSUMER PRODUCTS PLANT
HOLDREDGE, NEBRASKA

STATUS	# SAMPLED (TOTAL #)	%EXP	%MALE	MEAN YR BIRTH	MEAN YR 1ST EXP.	MEAN YR LAST EXP	SAMPLE PYRS.	EST. TOTAL[c] STUDY PYRS
Active	28(556)	21%	17%	1939	1972	1981	68	1350
Former	134(2672)	6%	50%	1948	1973	1975	106	2113
Total	162(3228)	9%	36%	1945	1973	1977	174	3463

a. Workers included in this analysis must have worked for at least 3 months prior to 1978 in one of the jobs and departments listed in Appendix A.
b. The following abbreviations are used in this table; exp for exposed, yr for year, est for estimated, and pyrs for person-years.
c. The total number of study person years was estimated by multiplying the number of person-years in the sample times the inverse of the fraction of records sampled.

DESCRIPTION OF MEDICAL, INDUSTRIAL HYGIENE AND SAFETY PROGRAMS

Medical

This plant does not employ a physician or nurse. Individuals trained in first aid are working on each of the plant shifts. Until 1984, preemployment exams were given to potential employees. Annual physical examinations for individuals exposed to EtO and for forklift operators are conducted.

Industrial Hygiene and Safety

As mentioned previously, the company has conducted personal exposure monitoring for EtO. This sampling has been conducted periodically since 1982. Hearing protection, safety glasses, and safety shoes are provided and required in certain areas of the plant. Since March of 1985, sterilizer operators have been supplied and required to wear MSA air purifying respirators during movement of EtO sterilized product. An MSA explosive level monitor, equipped with audible and visual alarms, samples the air at eighteen points in the sterilizer area. Scott® Air Paks are required in order to enter the sterilizer area when EtO levels actuate the alarm system. Eye wash stations are strategically located throughout the sterilizer area.

The plant has an active employee safety committee which meets once per month. There is also a plant management safety committee (plant manager is the chairman) which meets to act on input from the employee safety committee.

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

With only a few minor exceptions, personnel records are adequate to determine who was exposed based on job categories. Limited EtO exposure sampling data for job categories in this facility exists and it is possible to construct a simple exposure characterization matrix (i.e. high exposure-direct exposure, medium exposure-indirect exposure, low to non-exposed) for this facility.

Based on the findings of this survey, 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 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 workers must not have had any serious confounding exposures to a known leukemogen.

Recommendations concerning proper location of remote sampling probes for monitoring EtO concentrations throughout the sterilization area were offered.

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