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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Centers for Disease Control
National Institute for
Occupational Safety & Health
Robert A. Taft Laboratories
4676 Columbia Parkway
Cincinnati OH 45226-1998

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March 10, 1995

Mr. Philip Fox
General Manager
Aerovox Incorporated
740 Belleville Avenue
New Bedford, Massachusetts 02745

Dear Mr. Fox:

We would like to notify you of a study being developed by NIOSH to examine whether exposure to polychlorinated biphenyls (PCBs) is associated with an increased risk of breast cancer. The study will include women from all capacitor manufacturers previously studied by NIOSH and will be questionnaire-based. This study is separate from the PCB mortality study currently underway. NIOSH's legal authority for this study is derived from the Occupational Safety and Health Act of 1970 (Public Law 91-596).

The enclosed draft protocol is a detailed study plan which contains study design, methods, and samples of worker contact documents. It has been submitted to our Human Subjects Review Board to ensure that individual rights are protected. You will note in the protocol that we also plan to evaluate the incidence of breast cancer in women exposed to ethylene oxide from a different group of facilities previously studied by NIOSH.

We are sending this letter and protocol to you as part of our tripartite review process. Please forward any comments on the protocol to me by March 31st. This letter is also being sent to Dr. Steven Hamilton of General Electric Company, David Millen of ABB Power T and D Company, Ed Bloch of the United Electrical, Radio, and Machine Workers of America Local 332, Joseph Santos of the International Brotherhood of Electrical Workers (IBEW) Local 1499, Dan Potts of IBEW Local 2031, and John Riley of the Association of Bloomington Salaried Employees.

If you have any questions or need additional information, please feel free to contact me at 513-841-4437. Thank you.

Sincerely yours,

Elizabeth Whelan

Elizabeth A. Whelan, Ph.D.
Senior Epidemiologist
Industrywide Studies Branch
Division of Surveillance, Hazard
Evaluations and Field Studies

Enclosure
cc: Karen Davis-King, M.P.H.

Women's Occupational Health Study: Breast Cancer Incidence in Occupational Cohorts Exposed to Ethylene Oxide and Polychlorinated Biphenyls

Protocol

Co-Project Officers:

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Kyle Steenland, Ph.D.

Industrywide Studies Branch
National Institute for Occupational Safety and Health
Cincinnati, OH

December 5, 1994

Abstract

This cancer incidence study will determine whether women who are exposed to two potential breast carcinogens are at increased risk of breast cancer and whether the risk is dose-related. The study will include 9,929 women exposed to ethylene oxide (ETO), a direct alkylating agent which induces mammary tumors in mice, and 13,736 women exposed to polychlorinated biphenyls (PCBs), compounds which are suspected breast carcinogens because of their estrogenic and lipophilic properties. Both cohorts have been previously assembled by NIOSH. The ethylene oxide cohort includes workers from 14 medical supply manufacturers, while the PCB cohort includes workers from three capacitor manufacturing facilities.

Incident breast cancer cases will be identified from death certificates and questionnaires to living subjects and next-of-kin of deceased subjects. The questionnaire will also provide information about non-occupational risk factors for breast cancer such as parity. The incidence of breast cancer in the occupational cohorts will be compared to that in the general population, with adjustment for factors such as lower parity which might increase breast cancer risk in an occupational cohort independent of chemical exposure. The exposure-response relationship within each cohort will be examined using a quantitative dose-metric based on historical exposure data for the ethylene oxide group and a non-quantitative dose metric for the PCB cohort. The results will apply to the general population exposed to PCBs and to more than 100,000 women who are occupationally exposed to ETO in the United States.

Introduction

Breast cancer is the most common incident cancer among U.S. women, and the second leading cause of cancer mortality in U.S. women.[1] Increasing numbers of women are employed outside the home. Women in traditional female occupations, such as cosmetologists exposed to hair dyes and nurses exposed to chemotherapeutic drugs, as well as women in non-traditional occupations, such as production workers in the chemical and plastics industries, face potential carcinogenic exposures on the job.[2] Few studies of breast cancer etiology have addressed occupational and environmental chemical exposures, and many cancer studies of industrial cohorts have excluded women.[3] Occupational exposure to carcinogens may be of particular concern when the exposures occur during periods of rapid cell division, such as menarche, pregnancy or lactation.[3]

Only recently has the importance of studying occupational cancer among women workers been recognized.[4] Identification of carcinogenic hazards among women workers will be of benefit not only to individuals with occupational exposures, but also to the general population, if identification of a hazardous chemical leads to reduction of environmental exposure.

The National Institute for Occupational Safety and Health (NIOSH), a component of the Centers for Disease Control and Prevention, has played a major role in Occupational Cancer Research in the past two decades. The Institute has unique legislative authority to enter and make inspections of U.S. workplaces, to obtain medical and personnel records necessary to conduct research, and to trace vital status of occupational cohorts through other government agencies including the Internal Revenue Service (IRS). NIOSH studies of workers exposed to benzene, radon daughters, asbestos, beryllium, cadmium and dioxin have contributed substantially to evaluations by the International Agency for Research on Cancer (IARC) of the carcinogenicity of chemicals and to occupational and environmental health regulations in the U.S. and abroad.

We propose here to evaluate breast cancer incidence in two large study cohorts, which have been previously assembled by NIOSH. One of the cohorts includes 9,929 women with exposure to ethylene oxide (ETO), a direct alkylating agent which produces mammary tumors in mice.[5,6] The other cohort includes over 13,000 women exposed to polychlorinated biphenyls (PCBs), a group of chemicals suspected to be carcinogenic to the breast because of their lipophilic and estrogenic activities. Each cohort represents the largest and best defined female study cohort in the U.S. for the respective exposure. Each of the proposed breast cancer incidence studies will have adequate statistical power to detect at least a 1.4 fold increased risk of breast cancer, and to evaluate exposure-response relationships.[7]

Background

The incidence of breast cancer in the U.S. has increased in the past two decades.[1] Known epidemiologic risk factors for breast cancer include a family history of breast cancer, early age at menarche, nulliparity or late age at first birth, and later age at menopause.[8] It has been hypothesized that exposure to chemicals in environmentally contaminated food is related to the increasing incidence of breast cancer.[9] According to this hypothesis, chemicals that bioaccumulate in fatty tissues and those that are estrogenic are most likely to be associated with breast cancer risk. Many chlorinated hydrocarbons, including tetrachlorodibenzo-p-dioxins, polychlorinated biphenyls and some pesticides are lipophilic and estrogenic to varying degrees. One recent study found elevated PCB concentration in the mammary tissue of patients with breast cancer compared to patients with benign breast disease.[10] Another study did not find a significant association between serum PCB concentration and risk of breast cancer, but did find a significant association for DDE (a metabolite of DDT).[11]

Potential breast carcinogens are not limited to estrogenic chemicals that act to promote proliferation in breast tissue. Agents that act directly on DNA, such as radiation and chemical alkylating agents, have also been shown to be carcinogenic in mammary tissue in animal studies and in humans.[9] Although the chemicals that induce breast cancer in humans are not well-defined, it is reasonable to suspect that chemicals that produce mammary tumors in rodent bioassays may also be breast carcinogens in humans.[12]

Examining cancer mortality in occupational groups with exposure to potential carcinogens has been the most widely used epidemiologic technique for establishing the carcinogenicity of a substance in humans. Mortality studies conducted solely from occupational records and death certificates are satisfactory for cancers which are usually fatal. Occupational groups often have prolonged exposures to substances at levels thousands of times higher than those possible from environmental exposures. Thus, studies of women occupationally exposed to potential breast carcinogens offer the best opportunity of detecting and ultimately preventing an increased risk of breast cancer related to these substances.

There are, however, two problems in using cancer mortality studies to evaluate the risk of breast cancer in occupational cohorts. The first is that mortality is not a sensitive outcome measure for breast cancer, because in the U.S. the five year survival rate for white women is over 75% and for black women is over 60%.[1] The second is that without information on non-occupational risk factors, particularly reproductive history, it is difficult to determine whether an observed excess in breast cancer mortality is due to chemical exposures or to other factors such as delayed age at first birth.[2] These difficulties can be overcome by studying breast cancer incidence rather than mortality and by collecting data on the non-occupational risk factors by questionnaire.

The Industrywide Studies Branch of the National Institute for Occupational Safety and Health has assembled two occupational cohorts exposed to potential mammary carcinogens. One group of 9,929 women was exposed to ETO, a direct alkylating agent which has induced mammary tumors in mice. A second group of 13,736 women, was exposed to polychlorinated biphenyls in capacitor manufacturing plants. Each of these cohorts presents an opportunity to determine whether a chemical exposure of public health importance is associated with an increased risk of breast cancer:

a. Ethylene oxide

Ethylene oxide is a gas used as a chemical intermediate in the manufacture of ethylene glycol and other products. Since the 1950's it has also been used to sterilize medical supplies. NIOSH estimates that 96,000 U.S. hospital workers are exposed, and an additional 21,000 workers in the U.S. are exposed during the commercial sterilization of medical supplies.[5] The estimate for the number of female workers exposed to ethylene oxide in any industry in the U.S. is 120,086.[13] Ethylene oxide exposure has been associated with an increased frequency of sister-chromatid exchanges in peripheral lymphocytes of U.S. hospital workers and in other populations.[14] IARC has determined that ethylene oxide is a carcinogen based on limited evidence in humans and sufficient evidence in animals (IARC, 1987).[15] The IARC determination was based primarily on leukemia and brain cancer in animals, and leukemia in humans. However, there was also some evidence of mammary cancer in animals and breast cancer in humans exposed to ethylene oxide.

In a well-designed lifetime chronic inhalation study in mice, ethylene oxide caused significant excess cancer of the mammary glands in treated v. control animals.[6] Only 1 of 49 control

ice had a tumor, while 8 of 48 animals treated at 50 ppm and 6 of 49 treated at 100 ppm had mammary gland tumors. Uterine tumors were also elevated in treated female mice (5 of 49 in the high dose group v. 0 of 49 in the controls and 1 of 47 in the low dose group). Two inhalation studies in rats did not show excess mammary cancers, but were positive for leukemia and brain cancer.[16, 17]

Data on women exposed to ethylene oxide are sparse. Besides the NIOSH cohort, which is described below, breast cancer among women exposed to ethylene oxide has been examined in four relatively small cohorts, three of which considered incidence and one mortality. Most of these studies involved relatively short potential latency periods and limited statistical power. Of the three with incidence data, one reported a significant excess, one reported a deficit, and one did not report data on breast cancer (apparently finding no excess).

The positive incidence study, unpublished, considered incidence among 929 women working at a plant where ETO was used during 1974-1980. These women were potentially exposed, but actual exposure data was not available. These women were followed for approximately 10 years through 1985 resulting in about 7,000 person-years of observation. The results of this study were forwarded to NIOSH by the employer who conducted the study. In this study, 10 breast cancers were observed versus 5 expected, for a significant 2-fold excess.[18]

Another cancer incidence study was conducted among 1,309 women exposed in Sweden from 1964-1985 during commercial sterilization.[19] These women contributed approximately 8,000 person-years of observation during the 1976-1986 period. Exposures were estimated to have varied from 5 to 75 ppm before 1975 and were considerably lower (0.1-4 ppm) thereafter. This study was negative in that only four breast cancers were observed versus 6.4 expected (SIR 0.64). However, this study had low statistical power to detect an excess due to the small number of expected cases.

A third incidence study, also in Sweden, was conducted among 330 women exposed to ETO in commercial sterilization in the 1960's and 1970's. Follow-up through 1981 showed that 10 cancer cases had occurred in women, with 5.2 expected. No data were given on breast cancer specifically, but the authors noted that the principal excesses among women were due to leukemia and cervical cancer, thus implying that breast cancer was not elevated. Again, the expected number of breast cancers was very small and this study had very limited power to detect a risk.[20]

A mortality study of 1,012 women exposed to ETO during food sterilization in England indicated 4 breast cancer deaths compared to 5.9 expected (SMR=0.68), but no data on incidence were available.[21]

NIOSH has assembled by far the largest the largest existing cohort of ethylene oxide-exposed workers (n=18,000).[5] This cohort includes 9,929 women, contributing 196,788 person-years of observation through 1991. All were exposed in the commercial sterilization industry. The average year of first exposure was 1970, and the average length of exposure was 5

years. Mortality follow-up through 1987 of this cohort showed 42 breast cancer deaths versus 49 expected. However, mortality analyses are relatively insensitive for breast cancer. Additionally, the mortality follow-up for this relatively young cohort was conducted through 1987 when the average potential latency or induction period was 18 years. It will be possible to identify incident breast cancers in this population. New follow-up for incidence would add 4 years to this average potential latency period. Additionally, based upon known incidence rates and the age distribution of the cohort, we estimate that 220 incident breast cancers would be expected in this cohort through 1991. This expected number of breast cancers is about 30-40 times larger than any other study conducted to date, providing much increased statistical power to detect any excess risk. The study will have 80% statistical power to detect a Standardized Incidence Ratio (SIR) of 1.4 (alpha = 0.05) among female workers exposed to ETO.[7]

The NIOSH cohort also has an important advantage in that considerable effort was spent in developing an estimate of ETO exposure for each worker in the study for each of their jobs held throughout employment. Over 2,300 personal samples were obtained for the 1979-1985 period at 12 different plants, and these as well as knowledge of historical processes were used to estimate exposures. The resulting "job-exposure" matrix has been cited as one of the better estimates of historical exposures in occupational epidemiology, and it permits quantitative dose-response analyses which can rarely be done in most historical epidemiologic studies.[22, 23, 24] Average ETO exposures in this cohort were 5 ppm, with higher exposures occurring in the 1960's and 1970's. Using the job-exposure matrix we will be able to determine whether the risk of breast cancer increases with increasing dose.

b. Polychlorinated biphenyls

PCBs are a synthetic group of polycyclic hydrocarbons produced commercially from 1929 to 1977.[25] They were used widely in the electrical industry due to their high stability, dielectric properties and resistance to oxidation.[25, 26] PCBs have long half-lives as a result of these properties and were documented to remain in humans and in the environment.[26, 27, 28] The exact length of retention is related to the degree of chlorination of the PCB isomer with more highly chlorinated isomers persisting longer.[27] Due to increasing concern about the persistence of PCBs in the environment and potential health risks, PCBs were banned from production and distribution in 1977.[25] PCBs remain a potential occupational exposure, especially to persons who repair electrical equipment, and are widespread in the environment.

According to the IARC rating scheme, PCBs are probable human carcinogens[15] with sufficient evidence from experimental animal studies to classify PCBs as carcinogenic, but limited evidence from human studies. The Environmental Protection Agency (EPA) also classified PCBs as probable human carcinogens; as with IARC, EPA reported animal carcinogenicity data to be sufficient but human carcinogenicity data to be inadequate (IRIS database).[29] The National Toxicology Program (NTP) reported there was sufficient evidence

to consider several PCB mixtures to be carcinogens in animals. There was, however, sufficient evidence to conclude PCBs were carcinogenic in humans.[30]

An association between PCBs and breast cancer is suspected because PCBs are estrogenic and accumulate in fatty tissues. Two recent studies presented limited evidence of an association between breast cancer and PCBs. Wolff et al (1993)[11] presented findings of a nested case-control study of women with breast cancer. Controls were randomly selected from risk sets of cohort members who were alive and disease free at the time of diagnosis of the case and were matched on several factors with the cases. PCBs were measured in sera. Although women with breast cancer tended to have higher serum PCB concentrations, the trend was not statistically significant. Falck et al (1992)[10] examined levels of PCBs and DDE, measured in the mammary adipose tissue, in twenty women with breast cancer and twenty women with benign disease. Mean concentrations of PCBs and DDE in women with malignancies was 50-60% higher than in women with benign disease and differences were statistically significant. Differences remained when multivariate models were run to control for potential confounders (age, Quetelet index, and smoking status). A previous study, however, did not demonstrate a relationship between elevated PCB levels in mammary adipose tissue and breast cancer.[31]

NIOSH investigators are currently conducting retrospective cohort mortality studies of workers exposed to polychlorinated biphenyls at three capacitor manufacturing plants. The study originally performed by Brown and Jones (1981)[32] and updated by Brown (1987)[33] included workers in plants in New York State and Massachusetts which produced electrical capacitors. Brown et al studied only the most highly exposed workers (approximately 2,500 individuals, including 1,318 females). The cohort has now been expanded to include all workers at both facilities, 12,871 of whom are women. A second NIOSH retrospective cohort study[34] was conducted in a capacitor manufacturing plant located in Indiana. The cohort included 865 females and was followed through January 1, 1986. Thus, a total of 13,736 PCB-exposed women constitute the cohort to be studied.

Workers at the capacitor plants under study had considerably higher PCB exposure than individuals in the general population. Smith et al (1982)[35] examined serum PCB levels of 224 active, production and non-production workers at the Indiana plant studied for mortality by Sinks et al[34]; PCBs were quantified as lower chlorinated biphenyls (L-PCBs), defined as having 4 or fewer chlorine molecules, and higher chlorinated biphenyls (H-PCBs), defined as having 5 or more chlorine molecules. Geometric mean L-PCB levels ranged from a low of 89 (ng/ml) among individuals with no known employment in high exposure department to a high of 502 (ng/ml) among workers currently in the processing, finish and test areas; the values for the H-PCB levels were 22 (ng/ml) and 51 (ng/ml) for these same job classifications, respectively. The mean serum L-PCB levels were approximately 8 to 50 times the background level (i.e. community residents with no known exposure to PCBs) and 4 to 25 times the level among utility workers not exposed to PCBs. Mean serum H-PCB levels were 2 to 4 times the community levels and 3 to 7 times the utility workers levels. Using different analytic methods, Lawton et al (1985)[36] measured serum PCB levels among

workers with potential for high exposure to PCBs in the New York facilities studied by Brown et al[32, 33]. The mean and 95% confidence limits were for L-PCB levels 363 (57-2270) and for H-PCB levels 30 (6-142) in 1976.

The three capacitor plants where the PCB-exposed women worked had ceased using PCBs in 1976 or 1977. Serum PCB measurements are available for only a small fraction of workers. Although it is not feasible to construct an exposure matrix for PCBs based on air concentrations (because of the limited number of air samples available and potential for dermal absorption of PCBs), we will be able to classify jobs as having had high, medium or low exposure. Thus we can determine whether the risk of breast cancer rises with increased dose.

The number of female workers in the three plants combined is 13,736, representing the largest the largest existing cohort of females occupationally exposed to polychlorinated biphenyls. Using known incidence rates and the age distribution of the cohort, we estimate that approximately 486 incident breast cancers would be expected in this cohort through 1991. The study will have 80% power to detect a Standardized Incidence Ratio for breast cancer of 1.3 (alpha = 0.05) in the cohort of female capacitor workers.[7]

Hypotheses

a. Women occupationally exposed to ethylene oxide may have increased risk of breast cancer.

b. Women occupationally exposed to polychlorinated biphenyls may have an increased risk of breast cancer.

Objectives

a. To evaluate whether exposure to ETO or PCBs is associated with increased breast cancer.

b. To identify incident cases of breast cancer in the ETO and PCB cohorts and to collect information on exposures and relevant risk factors by questionnaire surveys of living women and the next-of-kin of deceased women.

c. To determine whether the incidence of breast cancer is elevated in each cohort compared to the general population, controlling for non-occupational factors that may be associated with both breast cancer risk and employment status (i.e., nulliparity, age at first birth).

d. To evaluate the exposure-response relationship within each cohort, controlling for non-occupational risk factors.

e. If either study is positive, to provide data for risk assessments to estimate risk in the general population.

Approach

Given the high survival rates for women diagnosed with breast cancer (>75% for white women and >60% for black women, cancer incidence is a much more sensitive indicator of increased risk than cancer mortality. Longstanding population-based cancer registries are available for only one of the three PCB cohorts, which is located in New York State and three of the 14 ETO plants. Thus, cancer incidence will have to be determined through the use of questionnaires. (Registry matching will be done for the plants in areas covered by population based-registries since this will provide an additional means of identifying cases, particularly for individuals who could not be contacted). The questionnaire approach will also allow the collection of data on non-occupational risk factors, which are required for the full interpretation of the incidence study results.

The analysis of the study will require the use of external referent rates, because neither cohort includes an unexposed internal referent group. However, the use of population-based referent rates is problematic because employed women are likely to differ from the general population with respect to factors such as parity which influence both employment status and risk of breast cancer. We will apply methods developed to estimate the effect of smoking habits in occupational cohorts on lung cancer risk[37]. This method will estimate the increased risk expected in the occupational cohort based on differences in their reproductive experience alone. This approach will use risk estimates for particular factors (such as nulliparity) derived from breast cancer case-control studies, and survey data on the distribution of the risk factor in the general population. The conclusions of this analysis will be limited because any estimate of the increased risk expected in the cohort based on their reproductive experience is crude. A second analysis will utilize low-exposed women as an internal comparison group. It will examine whether there is an exposure-response relationship within the cohort. In this analysis, both occupational and non-occupational risk factors will be compared between cases and others in the cohort who did not develop breast cancer. We will be able to analyze the exposure-response relationship using a quantitative dose metric only for the ETO cohort. For the PCB cohorts, we will be able to analyze duration of exposure in high, medium or low exposure jobs.

Although ascertaining breast cancer incidence by questionnaire is costly and time consuming, use of existing cohorts substantially reduces the time and resources required to conduct the study. For example, the ETO cohort of 18,000 persons was assembled and followed-up, and the exposure matrix developed, over a period of 8 years at an estimated cost of over $1,000,000. In a prior NIOSH studies where questionnaires have been administered to living

cohort members and their next-of-kin, cancer incidence and smoking data were collected for 79% of living subjects and 59% of deceased subjects.[38] Thus, the approach outlined in this proposal is both cost-effective and feasible, and project investigators have had experience with these methods.

Methods

For both cohorts, data from personnel records has already been coded into a standard computer file containing demographic, and work history information. Vital status was determined though data supplied by the Social Security Administration (SSA), the National Death Index (NDI), the Internal Revenue Service (IRS) and the U.S. Postal Service. For the purposes of the present study, the vital status of each of the cohorts will be updated through the most recent year available in the NDI (currently 1993). It is necessary to update vital status before conducting the incidence study because death certificates will be one source for identification of breast cancer cases and the address of the next-of-kin. In addition, the date of death (from any cause) will be used in the incidence analysis to calculate "person-years-at-risk" for each person in the study.

All females in the ethylene oxide cohort (N = 9,929) and in the three PCB cohorts combined (N = 13,736) will be included in the breast cancer incidence study. Incident breast cancer cases will be identified from various record sources (coding and searching all causes of death on the death certificates, matching against population-based cancer incidence registries) as well as by questionnaires to living individuals and next-of-kin of deceased individuals. The diagnosis will be confirmed by medical records.

The questionnaire design and administration and medical record confirmation will be done under contract. The questionnaire will focus on (1) the identification of incident breast cancer cases, collection of information necessary to confirm the diagnosis, and permission to obtain the medical records; (2) the collection of information on relevant non-occupational risk factors for breast cancer, such as family history and reproductive history; and (3) additional data on work history, including other jobs held.

The current address of living individuals will be determined by NIOSH through IRS. NIOSH has a special authority to obtain addresses from the IRS for the purposes of tracing individuals in occupational health studies. A cover letter and consent form, that participants are asked to sign and return, will be mailed with the questionnaire (sample cover letters are provided in Appendix 1 and consent forms are given in Appendices 2 and 3). Nonrespondents to the first mailing will receive a second mailing if the address is deemed correct. Women not responding to the second mailing will be contacted and interviewed by phone using the same questionnaire. For individuals who report cancer, a letter will be sent to the medical provider asking for confirmation of the cancer (sample letter attached in Appendix 4).

Questionnaire data will be coded and provided to NIOSH by the contractor. The contractor will also provide copies of all the medical records obtained along with the ICD and ICD-O code for each breast cancer identified. NIOSH investigators will merge the questionnaire and medical data files with the information on work history and vital status contained in the NIOSH masterfile. A list of tasks to be completed for this study is provided in Appendix 5.

Two types of analysis will be conducted. The first analysis will answer the question of whether the incidence of breast cancer in the study cohort is higher than that in expected in the general population. The number of incident breast cancers expected in the cohort if they were developing breast cancer at the same rate as the general population will be calculated using the NIOSH life table analysis system (LTAS).[39, 40] The LTAS allocates each person-day into the appropriate age, race, gender, calendar time, duration of exposure (or cumulative exposure) and time since first exposure correct stratum.[40] A referent rate file will be constructed by combining data from population-based cancer registries. The potential effect of non-occupational risk factors that may be related to both employment status and disease, such as age at first birth and parity, will be estimated using a method proposed by Axelson and Steenland (1988)[37] for assessment of the effects of smoking habits in a cohort on lung cancer mortality. This analysis will use data on the odds ratio associated with certain risk factors (primarily parity and age at first birth) from a large nested case-control study such as the one conducted by Layde et al. (1989)[41] among 4,599 cases and 4,536 controls from eight geographical areas in the United States. The analysis will use published data on parity in the U.S. population such as the fertility tables for birth cohorts.[42]

The second analysis will evaluate the risk of occupational exposure within each cohort, controlling for non-occupational risk factors. In the analysis of the ethylene oxide cohort, the dose matrix based on historical ethylene oxide air concentrations will be used.[22] For the PCB cohort, duration of exposure in high, medium and low exposure jobs will be used as the exposure surrogate. The exposure-response relationship will be evaluated using regression analyses (eg. Cox and Poisson regression). Papers will be prepared for publication in peer-reviewed journals describing the results of both studies.

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Appendix 1

Sample Cover Letters to Study Participants

Sample cover letter to living study participants

Dear Ms. :

The National Institute for Occupational Safety and Health (NIOSH) is a Federal agency which conducts occupational health research in the work place. NIOSH is conducting a research study called the Women's Occupational Health Study. The main purpose of the study is to determine whether women who are (or were) employed at [name of company] are at increased risk of breast and other cancers. We are doing this research because there is evidence that some chemicals used at the companies, such as ethylene oxide (ETO) or polychlorinated biphenyls (PCBs), might be related to breast cancer. You were selected to be part of this study because you worked at [company name] during the time when [PCBs or ETO] were used. This study will contact all women who were employed at the plant and request that they complete a questionnaire.

Your participation in this study will involve reading and signing the enclosed informed consent form and completing the enclosed questionnaire. The questionnaire should take about 30 minutes to complete. Your participation is voluntary, but the success of the Women's Occupational Health Study depends on obtaining information from as many women as possible. Any reports from this study will be in summary form with no reports on individuals. We will notify you of the results when the study is finished.

Please mail your signed consent form and completed survey to us in the enclosed pre-paid envelope as soon as possible. If you have any questions, please call the Project Director, Elizabeth Whelan, collect, at 513-841-4411 during business hours (8 am - 5 pm, EST).

Thank you in advance for helping with a study that could benefit many others.

Sincerely yours,

Elizabeth A. Whelan, Ph.D.
Project Director
Women's Occupational Health Study

Sample cover letter to next-of-kin of deceased study participants

Dear Ms./Mr. :

The National Institute for Occupational Safety and Health (NIOSH) is a Federal agency which conducts occupational health research in the work place. NIOSH is conducting a research study called the Women's Occupational Health Study. The main purpose of the study is to determine whether women who worked at [name of company] are at increased risk of breast and other cancers. We are doing this research because there is evidence that some chemicals used at the companies, such as ethylene oxide (ETO) or polychlorinated biphenyls (PCBs), might be related to breast cancer. Your deceased (wife/mother/sister), Ms./Mrs._____, was selected to be part of this study because she was employed at [company name] during the time when [PCBs or ETO] were used. This study will contact all women who were employed at the plant, and next-of-kin of former employees, and request that they complete a questionnaire.

Your participation in this study will involve reading and signing the enclosed informed consent form and completing the enclosed questionnaire. The questionnaire asks for information about your (wife's/mother's/sister's) medical history and other factors that might influence a person's risk of cancer. The questionnaire should take about 30 minutes to complete. Your participation is voluntary, but the success of the Women's Occupational Health Study depends on obtaining information about as many former employees as possible. Any reports from this study will [illegible] in summary form with no reports on individuals. We will notify you of the results when the study is finished.

Please mail your signed consent form and completed survey to us in the enclosed pre-paid envelope as soon as possible. If you have any questions, please call the Project Director, Elizabeth Whelan, collect, at 513-841-4411 during business hours (8 am - 5 pm, EST).

Thank you in advance for helping with a study that could benefit many others.

Sincerely yours,

Elizabeth A. Whelan, Ph.D.
Project Director
Women's Occupational Health Study

Appendix 2

Consent form for living participants

NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH (NIOSH)
CENTERS FOR DISEASE CONTROL AND PREVENTION, U.S. DEPT. OF HEALTH AND HUMAN SERVICES

lease sign and return one copy of this consent form. Keep the other for your records.

ONSENT TO PARTICIPATE IN A RESEARCH STUDY

You are being asked to participate in a NIOSH research study called the Womens' Occupational Health Study. The urpose of the study is to determine whether women who worked at the (name of company) or other companies are : increased risk of cancer because of exposure to a chemical called ethylene oxide (or PCB's).

. Your participation in this study will involve completing the enclosed questionnaire, which takes about 30 minutes, nd returning it to us in the enclosed envelope. Questions include whether you have had cancer, or whether you ave various risk factors for cancer (for example, smoking, reproductive history). If you have had cancer, we seek ermission to contact your physician for confirmation. If you do not return the questionnaire, an interviewer may call make sure you received it and ask if you would answer the questions by telephone.

.The benefit to you from participating in the study is helping answer the question about whether ethylene oxide (or CB's) causes cancer. Furthermore, you will be notified of the results of the study.

You are authorized all necessary medical care for injury or disease which is the proximate result of your rticipation of this research. Other than medical care that may be provided, you will not receive any compensation r your participation in this research study; however, you understand that this is not a waiver or release of your legal ghts.

. The National Institute for Occupational Safety and Health (NIOSH) of the Centers for Disease Control and evention (CDC), an agency of the Department of Health and Human Services, is authorized to collect this formation, including your Social Security number, under provisions of the Public Health Service Act, Section 301 2 U.S.C. 241); Occupational Safety and Health Act, Section 20 (29 U.S.C. 669); The information you supply is oluntary and there is no penalty for not providing it. The data will be used to evaluate whether women exposed to CB's (or ETO) have an increased risk of breast cancer. Data will become part of CDC Privacy Act system [09-20-147, "Occupational Health Epidemiological Studies"] and may be disclosed: to appropriate state or local health partments to report certain communicable diseases; to the State Cancer Registry to report cases of cancer where e state has a legal reporting program providing for the information's confidentiality; to private contractors assisting IOSH; to collaborating researchers under certain limited circumstances to conduct further investigations; to one or ore potential sources of vital statistics to make a determination of death; to the Department of Justice in the event litigation; and to a congressional office assisting individuals in obtaining their records. Representatives from the rmy Medical Research, Development, Acquisition and Logistics Command, which has provided funding for this study, e eligible to inspect the records of this research as part of their responsibilities to protect human subjects in search. An accounting of the disclosures that have been made by NIOSH will be made available to you upon quest. Except for these and other permissible disclosures expressly authorized by the Privacy Act, no other sclosure may be made without your written consent.

I. If you have any questions about the study, or your participation, you may contact Dr. Kyle Steenland, project rector at (513) 841-4203, or Dr. Michael Colligan, Chairperson, NIOSH Human Subject's Review Board at (513) 33-8225.

II. Your participation is voluntary and you may withdraw your consent and your participation in this study at any time ithout penalty or loss of benefits to which you are otherwise entitled.

III. SIGNATURES. I have read this consent form and I agree to participate in this study.

ARTICIPANT_____ Date _____
(sign and print your name)

possible, please have someone witness your signature, by signing and printing their name below:

ITNESS_____ Date_____

blic reporting burden for this collection of information is estimated to average 30 minutes per response, including the time r reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and eviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of nformation, including suggestions for reducing this burden to PHS Reports Clearance Officer: ATTN: PRA; Hubert H. Humphrey ldg, Rm 721-B; 200 Independence Ave., SW; Washington DC 20201, and to the Office of Management and Budget; Paperwork Reduction roject (0920-XXXX); Washington, DC 20503.

Appendix 3

Consent Form for Next-of-Kin

NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH (NIOSH)
.CENTERS FOR DISEASE CONTROL AND PREVENTION, U.S. DEPT. OF HEALTH AND HUMAN SERVICES

lease sign and return one copy of this consent form and keep the other for your own records.

ONSENT TO PARTICIPATE IN A RESEARCH STUDY : NEXT-OF-KIN

You are being asked to participate in a NIOSH research study called the Womens' Occupational Health Study. The urpose of the study is to determine whether women who worked at the (name of company) and other companies are t risk of cancer because of exposure to a chemical called ethylene oxide (or PCB's).

.Your participation in this study will involve completing the enclosed questionnaire. The questionnaire asks whether ls./Mrs. _____ was diagnosed with cancer during her lifetime. The questionnaire also asks about factors that ıay influence a person's risk of cancer, such as smoking habits and reproductive history. It should take about 30 ıinutes to complete. If you do not return the questionnaire, a study interviewer may call you to make sure you ›ceived it and ask if you would like to answer the questions by telephone.

I.The benefit to you from participating in the study is helping answer the question about whether ethylene oxide (or CB's) causes cancer. Furthermore, you will be notified of the results of the study.

/. You are authorized all necessary medical care for injury or disease which is the proximate result of your ırticipation of this research. Other than medical care that may be provided, you will not receive any compensation ›r your participation in this research study; however, you understand that this is not a waiver or release of your legal ghts.

. The National Institute for Occupational Safety and Health (NIOSH) of the Centers for Disease Control and revention (CDC), an agency of the Department of Health and Human Services, is authorized to collect this formation, including your Social Security number, under provisions of the Public Health Service Act, Section 301 :2 U.S.C. 241); Occupational Safety and Health Act, Section 20 (29 U.S.C. 669); The information you supply is ›luntary and there is no penalty for not providing it. The data will be used to evaluate whether women exposed to CB's or ETO have an increased risk of breast cancer. Data will become part of CDC Privacy Act system [09-20-147, "Occupational Health Epidemiological Studies"] and may be disclosed: to appropriate state or local health ›partments to report certain communicable diseases; to the State Cancer Registry to report cases of cancer where ıe state has a legal reporting program providing for the information's confidentiality; to private contractors assisting IOSH; to collaborating researchers under certain limited circumstances to conduct further investigations; to one or ore potential sources of vital statistics to make a determination of death; to the Department of Justice in the event litigation; and to a congressional office assisting individuals in obtaining their records. Representatives from the rmy Medical Research, Development, Acquisition and Logistics Command, which has provided funding for this study, e eligible to inspect the records of this research as part of their responsibilities to protect human subjects in search. An accounting of the disclosures that have been made by NIOSH will be made available to you upon quest. Except for these and other permissible disclosures expressly authorized by the Privacy Act, no other sclosure may be made without your written consent.

I. If you have any questions about the study, or your participation, you may contact Dr. Kyle Steenland, project rector at (513) 841-4203, or Dr. Michael Colligan, Chairperson, NIOSH Human Subject's Review Board at (513) 33-8225.

II.Your participation is voluntary and you may withdraw your consent and your participation in this study at any time ithout penalty or loss of benefits to which you are otherwise entitled.

III. SIGNATURES. I have read this consent form and I agree to participate in this study.

ARTICIPANT_____ Date _____
(sign and print your name)

_possible, please have someone witness your signature, by signing and printing their name below:

/ITNESS_____ Date_____

blic reporting burden for this collection of information is estimated to average 30 minutes per response, including the time ır reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and viewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of formation, including suggestions for reducing this burden to PHS Reports Clearance Officer: ATTN: PRA; Hubert H. Humphrey dg, Rm 721-B; 200 Independence Ave., SW; Washington DC 20201, and to the Office of Management and Budget; Paperwork Reduction ıject (0920-XXXX); Washington, DC 20503.

Appendix 4

Sample letter to medical provider requesting medical record confirmation of reported cancer diagnoses

Sample letter to medical provider requesting medical record confirmation of reported cancer diagnoses

Dear Dr. :

The National Institute for Occupational Safety and Health (NIOSH) is authorized under Section 20 of the Occupational Safety and Health Act of 1970 to conduct research related to the health protection of workers. Currently, NIOSH is conducting a study of cancer incidence and mortality among women working in selected occupations.

Ms./Mrs._____ is part of this study and has indicated to us that she had cancer. She has authorized us (see attached authorization) to contact you to confirm this.

Please send to me at the above address all medical records, including pathology reports, that relate specifically to this diagnosis, especially the date of diagnosis. If you have any questions, please contact Elizabeth Whelan at 513-841-4411. A pre-addressed envelope is enclosed for your convenience. Thank you very much for your assistance with our research study.

Sincerely yours,

Geoffrey M. Calvert, M.D., M.P.H.
Medical Officer
Industrywide Studies Branch
Division of Surveillance, Hazard
Evaluations and Field Studies

Appendix 5

List of Tasks to be Completed

Breast Cancer Incidence Among Women Exposed to Polychlorinated Biphenols and Ethylene Oxide

Task 1, Conduct Vital Status Follow-up, Months 1-12:

1. Update vital status through 1993 though the National Death Index, obtain death certificates and code all underlying and contributory causes of death.
2. Obtain current addresses and phone numbers of all living members of the study cohort or their next-of-kin through data supplied by the Internal Revenue Service, the U.S. Post Office, case-location services and telephone directories.

Task 2, Prepare for Data Colection Phase of Study, Months 6-12:

1. Obtain clearance for the questionnaire study from the NIOSH Human Subjects Review Board (HSRB) and OMB approval.
2. Prepare a Request for Negotiated Contract to collect breast cancer incidence data, and award contract competitively.

Task 3, Collect Questionnaire & Medical Record Data, Months 10-24:

This task will be completed by a contractor with expertise in survey administration.

1. Develop spreadsheet for tracking medical records request from death certificates and registry data provided by NIOSH.
2. Develop and pre-test the questionnaires for living study subjects and their next-of-kin.
3. Mail questionnaires to living subjects and next-of-kin. If questionnaire is returned as undeliverable, initiate additional tracing procedures. If the questionnaire is not returned, contact subjects and conduct telephone interview.
4. Match study cohorts against population-based incidence registries (if available).
5. Code all questionnaire data and registry information for each subject.
6. Provide both hard copy and coded data to NIOSH.

Task 4, Data Analysis & Completion of Final Report, Months 24-36:

1. Merge questionnaire and registry data contained in the files obtained from the contractor with the work histories contained in the NIOSH masterfiles.
2. Complete incidence analyses.
3. Complete exposure-response analyses.
4. Complete final reports.