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Exposure to ethylene oxide and relative rates of female breast cancer mortality: 62 years of follow-up in a large US occupational cohort

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Abstract

Background: Ethylene oxide (EtO) is a recognized carcinogen of concern in occupational and environmental settings, but evidence of cancer risks in humans remains limited. Since new EtO emission standards and mitigation measures have been proposed, further investigation of EtO cancer risks is needed to inform quantitative risk assessment.

Objective: Our objective was to estimate the association between cumulative EtO exposure and risk of death from breast cancer.

Methods: We had data on 7,549 women from the largest cohort of EtO-exposed workers who were employed for at least 1 year at one of 13 US facilities, with mortality follow-up from January 1, 1960, to December 31, 2021. We estimated relative rates (RR) of the association between cumulative EtO exposure [parts per million days (ppm-days)] and breast cancer mortality using Cox proportional hazard models, using a matched risk-set sampling design with attained-age as the underlying time scale. We further examined a subcohort of women who participated in interviews which contained information about breast cancer risk factors.

Results: Cumulative exposure to EtO was associated with elevated RRs of breast cancer mortality (181 deaths). In a log-log model with a 20-year lag fit, workers who accrued 3,650 ppm-days of exposure (equivalent to 10 years exposed at a rate of 1 ppm) had over three times the rate of breast cancer death compared to unexposed workers (RR at 3,650 ppm-days = 3.15; 95%CI: 1.78, 5.60). This RR remained elevated for the subset of the cohort with interview data after matching on potential confounders (RR at 3,650 ppm-days = 3.22; 95%CI: 1.52, 7.13). We observed evidence of variation in RRs by time since exposure and exposure rate.

Discussion: This updated analysis of an EtO exposed worker cohort builds upon evidence that EtO is a human breast carcinogen and supports recent exposure reduction proposals. Given the high prevalence of breast cancer, the large number of workers exposed to EtO, and the potential for widespread environmental exposure, increased risks observed even in the low exposure range are of serious public health importance.

Introduction

Ethylene oxide (EtO) is a chemical made from the oxidation of ethylene, and is produced industrially in large quantities globally.[1] EtO is used as a medical sterilant for almost half of all medical supplies in the United States (US),[2] as a fumigant for dry foods and spices, and as an intermediate product in a wide array of consumer products such as polyester fibers, plastics, cosmetics, soap, adhesives, paint, and antifreeze.[3] Workers are exposed to EtO and materials that contain EtO in commercial sterilization facilities, hospitals, dental and veterinary practices, and in chemical, plastic, and pharmaceutical production.[1,4,5] EtO is also an environmental concern for residents of communities chronically exposed to EtO in air from commercial sterilization facility emissions.[6] An assessment based on data from the US Environmental Protection Agency (EPA) Air Toxics Screening Assessment determined that over 14 million people in the US live within five miles from a commercial sterilization facility.[6]

Ethylene oxide is a known human carcinogen as classified by several agencies including the US National Toxicology Program (NTP) Report on Carcinogens[7] and the International Agency for Research on Cancer, World Health Organization (IARC).[1] IARC has evaluated the carcinogenicity of EtO several times based on evolving evidence, and in the latest two evaluations (1994 & 2008) IARC determined that EtO was a Group 1 human carcinogen, with classifications based on limited evidence in human epidemiological studies, sufficient evidence in experimental animals, and strong evidence in mechanistic studies.[1,8] While lymphatic and hematopoietic cancers were the most frequently studied cancers in relation to EtO, breast cancer was also an area of focus for the IARC working groups.[1] However, there were few epidemiological studies evaluating breast cancer among female workers.[9] The majority of human evidence on breast cancer risk is from the US National Institute for Occupational Safety and

Health (NIOSH) cohort of over 18,000 US workers occupationally exposed to EtO.[1] Investigators observed an increased risk of breast cancer and there was evidence of an exposure-response relationship between EtO and breast cancer mortality in internal analyses.[10-12] The 2009 IARC monograph evaluation of EtO deemed the NIOSH study to be "by far the most informative epidemiological investigation" due to higher statistical power, lower potential for confounding by occupational co-exposures, and more detailed individual exposure assessments than other available studies.[1]

Extended follow-up of this cohort can provide additional risk information. The last mortality and cancer incidence follow-ups of the cohort were in 1998, leaving almost a quarter century of follow-up time to be examined. Since breast cancer may have a long latency and induction period,[13] additional follow-up can provide more information on breast cancer risks that inform both occupational and environmental standards. While average exposures to workers have tended to decrease in the last several decades,[14] doses of ethylene oxide experienced by the general population and contemporary workers may still pose important risks and require additional characterization.

To improve on existing cancer risk estimates for EtO exposure, we here aim to update the female breast cancer mortality experience of the NIOSH cohort[10-12,15-19] through 2021 to provide important information on EtO risks relevant to both occupational and environmental decision-making. We report relative rates using models of the exposure-response association between cumulative occupational exposure to EtO and breast cancer mortality. To best inform contemporary risk estimates, we focus some of our analyses on estimating the shape of the dose-response association, particularly at low cumulative exposures (e.g. <1000 ppm-days cumulative exposure) and low exposure intensities (e.g. <0.1 ppm).

Methods

Cohort enumeration and follow-up.

This analysis is based on the NIOSH study of 18,235 US workers occupationally exposed to EtO; cohort enumeration has been described in detail elsewhere.[10-12,17-19] Briefly, the cohort was enumerated from employment records which were collected from 13 medical supply facilities and one spice sterilization facility in 11 US states. Demographic data was extracted from employment rosters including date of birth, sex, and race. In the current analysis, the cohort was restricted to female workers ever exposed to EtO at their jobs and also employed for at least 1 year. This 1-year restriction was also chosen in order to utilize survey data collected among a subset workers employed for at least one year. As in prior analyses, the cohort was further restricted to the 13 of 14 facilities with adequate records for exposure reconstruction.[17]

Prior to 1979, date and cause of death (underlying and multiple causes of death) were obtained through state death certificates, and after 1979 through linkage with the US National Death Index (NDI). Causes of death were coded based on the revision of the International Classification of Disease (ICD) in effect at the time of death. Mortality follow-up began January 1, 1960 and ended on December 31, 2021. Data from the LexisNexis Accurint product and the Social Security Administration Death Master File were used to ensure the quality of matches between cohort records and the NDI results, and to confirm vital status.

Since female breast cancer mortality is the outcome of interest, we restricted our analyses here to the 7,549 women in the cohort who were employed for at least 1 year. Prior mortality analyses were restricted to 9,885 women employed for at least 3 months,[11] and prior incidence analyses were based on a subset of 7,576 women employed for at least one year[12] (we removed

27 women whose dates of birth could not be confirmed). Furthermore, we analyzed data from a subcohort of 5,132 women employed for at least one year, on whom investigators collected interviews on risk factors of breast cancer in the late 1990s. This population and interview data collection methods are described in detail elsewhere.[12] In summary, all women in the cohort were contacted by mail, and if necessary, by phone. In the case of deceased cohort members, interviews were conducted via proxy (next-of-kin). Interview questions focused on risk factors of breast cancer, including age at menarche, age at menopause, parity, breastfeeding, body mass index (BMI), use of oral contraceptives, use of hormones for treatment of menopausal symptoms, smoking, alcohol, mammograms, and breast cancer among first degree relatives. Participants with missing data (n = 23 with missing date of birth) were not included in any analyses. This study was reviewed and approved by the National Institute for Occupational Safety and Health Institutional Review Board. Informed consent was waived for this records-based study.

Exposure estimation

Several prior publications detail the exposure measurement methods and statistical models used to predict worker exposures in the 13 medical and spice sterilization facilities.[15,16] Over 2,000 individual exposure samples were collected between the mid-1970s and 1980s; these samples formed the basis of a regression model which performed well in validation tests, meaning they could explain the majority of the variability in the ethylene oxide exposure measurements.[15,16] This model was used to predict the exposure levels for each worker based on job title, calendar year, facility, and department.[17] As part of a prior mortality update of this cohort, investigators collected additional occupational history records through 1998 for any workers still employed after initial work history data collection, which took place in the late

1980s. Investigators updated end of employment dates, and updated exposures under the assumption that workers had not changed their job title.[11,12] In the current update, we were unable to extend information on occupational histories for any workers still employed after 1998. However, this only represented 0.8% of the women in the cohort, which was further made inconsequential by the application of lagged exposures.

Cumulative exposure was estimated for each worker based on duration of employment at each corresponding estimated level of exposure. Cumulative exposures (parts per million days, ppm-days) were calculated using an *a priori* lag of 20 years which also was the best fit the data in prior mortality analyses.[11] Previously, investigators evaluated alternative exposure metrics including average exposure, maximum exposure intensity, and duration of exposure. Here we focus on cumulative exposure, which is an informative and commonly-used exposure metric in occupational studies of cancer mortality.[20] Cumulative exposure also empirically fit the data better than average exposure or duration of exposure.

Statistical methods

We first calculated standardized mortality ratios (SMR) using the NIOSH Life Table Analysis System for R (LTASR).[21] We compared the observed breast cancer deaths among the women in the cohort to the expected number of deaths based on rates of breast cancer mortality among women in the US population. Mortality rates were restricted to women and standardized by race (white/non-white), 5-year age group, and 5-year calendar period, and 95% confidence intervals were calculated using the Byar approximation of the Poisson distribution.[22] SMRs reported by exposure categories included a 20 year exposure lag. We report summary estimates and results in exposure categories (0, >0-500, >500-1,000, >1,000-5,000, >5,000-15,000, >15,000-25,000, and >25,000 ppm-days).

We next estimated the association between cumulative exposure to ethylene oxide and breast cancer mortality with Cox proportional hazard models, using a matched risk-set sampling design with attained-age (years) as the underlying time scale, where risk sets for each breast cancer death were created based on the age at death of the case.[23,24] To control for potential confounders, we further matched these risk sets on birth cohort within 5 years of each case, and race (white/non-white). This analysis is equivalent to conditional logistic regression.[24] Race by white and non-white racial categorization is considered a potential confounder in the analysis via occupational segregation (non-white workers may have higher exposures than white workers) and social differences in breast cancer risk factors (non-white workers may have higher breast cancer mortality rates than white workers).

Healthy worker survivor bias (HWSB) is a concern in observational occupational epidemiology studies where workers who stay employed longer are typically healthier than workers who leave employment sooner. [25,26] Standard control for employment factors can partially address HWSB[27, 28], therefore, main models additionally matched on duration of employment in four intervals (≤5, >5-10, >10-20, and >20 years of employment).[27] Additionally, in the subcohort of workers with interview data, we matched for the aforementioned variables, as well as for parity (0 vs. 1+ live birth), late age (>55 years) at start of menopause, ever/never use of oral contraceptives, and ever/never having been screened for breast cancer via mammogram. Nulliparous women, women with late age at start of menopause, and women who never received a mammogram had higher cumulative EtO exposures than their counterparts. Women who ever used oral contraceptives had lower cumulative EtO exposures than their counterparts. Since these four factors vary with EtO exposure and have a higher risk of breast cancer mortality, they were matched on to control for potential confounding of the association between EtO and breast

cancer death risk. Other risk factors for breast cancer collected in interview data (age at menarche, breastfeeding, BMI, use of hormones for treatment of menopausal symptoms, smoking, alcohol, and breast cancer among first degree relatives) were not associated with exposure and they were not included in this model.

Model results are reported as relative rates (RR) and corresponding profile likelihood 95% confidence intervals (95% CI). The generalized linear model form for the Cox regression is $rate = r_0 f(d)$where r_0 is the baseline risk function and $f(d)$ is a generic function of exposure, which also describes the rate ratio as a function of dose, described in more detail below.

Estimating the shape of the exposure-response association between ethylene oxide and breast cancer is important for informing occupational and environmental exposure limits. Following the general approach from a prior investigation of breast cancer in this cohort,[10] we fit a variety of model forms: a categorical model with 0, >0-500, >500-1,000, >1,000-5,000, >5,000-15,000, >15,000-25,000, and >25,000 ppm-day cumulative exposure categories, a log-log model as $f(d) = \exp(\beta_1 * \ln(d+1))$, and a linear model as $f(d) = 1 + \beta_1 d$. We assessed model fit through visual inspection and using the Akaike information criterion (AIC), a statistical estimator of relative model quality where a lower AIC indicates a better fit to the data. Continuous model results were presented as summary estimates at 365 ppm-days and 3,650 ppm-days. These levels were chosen to provide relevant risk estimates for working populations. 365 ppm-days approximates cumulative exposures accrued over 10 years at 0.1 ppm, and the NIOSH recommended time weighted average exposure limit for EtO is <0.1 ppm. 3,650 ppm-days approximates cumulative exposures accrued over 10 years at 1 ppm, and the Occupational Safety and Health Administration (OSHA) time weighted average exposure limit for EtO is 1 ppm.[29] It is important to note that while these are useful levels to report relative rates, in this cohort

exposures were accrued at various rates (i.e. 3,650 ppm-days could also represent a cumulative exposure accrued by a worker over 5 years at 2 ppm, or 20 years at 0.5 ppm, or a mix of rates).

Time since exposure is a temporal modifier which may substantially modify the association between EtO and exposure and breast cancer. We modeled relative rates allowing for modification across five moving windows of time since exposure (0-<10, 10-<20, 20-<30, 30-<40, 40+ years) using the loglog model form, since this was found to be best fitting as judged by the AIC value. The general model form is $f(d) = \exp\left(\sum_{i=1}^{k=x} \beta_i \log\left(d_i + 1\right)\right)$ where d_i is the amount of exposure in the *i*th window. Specifically, d_i represents partitions of temporal cumulative exposures accrued at 0-<10, 10-<20, 20-<30, 30-<40, and 40+ years prior to the current attained age of the case in each risk set, and therefore, $\sum_{i=1}^{k=5} d_i$ is the total cumulative exposure. Note that moving windows of time since exposure are not synonymous with time since first exposure. Rather, exposure is simultaneously partitioned across several moving time intervals ("windows").[30] We also used the same general log-log model form to evaluate modification of the relative rate by exposure rate, using two moving windows of exposure rate (0.1-1, >1 ppm). In this case, we use the same general model $f(d) = \exp\left(\sum_{i=1}^{k=x} \beta_i \log\left(d_i + 1\right)\right)$, but the d_i now represents partitions of temporal cumulative exposures accrued at 0.1-1, and >1 ppm levels that occurred at the attained age of the case in each risk set. Again, $\sum_{i=1}^{k=2} d_i$ represents total cumulative exposure. As with moving windows of time since exposure, with age as the underlying timescale this piecewise constant model partitions lagged cumulative exposures across the windows of the exposure rates at which the exposures were accrued. Therefore, a worker who accrued exposure at 0.1-1 ppm at one time in their career and >1 ppm at another time in their career would contribute information to rate estimates for each intensity of exposure. An example illustrating the data structure of exposure rate windows, and windows of

exposure compared to lagged exposure is provided in the Supplemental Table S1. All analyses were conducted using R statistical software.[31]

Sensitivity analyses.

Using the modeling approaches described above, we conducted a variety of sensitivity analyses to evaluate the impact of lag periods, exposure measurement uncertainties, and model specification. Specifically, we conducted the following analyses: (1) in addition to the *a priori* 20-year lagged exposure, we empirically evaluated various lag periods by fitting models with lags in 5-year increments ranging between 0 – 50 years (assuming 0 exposure during the lag period), and assessing model fit using the AIC, (2) to evaluate the influence of high exposure estimates which may be especially susceptible to misestimation, we repeated the main analyses restricting the person-time and events to those that occurred in the below 5,000 and 1,000 ppm-days of cumulative EtO exposure, and (3) to evaluate model specification, we repeated the main analyses not controlling for duration of employment.

Results

In this mortality update of the cohort, there were 7,549 women with more than one year employment and 181 deaths with breast cancer as the underlying cause. Table 1 summarizes key characteristics among all women meeting the cohort definition and among women with interviews. Among all women, the median cumulative exposure was 3,056 ppm-days. The mean exposure was 8,503 ppm-days, illustrating the positive skew of the exposure distribution. Median duration of follow up was approximately 44 years, and the median age at breast cancer death was 64 (Table 1). Demographic characteristics of the subcohort of women with interview data was generally similar to the full cohort of women, with women who were interviewed having

slightly longer median duration of employment and older age at breast cancer death (Table 1). Women who were interviewed also had a slightly lower proportion of death from all causes compared to all women (50.5% vs 53.1%). Demographic characteristics of the subcohort of women with interview data by interview type (participant interview or proxy interview) are reported in Supplemental Table S2. Compared to women who participated in interviews, women whose interviews were conducted via proxy were older at first exposure, employed longer, experienced higher cumulative exposures, and followed for a shorter time.

The summary SMR was 1.05 (95%CI: 0.90, 1.21) indicating that workers in this cohort had a slightly higher rate of breast cancer mortality than the standard US population.[32] The SMR for those unexposed with a 20-year lag was 0.83 (0.58, 1.13), but we observed that SMRs for the >500-1000, >5000-15000, >15000-25000, and >25000 categories were elevated (Table 2).

We observed elevated relative rates (RR) in all categories of exposure in the internal analyses using the Cox model (Table 3 and Figure 1). Notably, the rate of breast cancer mortality was substantially elevated in the lowest category above the referent ($RR_{>0 \text{ to } 500 \text{ ppm-days}} = 2.32$; 95%CI: 1.11, 4.83). The log-log model was visually similar to the categorical results, and fit the data the best of all four models (AIC = 1867.9) with a steep increase of the RR in the low exposure range, and an elevated RR at 365 ppm-day cumulative exposure ($RR_{365 \text{ ppm-days}} = 2.28$; 95%CI: 1.52, 3.45) as well as at 3,650 ppm-days cumulative exposure ($RR_{3,650 \text{ ppm-days}} = 3.15$; 95%CI: 1.78, 5.60). The linear model showed increased RRs at the lower exposure level of 3,650 ppm-days ($RR_{linear} = 1.16$; 95%CI: 1.04, 1.38), albeit this increase was less pronounced than the log-log and categorical models. These trends are displayed in Figure 1, which illustrates the categorical, linear (overall and restricted to cumulative exposure less than 5000 and 1000 ppm-days), and log-log models reported for all women in the cohort reported in Table 3. A magnified

version of the low-exposure range in Figure 1 is provided in Supplemental Figure S1.

Restricting the linear model to person time and events accrued at less than 5,000 and 1,000 ppm-days is also reported in Figure 1 and Table 3, and resulted in a higher slope of the exposure-response curve, particularly among the 1,000 ppm-day restriction ($RR_{365\ ppm\text{-}days} = 2.05$; 95%CI: 1.21, 4.01).

Matching on parity, age at menopause, oral contraceptive use, and mammogram screening among the subcohort of women who provided interview data caused minor changes in estimates, but rates remained elevated (Table 3).

Duration of employment had a pronounced impact on estimates. Supplemental Table S3 reproduces estimates from Table 3 without matching for duration of employment, and illustrates that estimates are lower when not matched for duration of employment.

There is also evidence of strong modification by time since exposure, which is displayed by decade in Figure 2. Supporting the *a priori* 20-year lag analyses, relative rates within windows of time since exposure are below 1 prior to 20 years since exposure, with a pronounced and persistent increase in the 20-30, 30-40, 40+ year windows indicating the effect of exposure persists 40+ years after exposure. In the empirical evaluation of lag times the best fitting lag remained at 20 years, as shown in Supplemental Figure S2. Modification of the association between cumulative exposure and breast cancer mortality by moving windows of exposure rate is shown in Figure 3. Relative rates are elevated among the 0.1 to 1 ppm and >1 ppm concentration window.

Discussion

This analysis of the largest and most informative cohort of EtO-exposed workers builds upon and strengthens previous findings on elevated breast cancer risks from cumulative exposure

to ethylene oxide. As was observed in prior mortality and incidence updates of this cohort, there appears to be a steep increase in risk at low cumulative exposures, given a 20-year lag. Despite a large increase in the length of follow-up, we did not observe an attenuation in risk compared with earlier results, likely because solid cancer types tend to have long latency and induction periods. With additional follow-up, we were able to examine elevated rates with improved precision, which also allowed us to examine temporal and exposure concentration variations important to risk estimation. These findings of consistent temporal trends in risk add to the causal evidence that EtO is a breast carcinogen. Additionally, we partially evaluated the impact of healthy worker survivor bias by matching for duration of employment, which had quite an important impact on estimates across all levels of cumulative exposure. More work evaluating components of HWSB is needed in order to determine if standard control methods is sufficient or if using g-methods would be necessary to correctly control for time-varying HWSB in this cohort.[33] Our present analysis of duration of employment indicates that the HWSB likely causes bias towards the null.

We also provided information on SMRs overall and by categories of exposure. SMRs were mostly above the null, although SMRs for exposure categories 0, >0-500, and >1000-5000 ppm-days were at or below the null. This is not unexpected and most likely reflects that the active workforce tends to be healthier than the general population (healthy worker effect), and this often causes SMRs to be biased towards the null. Greater weight should be given towards the findings from our internal analyses since SMRs by exposure level are not directly comparable and are strongly subject to biases from heathy worker effect and other differences in risk factors between the US standard population and our study population.

One limitation of the present analysis is that the outcome is readily-available mortality data, rather than incidence data. Although breast cancer prevalence is high in the US, the death rate in the US is low with the current 5-year survival rate estimated to be approximately 91%. Therefore, we are missing the majority of incident breast cancers, and have no information on breast cancer type. Often, when a cancer is not highly fatal or the survival time is long, risks tend to be underestimated in mortality studies due to outcome misclassification. Therefore, we expect our breast cancer mortality risk estimates underestimate breast cancer incidence risks. However, the new Virtual Pooled Registry-Cancer Linkage System[34] could facilitate future incidence analyses in which we would expect an increase in statistical power and the ability to evaluate distinctions by cancer subtypes and age at diagnosis.

Breast cancer incidence studies tend to support our findings of an association of ETO with increased breast cancer, although incidence studies are few.[1,12,35-38] The first epidemiological study to detect an increase in breast cancer morbidity among workers ever exposed to EtO was a study of 928 women employed in a New York medical sterilization facility, which identified a 155% increase in the breast cancer morbidity, compared to the state standard population rate.[35] To our knowledge, only four epidemiological studies have estimated incidence exposure-response associations using internal comparisons.[12,36-38] In a prior update of this cohort, incidence data was collected from a combination of state registries, medical records, and interviews. While there was evidence of an exposure-response association, the authors expressed concerns about potential biases from incomplete ascertainment of cancer incidence data.[12] A small Swedish study of 1,309 female sterilant workers also observed a cumulative exposure-response association between EtO and breast cancer incidence.[36] In a 2023 US study, investigators estimated environmental exposures based on proximity to EtO-emitting facilities

among a large cohort of postmenopausal women; living within 10 kilometers of an EtO-emitting facility was associated with in situ breast cancer incidence.[37] A study examining environmental exposures to ethylene oxide and incident invasive breast cancer in the Nurses Health Study found a slightly increased but imprecise hazard ratio.[38]

A strength of this study is that we were able to evaluate the impact of some potential confounders of the association between EtO exposure and breast cancer mortality; we had information on a variety of risk factors associated with increased breast cancer risk. These data were collected through interviews and is therefore subject to some selection and recall bias. However, we did not observe important differences in the characteristics between selected interviewed women and non-interviewed women (Table 1). Ultimately, in our analyses restricted to women who responded to the interview, we controlled for four breast cancer risk factors that were associated with exposure: parity, age at menopause, oral contraceptive use, and mammogram screenings, but did not observe important changes in estimates that would alter the conclusions or magnitude of our findings. These four potential confounders are significant life events for which we do not expect recall to differ by case status.

These interviews to determine risk factors for breast cancer were conducted mainly in 1998 or 1999, and have not been updated since. However, other prior studies indicated that it is unlikely that risk factors for breast cancer substantively bias the EtO-breast cancer association. In the prior cancer incidence study of this cohort, investigators did not observe a substantive change in estimate between minimally matched models and models matched for parity and breast cancer in first degree relatives (<10% change in estimate in the top quintile of cumulative exposure).[12] Similarly, a recent study evaluating proximity to EtO-emitting facilities and incident breast cancer evaluated the impact of adjusting for a large number of different risk factors of breast

cancer, but did not observe substantive changes in estimate when adjusting for any of these variables.[37] While it was not feasible to update the interviews, these prior studies indicated that it is unlikely that these predictors of breast cancer risk substantively bias the EtO-breast cancer estimates.

Further, the findings of this study are supported by mechanistic and laboratory animal studies indicating EtO is a breast carcinogen.[39] A study in female mice found a dose-response association between EtO and mammary gland adenocarcinomas.[40] EtO is genotoxic as direct-acting alkylating agent, and studies of workers exposed to EtO have demonstrated evidence of genotoxicity[41,42], a key characteristic of carcinogenicity. Beyond human and mechanistic studies providing support that EtO is a female breast carcinogen, the current analysis provides exposure-response analyses that suggest that workers exposed for a decade at the commonly-adopted occupational limit of 1 ppm measured as an8 hour time weighted average, and even at the more protective 0.1 ppm measured as an 8 hour time weighted average, experienced a substantially increased rate of breast cancer death compared to unexposed workers.

We consistently observed that the best estimate of the shape of the exposure-response curve between cumulative EtO exposure and breast cancer mortality was supra linear, which is often observed in cohort mortality studies.[43] This was the case for the main model, the breast cancer confounder controlled model, and models uncontrolled for duration of employment. The log-log models empirically fit the data best, and most closely resembled the categorical analyses upon visual inspection. The linear model was a poor fit to the data as judged by the AIC, however, when the linear model was restricted to person time and events accrued at exposures less than 1,000 ppm-days, the linear model closely resembled the low-exposure region of the log-log model (Figure 1, Figure S1). The difference in the unrestricted and restricted linear models

illustrates the influence of the very high exposed cases, which may be subject to more exposure misclassification than lower exposed cases. Accounting for the observed high rates at low exposures has important implications for population-level risk assessment, as relying on an unrestricted linear model or other poorly specified model would severely underestimate risks. Furthermore, this study in an adult working population does not capture risk associated with EtO exposures which occur in children and older adults, who may be more susceptible to EtO exposures;[44] therefore, risks in the general population may differ from risks estimated from this working population. Excess rates may be different in the general population than predicted from our models, given differences in the pattern of exposure. Residents living near a EtO facility could potentially be exposed for 24 hours per day and 7 days per week, whereas workers are typically only exposed for 8 hours per day and 5 days per week.

This updated analysis in the most informative cohort of workers exposed to EtO demonstrates continued evidence that EtO is a breast carcinogen and supports recent exposure reduction proposals and mitigation efforts. With 23 additional years of mortality follow-up, we observed substantial increases in breast cancer rates among women even in the lowest categories of occupational exposure. These elevated rates are most apparent when exposures are lagged by 20 years, consistent with known long latency and induction periods. Given the high prevalence of breast cancer in the general population, the large number of workers exposed to EtO, and the potential for environmental exposure, increases observed even in the low exposure range are of serious public health importance.

Acknowledgments

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Tables and Figures

Table 1. Employment, exposure, and mortality characteristics of female workers in the NIOSH ethylene oxide (EtO) cohort, follow-up 1960-2021.*

Characteristic (median (IQR) unless otherwise specified)	Full Cohort	Interviewed
Number of workers, n	7549	5132
Year of Birth	1939 (1927, 1948)	1940 (1929, 1948)
Race, n (%)		
white	6120 (81.1%)	4188 (81.6%)
Non-white	1429 (18.9%)	944 (18.4%)
Duration of employment in years	7.4 (2.7, 17.4)	7.7 (2.8, 17.7)
Duration of exposure in years	3.5 (1.6, 9.6)	3.5 (1.6, 9.9)
Cumulative exposure to EtO in ppm-days (mean, median, (IQR))	8503, 3056 (865, 9712)	8203, 3166 (899, 9877)
Rate of exposure in ppm (mean, median, (IQR))	3.7, 2.4 (1.0, 5.1)	3.7, 2.4 (1.0, 5.1)
Deceased, n (%)	4010 (53.1%)	2591 (50.5%)
Breast cancer deaths, n	181	111
Age at breast cancer death among deceased	64 (55, 74)	67 (57, 75)
Age at first employment	29 (22, 39)	29 (22, 38)
Person-years of follow-up	44.2 (36.6, 49.8)	45.1 (38.7, 50.3)
Age at end of follow-up	75 (68, 83)	76 (69, 83)

NIOSH = National Institute for Occupational Safety and Health, ppm = parts per million, IQR = interquartile range.
* excludes 23 women with a missing date of birth, and 2 women with a date last observed before the start of follow-up.

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Table 2: Standardized mortality ratios (with a 20 year lag) and 95% confidence intervals among a cohort US women employed in ethylene oxide sterilization facilities, by categories of cumulative exposure (parts per million-days), follow-up 1960-2021.

ppm-days	Cases	SMR
0	38	0.83 (0.58, 1.13)
>0-500	21	0.93 (0.58, 1.42)
>500-1000	20	1.45 (0.88, 2.24)
>1000-5000	38	0.85 (0.60, 1.18)
>5000-15000	34	1.33 (0.93, 1.84)
>15000-25000	16	1.46 (0.83, 2.36)
>25000	14	1.37 (0.75, 2.30)

Table 3. Cumulative exposure to ethylene oxide (EtO) and relative rate of death from breast cancer among a cohort US women employed in sterilization facilities, 1960-2021.

		Full cohort (all women)[a]			Subcohort of women with interviews[b]		
Model type	ppm-days	Deaths	RR (95% CI)	AIC	Deaths	RR (95% CI)	AIC
Categorical	0[c]	38	1 (1, 1)	1872.78	12	1 (1, 1)	774.68
	>0-500	21	2.32 (1.11, 4.83)		15	2.57 (0.94, 7.64)	
	>500-1,000	20	3.73 (1.74, 7.92)		10	3.07 (1.02, 9.71)	
	>1,000-5,000	38	2.30 (1.13, 4.70)		27	2.04 (0.79, 5.89)	
	>5,000-15,000	34	3.51 (1.69, 7.35)		29	4.30 (1.59, 12.85)	
	>15,000-25,000	16	4.76 (2.00, 11.12)		9	4.40 (1.33, 15.15)	
	>25,000	14	5.23 (2.16, 12.37)		9	4.67 (1.40, 16.05)	
Log-Log	at 365[d]	181	2.28 (1.52, 3.45)	1867.90	111	2.25 (1.31, 4.04)	768.71
	at 3,650[e]		3.15 (1.78, 5.60)			3.09 (1.45, 6.96)	
Linear	at 365	181	1.02 (1.00, 1.04)	1873.35	111	1.02 (1.00, 1.05)	771.54
	at 3,650		1.16 (1.04, 1.38)			1.17 (1.02, 1.51)	
Linear, restricted at 5000 ppm-days	at 365	117	1.06 (0.98, 1.20)		64	1.04 (0.97, 1.21)	
	at 3,650		1.58 (0.58, 3.01)			1.43 (0.68, 3.14)	
Linear, restricted at 1000 ppm-days	at 365	79	2.05 (1.21, 4.01)		37	1.53 (0.89, 3.90)	

All models include a 20 year exposure lag. AIC = Akaike information criterion, RR = relative rate, CI = confidence interval, NIOSH = National Institute for Occupational Safety and Health, OSHA = Occupational Safety and Health Administration. The log-log model is specified as $f(d) = \exp(\beta_1 * \ln(d+1))$, and the linear model as $f(d) = 1 + \beta_1 d$, where $f(d)$ describes the rate ratio as a function of dose.

[a]Matched for birth cohort, duration of employment, and race

[b]Additionally matched for parity (0/1+), age at start of menopause (≤55 or >55), never/ever use of oral contraceptives, and never/ever received a mammogram.

[c]0 ppm-days includes both unexposed person-time and lagged periods.

[d]365 ppm-days approximates cumulative exposures accrued over 10 years at 0.1 ppm. The NIOSH recommended time weighted average exposure limit for EtO is <0.1 ppm.

[e]3,650 ppm-days approximates cumulative exposures accrued over 10 years at 1 ppm. The OSHA time weighted average exposure limit for EtO is 1 ppm.

FIGURE CAPTIONS

Figure 1:

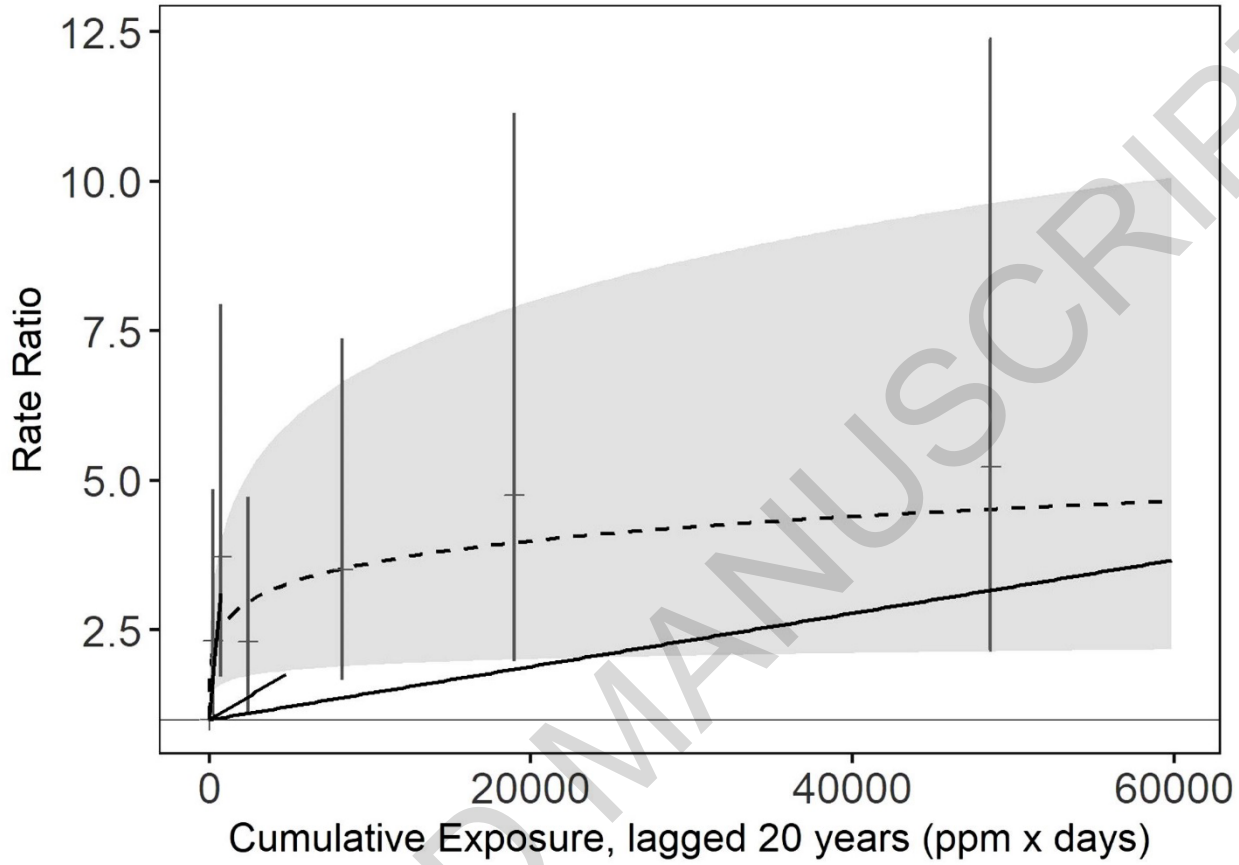

Figure 1: Exposure-response associations between cumulative ethylene oxide exposure and breast cancer mortality rates among a cohort of US women employed in sterilization facilities, follow-up 1960-2021. Log-log model (dashed line and corresponding shaded area); Linear model (three solid lines): unrestricted, restricted at 5,000 ppm-days, and restricted at 1,000 ppm-days; Categorical model (grey dashes and error bars): 0, >0-500, >500-1,000, >1,000-5,000, >5,000-15,000, >15,000-25,000, and >25,000 ppm-days and 95% profile likelihood confidence intervals. All models include a 20 year exposure lag. All models match for age, birth cohort, race, and duration of employment. Not shown: Cumulative exposure x-axis extends to approximately 250,000 ppm-days. Summary data can be found in Table 3.

Figure 2:

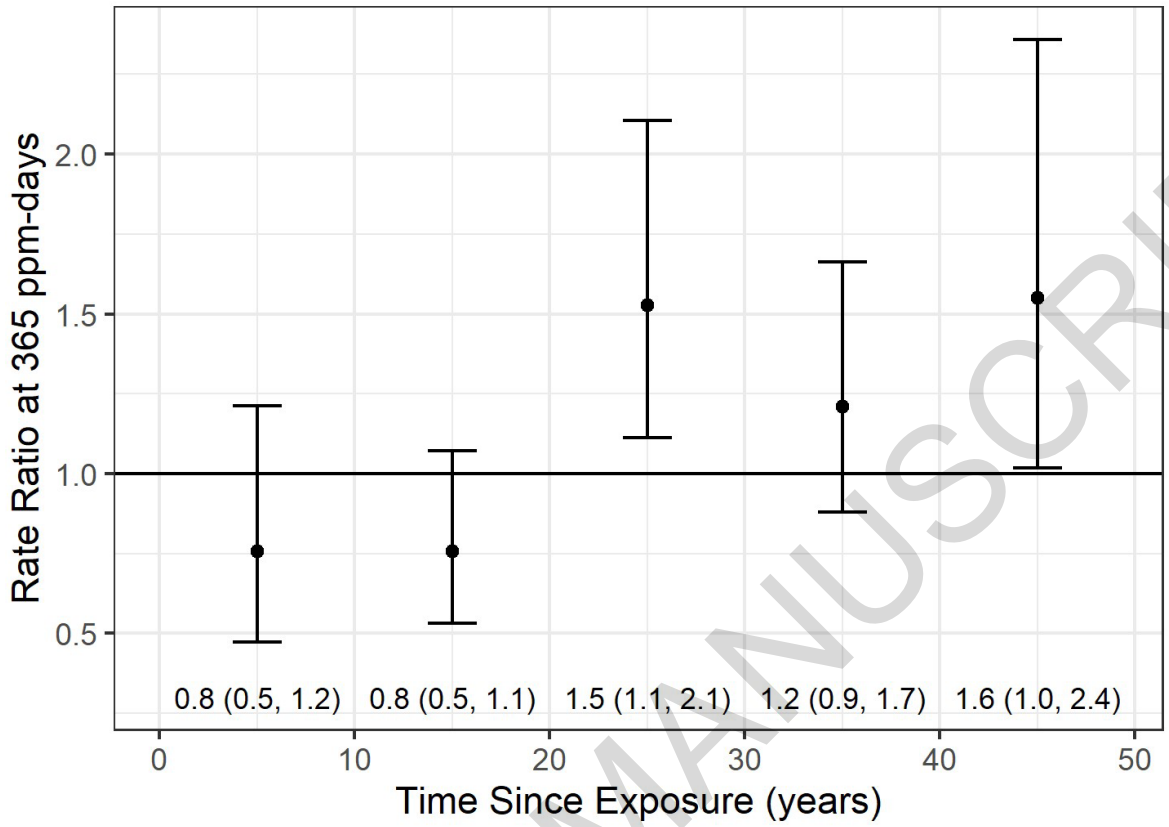

Figure 2: Modification of the relative rate of the association between cumulative ethylene oxide exposure and breast cancer mortality by temporal windows of time since exposure. US cohort of 7,549 women employed in sterilization facilities for at least 1 year, follow-up 1960- 2021. Results plotted from an unlagged log-log Cox proportional hazards model with attained-age as the underlying time scale, further matched on birth cohort, race, and duration of employment. Circles represent the relative rate of mortality from breast cancer per 3,650 ppm-days of cumulative exposure to ethylene oxide, by windows of temporal cumulative exposures accrued at 0-<10, 10-<20, 20-<30, 30-<40, and 40+ years. Error bars represent associated 95% profile likelihood confidence intervals.

Figure 3:

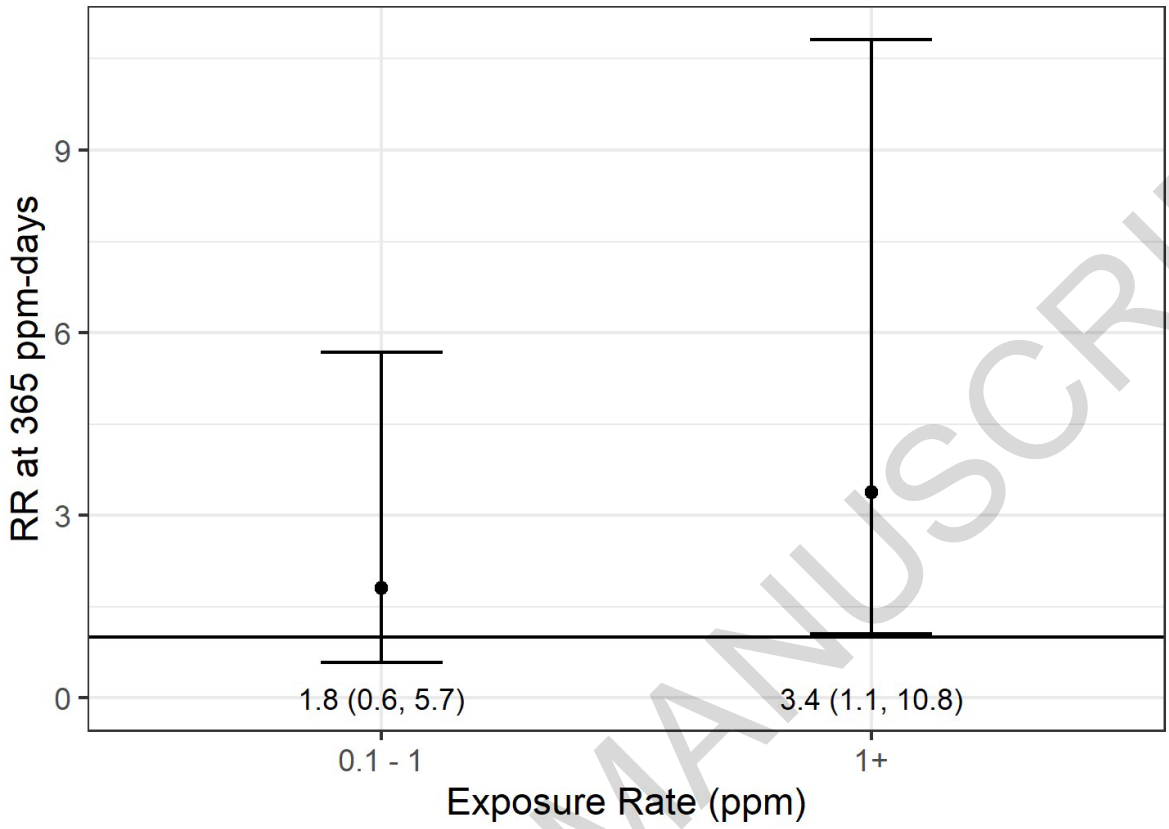

Figure 3: Modification of the relative rate of the association between cumulative ethylene oxide exposure and breast cancer mortality by temporal window of exposure rate. US cohort of 7,549 women employed in sterilization facilities for at least 1 year, follow-up 1960-2021. Results plotted from a 20-year lagged log-log Cox proportional hazards model with attained-age as the underlying time scale, further matched on birth cohort, race, and duration of employment. Circles represent the relative rate of mortality from breast cancer per 365 ppm-days of cumulative exposure to ethylene oxide, by windows of temporal cumulative exposures accrued at 0.1-1, and 1+ ppm levels. Error bars represent associated 95% profile likelihood confidence intervals.