



RESEARCH ARTICLE

Associations between exposure to ethylene oxide, job termination, and cause-specific mortality risk

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Abstract

Background: Previous analyses of mortality were conducted in a large cohort of ethylene oxide (EtO) exposed workers employed at 13 sterilization facilities throughout the U.S. and followed from the start of operation through 1998. Statistically significant elevated mortality was reported from hematopoietic cancer in men and breast cancer in women compared to the general population. Possible healthy worker survivor bias was not addressed.

Methods: To examine survivor bias in this cohort, employment termination was analyzed with statistical models stratified on sex and race that included age, employment duration, and cumulative EtO exposure. To reduce survivor bias employment duration was included in Poisson regression model specifications for estimating standardized mortality ratios for several cancer outcomes.

Results: Strong statistically significant effects of unlagged cumulative EtO exposure were observed on rate of employment termination, indicating potential *healthy worker survivor effect* bias. Adjustment for employment duration in analyses of mortality resulted in statistically significant and stronger associations between cumulative EtO exposure and lung cancer, female breast cancer and hematopoietic cancer. There was a striking reduction in nonmalignant respiratory disease mortality risk with increasing employment duration with a further (nonsignificant) reduction with cumulative EtO, suggesting that EtO itself is driving termination of workers with respiratory morbidity even though the average EtO exposures in this population were generally far below odor and acute irritancy thresholds.

Conclusions: Important survivor bias was present in this EtO cohort and may be present in many occupational settings involving irritant exposures.

KEYWORDS

breast cancer, employment duration, lung cancer, survivor bias

1 | INTRODUCTION

The *healthy worker survivor effect* (HWSE) has long been recognized as an important source of bias in occupational epidemiology,^{1,2} for example in studies of diesel exhaust, metalworking fluids and for

occupational asthma.³⁻⁶ The causes of these effects may include depletion by exposure of high-susceptible subpopulations, and selective removal from exposure of individuals with unaccounted-for confounding exposures such as smokers, or individuals experiencing early symptoms. If smoking were a risk factor for leaving employment, the

surviving workforce would have less cumulative smoking history but higher cumulative workplace exposures. Attenuation of exposure-response with higher cumulative exposures appears to be a manifestation of HWSE quite generally.⁷ Respiratory disease endpoints are particularly vulnerable to the *healthy worker effect* (HWE), reflecting selection at hire, and presumably also to HWSE.⁸

Chronic industrial exposure to reactive, irritant or sensitizing agents would be expected to exhibit a potentially strong HWSE. Ethylene oxide (EtO) is a reactive gas used to sterilize medical instruments, other manufactured products and even food materials like spices. In this analysis a previously studied cohort of workers exposed to EtO was examined with regard to HWSE for several mortality outcomes. Duration of employment was used as a means to adjust for HWSE in contrast to approaches using g-estimation and related methods.²

2 | METHODS

2.1 | Original data set

The study population has been previously compiled by NIOSH investigators and described,⁹⁻¹¹ consisting of all workers in 14 sterilization facilities with 3 or more months since first exposure to EtO. Use of EtO began as early as 1938 but nine of the facilities first used EtO after 1960. Follow-up of this cohort began with 3 months of EtO exposure and continued until 31 December 1998.¹⁰ An exposure matrix was constructed by these investigators based on over 2350 time-weighted exposure values from 18 plants and on modeling using a subset of samples for which detailed process information was available (relating to product type, sterilizer volume, ventilation, and aeration).¹² The result was estimated exposure levels in eight process categories (sterilizer operator, chamber area, maintenance, production, etc) over time which could be mapped to the work history available as department and/or job classifications.

The outcomes examined included those reported to be associated with EtO exposure by the previous investigators (all lymphopietic cancer (ICD-9: 200-208) and breast cancer [ICD-9: 174]) as well as lung cancer (ICD-9: 162) and nonmalignant respiratory diseases (ICD-9: 460-519). The previous analyses did not address possible survivor bias.

2.2 | Statistical analysis

Employment duration, defined as the period from date of first hire until last date of observation or date of final termination, whichever occurred first, was analyzed with Poisson regression. Follow-up in the employment duration model began 3 months after first EtO exposure and continued until the earlier of 5 years before death, 3 months before a plant closing, or 31 December 1998. Rates of termination were modeled using Poisson regression in SAS¹³ (see Appendix for modeling code) with a table constructed to jointly classify all observation time in demographic levels as well as detailed levels of time-

dependent employment duration, EtO exposure duration, and unlagged EtO cumulative exposures. The unit of observation was one person-day but observations were collapsed to a smaller file using fine stratification of the continuous variables. By definition in this model specification the employment duration variable remains fixed, after termination of employment, at the worker's final duration. For rate of employment termination the following model was specified and applied separately for each demographic group:

$$\text{quits} = \exp(a_0 + a_1 \times (\text{age}-40) + a_2 \times (\text{age}-40)^2 + b_3 \times \text{dur} + b_4 \times \text{cumEto}) \times \text{PY},$$

where, PY = person-years; quits = number of terminations in PY; dur = employment duration, in years from hire; cumEto = cumulative EtO, lagged or unlagged, in ppm-yr. In this model, $\exp(a_0)$ is the predicted annual termination rate in 40-year-old workers with no EtO exposure (and no duration).

Mortality analyses also utilized Poisson regression (see Appendix for model detail). A classification table was constructed for all observation time on demographic variables, time-dependent EtO exposure and employment duration metrics, and outcomes based on person-days and then collapsed using fine stratification. An offset was applied consisting of the expected number of cause-specific deaths in each classification cell based on U.S. national rates. Thus these were statistical models of standardized mortality ratios (SMR). Time-dependent cumulative exposure metrics, such as *cumEto*, for EtO were calculated with a lag to account for the delay following the tumor initiation process and the resulting death. For nonmalignant respiratory disease, a 2.5 years lag was applied because developing respiratory impairment is often a cause of exposure termination.¹⁴

To address possible survivor effects, models of mortality rates for specific outcomes were fit in two specifications (see Appendix for detailed rationale). The first

$$\text{deaths} = \exp(a_0 + a_1 \times \text{rac0} + a_2 \times \text{sex0} + a_3 \times \text{rac0} \times \text{sex0} + b_1 \times \text{dur}) \times (1 + c_1 \times \text{cumEto}) \times n_{\text{expected}},$$

applies employment duration as a multiplicative adjustment of baseline risk. To calculate the expected deaths, n_{expected} , U.S. age-, race-, sex-, and year-specific mortality rates¹⁵ were multiplied by PY in each cell. In these models, $\exp(a_0)$ is the predicted SMR for workers with no EtO exposure and no duration over the period of follow-up. This model specification would be appropriate if population susceptibility was changing with employment duration. The second

$$\text{deaths} = \exp(a_0 + a_1 \times \text{rac0} + a_2 \times \text{sex0} + a_3 \times \text{rac0} \times \text{sex0}) \times (\exp(b_1 \times \text{dur}) + c_1 \times \text{cumEto}) \times n_{\text{expected}},$$

applies employment duration as an additive adjustment of baseline risk. This specification would be appropriate if, for example, the selection on duration were the result of smokers generally terminating sooner than nonsmokers or if the observed EtO-associated

excess mortality did not depend on other modifiers of the baseline risk that depend on duration.

On prior mechanistic grounds, when exposure is appropriately identified, measured and specified for modeling an outcome, employment duration by itself would not be a confounder (or causing collider bias). If there are other violations of assumptions such as effect-modification by age, then duration could appear as a confounder (in which case that interaction would need to be part of *g*-estimation as well). Similarly, If there is substantial exposure misclassification, those leaving might have had higher exposures on average than those staying who have the same assigned exposures. This could introduce survivor bias: those with long employment would have systematically less true exposure than assigned (and *visa versa*) which would likely distort the estimated exposure response.

3 | RESULTS

3.1 | Demographic aspects

There were 18 235 workers available for study from 14 plants but one plant lacked exposure history, leaving a population of 17 460. Further exclusions due to unknown vital status, foreign deaths and missing demographic information resulted in 17 185 workers (98.4%) for analysis. White women were the largest demographic group ($n = 7878$) followed by white men ($n = 5858$), black women ($n = 1823$)

TABLE 1 Workers' final durations, and assigned EtO exposures based on an exposure matrix,^a by sex and race

		White men	Black men	White women	Black women	All
	N	5858	1626	7878	1823	17 185
Employment duration, y	Mean	8.5	8.3	8.9	9.1	8.7
	SD	9.5	8.6	9.5	8.9	9.4
	Maximum	63.1	43.3	52.8	39.7	63.1
Duration of EtO exposure, y	Mean	5.0	5.5	4.7	5.4	5.0
	SD	6.2	6.4	5.8	6.5	6.1
	Maximum	39.2	38.4	37.7	28.1	39.2
EtO exposure intensity, ^b ppm	Mean	7.8	7.9	4.5	3.8	5.9
	SD	11.9	10.9	8.9	3.3	10.0
	Maximum	328	144	296	31.2	328
Cumulative EtO exposure, ^c unlagged, ppm-yr	Mean	37.2	40.0	18.7	17.7	26.9
	SD	88.7	82.9	41.0	25.4	65.3
	Maximum	1219	1351	694	225	1351
Cumulative EtO exposure, lagged 10 y, ppm-yrs	Mean	34.6	38.2	18.1	17.3	25.6
	SD	84.2	77.0	40.1	25.2	62.1
	Maximum	1219	1351	694	225	1351

Abbreviation: EtO, ethylene oxide.

^aGreife.¹²

^bMean, across population, of career mean EtO concentration more than 0 over observation time.

^cCumulative exposure as of end of employment.

and black men ($n = 1626$) (Table 1). The employment and exposure history by the end of follow-up shows that workers were employed on average 8 to 9 years with black women having the longest duration, 9.1 year (Table 1). Workers' exposure to EtO occurred over an average of 5 years with white women having the least (4.7 years) and black women the most (5.4 years) (Table 1). Women generally had lower estimated time-averaged EtO exposure concentrations and lower (lagged and unlagged) cumulative EtO exposure, by a factor of about two. Black women had a much smaller standard deviation for cumulative EtO indicating less diverse work activities. The overall time-averaged EtO exposure was 5.4 ppm (26.91/4.96, from Table 1).

3.2 | Employment termination models

Out of the 17 185 workers, 14 314 met the criterion of voluntary or discretionary termination before end of follow-up for mortality. Poisson regression models of employment termination as functions of age, employment duration and (unlagged) cumulative EtO exposure in each of the demographic groups reveal a highly statistically significant negative effect of duration (diminishing rate of leaving with increasing time on job) and positive effects of EtO cumulative exposure that are highly significant for all but the smaller work group of black women (Table 2). All demographic groups have similar initial rates of termination of about 15% per year ($\exp[-1.9]$, at age 40) but

TABLE 2 Models of rate of employment termination (quits per person-year) on duration and cumulative EtO exposure (unlagged), controlling for age by Poisson regression, stratifying on sex and race

	β	SE $_{\beta}$	95% CL ^a	
1	White men			
	intercept	-1.91	0.03	-1.97, -1.85
	Duration	-.099	0.004	-0.11, -0.09
	Cum EtO unlagged	.0017	0.0002	0.001, 0.002
2	Black men			
	intercept	-1.88	0.06	-1.99, -1.76
	Duration	-.107	0.008	-0.12, -0.09
	Cum EtO unlagged	.0019	0.0004	0.001, 0.003
3	White women			
	intercept	-1.93	0.02	-1.97, -1.89
	Duration	-.088	0.0033	-0.094, -0.081
	Cum EtO unlagged	.0018	0.0004	0.001, 0.003
4	Black women			
	intercept	-1.98	0.05	-2.09, -1.88
	Duration	-.129	0.0097	-0.15, -0.11
	Cum EtO unlagged	.0027	0.0018	-0.001, 0.006

Note: Model: quits = $\exp(a_0 + a_1 \times (\text{age}-40) + a_2 \times (\text{age}-40)^2 + b_3 \times \text{dur} + b_4 \times \text{cumEtO}) \times \text{PY}$.

where, in each classification cell: PY, person-years; quits, number of terminations; dur, mean employment duration, in years from hire to observation; cumEtO, cumulative EtO, unlagged, in ppm-yr; follow-up until first of: 5 year before (death or end of study follow-up), 3 months before plant closings and date of termination; separate model for each demographic group.

^aCL, Wald confidence limits.

black women show the lowest rate of termination at low EtO exposures and progressively advance to the highest termination rate at higher EtO exposures (Figure 1). White women show a less pronounced progression and men (white and black) show a smaller dependence on EtO exposures.

3.3 | Mortality from nonmalignant respiratory disease

For 131 workers nonmalignant respiratory disease was the underlying cause of death. The standardized mortality ratio (SMR) for nonmalignant respiratory disease (NMRD) in this population was 0.93 for white men, rising to 1.25 for black women (Table 3; model 1), which are elevated compared to healthy industrial populations.⁸ There appeared to be a substantial *healthy worker effect* (hiring) for black men (SMR = 0.63 = $\exp(-0.064 - 0.392)$; Table 3, model 1). When modeled with Poisson regression, there was a further elevated intercept corresponding to SMR = 1.75 ($\exp(0.56)$) and a highly significant decline with duration of employment (Table 3; model 2): 6% for each year of employment ($1 - \exp(-0.062)$; 95%CL: 4.0, 8.1%). Addition of the term for unlagged EtO cumulative exposure resulted in no improvement in model fit (Table 3; model 4).

3.4 | Lung cancer mortality

Lung cancer was the underlying cause of death for 247 workers with SMR = 1.06. In contrast to NMRD, EtO was associated with excess lung cancer (Table 4). With terms only for 10-year lagged cumulative EtO in all men, white women and black women, the associations were not statistically significant (χ^2 from likelihood ratio test (LRT) (3 df) = 3.5; $P = .3$; model 1). However, including a multiplicative adjustment to baseline rate based on employment duration improved the model fit (χ^2 (3 df) = 4.6; $P = .2$; model 2), and with the additive adjustment to baseline there was further improvement (χ^2 (3 df) = 6.9; $P = .07$; model 3). Limiting the exposure terms to female workers produced a significant result (χ^2 (2 df) = 6.13; $P = .047$). Testing the significance of the sex difference in EtO effect using the interaction term yielded a P -value .18 (data not shown).

3.5 | Mortality from cancer of the female breast

For the 102 deaths from female breast cancer, there was no statistically significant difference in mortality on cumulative EtO exposure with a 10-year lag by race, black women having a slightly smaller association (Table 5; models 1 and 2). Adjustment for baseline risk, both additive and multiplicative, produced insignificant improvement in model fit; in the better fitting model, the contribution of (lagged) cumulative EtO exposure was not significant (χ^2 (1 df) = 1.55; $P = .21$) (Table 5, models 3 and 4). This analysis lacked important risk factor information such as parity or age at first live birth. However, with a 20-year lag, the contribution of cumulative EtO was significant (LRT: $P = .04$) and improved considerably with the multiplicative adjustment for baseline risk (LRT: $P = .01$) (Table 5; models 5-8).

3.6 | Mortality from all lymphopietic cancer

The 73 lymphopietic cancer deaths did not represent an overall excess (SMR = 0.96; 95% CI, 0.76-1.20), based on U.S. rates, particularly for white men (SMR = 0.92), and white women (SMR = 0.85), but among black workers, there was a statistically significant increase in SMR with cumulative EtO exposure (lagged 2.5 years; LRT: $P = .011$) (Table 6; model 1). A multiplicative adjustment to baseline risk with employment duration resulted in a modest improvement in model fit for the association with EtO exposure (for EtO effect; LRT: $P = .007$) (Table 6; model 2); the additive adjustment had slightly less effect (for EtO effect; $P = .008$) (Table 6; model 3).

4 | DISCUSSION

4.1 | Findings

With EtO, there appears not to be an overall association with NMRD mortality although an SMR of 0.93 is somewhat high for typical

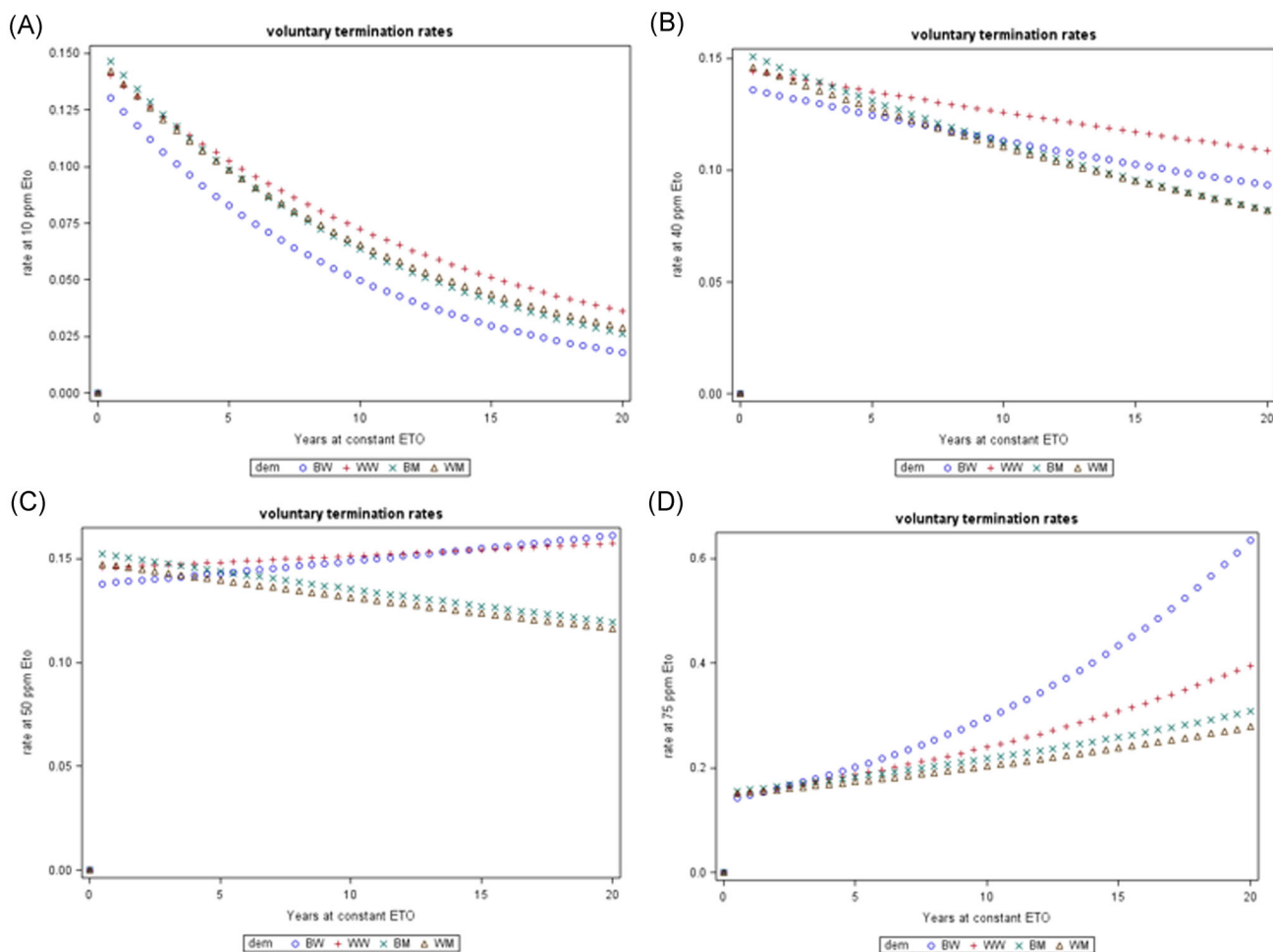


FIGURE 1 Predicted rates of employment termination with employment duration in four demographic groups at fixed ethylene oxide exposure concentrations: A, 10 ppm, B, 40 ppm, C, 50 ppm, D, 75 ppm [Color figure can be viewed at wileyonlinelibrary.com]

industrial populations free of respiratory threats, where SMRs range 0.5-0.8.⁸ An earlier mortality analysis of this cohort with follow-up through 1987 observed an NMRD SMR of 0.80.¹¹ In the present analysis of the EtO cohort, during follow-up with a small duration of employment (both during and following termination of employment), the predicted mortality rate was considerably elevated (from intercept, SMR = 1.75) (Table 3; model 2); after about 9 years of EtO exposure, the predicted NMRD deaths would be about as expected from U.S. rates ($\exp(0.56 \cdot 9 \times 0.062)$); at less than 9 years, there would be more NMRD deaths than expected without addressing the survivor effect and at greater than 9 years, fewer than expected. If not accounted for, this distortion in the baseline SMRs related to survival would confound a toxic effect of EtO on NMRD mortality, if present. The observation that EtO is a strong determinant of employment termination and employment duration is a strong predictor of declining NMRD risk but EtO itself is a weak (and negative) risk factor for NMRD (Table 3; model 4) suggests that EtO may be simultaneously modifying the baseline rate (by promoting selective termination of high-risk individuals) as well as increased risk for

NMRD. The EtO example presents an unusual opportunity to observe potential survivor bias related to occult health effects.

In other EtO studies lung cancer has been reported not to have significantly elevated incidence¹⁶ or mortality,¹⁷ although a strong HWE bias was evident in the mortality study (all-cause SMR = 0.79; 95%CI: 0.71-0.78; all-cancer SMR = 0.86, 95%CI: 0.71-1.04).¹⁷ The previous study of mortality in the present cohort¹⁰ did not report analyses of lung cancer mortality beyond the modest overall association (SMR = 1.05; 95% CI, 0.95-1.17). Because duration is contributing to any cumulative exposure metric, this method of controlling HWSE may fail if exposure intensity is relatively uniform across jobs and time, resulting in high collinearity. However, observing positive exposure effects in the same models with negative duration effects indicates that collinearity is not the problem, rather, that survivor bias is present violating underlying model assumptions. This method would fail if an extreme survivor bias is present, possibly driven by EtO exposure levels, which may have been the case in this cohort affecting NMRD mortality. Across all outcomes analyzed in the present work, the estimates for the duration effects were

Demographic groups with Duration or cumulative EtO	β	SE $_{\beta}$	95% CL ^a	SMR(0) ^b (% loss) ^c	Model -2lnL
1 White men (intcp)	-.064	0.140	-0.34, 0.21	0.93	2696.848
iBlack men ^d	-.397	0.403	-1.19, 0.39	0.63	
iWhite women ^d	.052	0.185	-0.31, 0.42	0.99	
iBlack women ^d	.234	0.614	-0.97, 1.44	1.25	
2 White men (intcp)	.560	0.164	0.24, 0.88	1.75	2659.238
iBlack men	-.457	0.403	-1.25, 0.33	1.11	
iWhite women	.019	0.185	-0.34, 0.38	1.78	
iBlack women	.157	0.614	-1.05, 1.36	1.32	
Duration	-.0617	0.0113	-0.08, -0.04	(6.0%)	
3 White men (intcp)	.146	0.150	-0.15, 0.44	1.16	2686.478
iBlack men	-.363	0.404	-1.15, 0.43	0.80	
iWhite women	-.046	0.186	-0.41, 0.32	1.11	
iBlack women	.180	0.615	-1.02, 1.38	1.14	
Cum Eto	-.0045	0.0017	-0.01, -0.001	(0.45%)	
4 White men (intcp)	.574	0.165	0.25, 0.90	1.77	2658.862
iBlack men	-.452	0.403	-1.24, 0.34	1.13	
iWhite women	.000	0.188	-0.37, 0.37	1.77	
iBlack women	.154	0.614	-1.05, 1.36	1.32	
Duration	-.0584	0.0124	-0.08, -0.03	(5.7%)	
Cum Eto	-.0010	0.0017	-0.004, 0.002	(0.10%)	

Note: Model: deaths = $\exp(a_0 + a_1 \times \text{rac0} + a_2 \times \text{sex0} + a_3 \times \text{rac0} \times \text{sex0} + b_1 \times \text{dur} + c_1 \times \text{cumEto}) \times n_{\text{expected}}$.

where, intcp, intercept; duration - time-dependent employment duration, in years from hire;

cumEto-cumulative EtO, lagged 2.5 y, ppm-yrs; rac0: 0=white, 1 = nonwhite; sex0: 0 = men

1 = women; n_{expected} -number of deaths expected based on U.S. rates; four separate models.

Abbreviations: EtO, ethylene oxide; NMRD, nonmalignant respiratory disease; SMR, standardized mortality ratio.

^aCL - Wald confidence limits.

^bSMR(0) - estimated baseline SMR; adjusted for cumEto or employment duration (models 2-4).

^c% reduction in NMRD mortality per year (duration) or per ppm-year (cumulative EtO).

^dincremental increase in log (SMR): for black men vs white men (iBlack men); for white women vs men (iWhite women); for black women vs. white women and men (iBlack women).

negative but statistically significant only for lung cancer (the outcome most associated with smoking).

In the present analysis cumulative EtO exposure was significantly associated with lung cancer death only in women, with a suggestion of substantially higher risk in black women. This brings up the possibility of important exposure misclassification. If within the defined broad exposure groups there was considerable sex/race-dependent differential assignment of job tasks such that men had lower exposures than average and women higher exposures, misclassification would result. This could happen, for example, if the tasks of unloading and processing sterilized materials were preferentially assigned to women, and the highest exposed jobs assigned to black women. The observation that black women were the least likely to terminate employment at low exposure but showed the strongest termination rate dependence on EtO supports the existence of such misclassification. Differential susceptibility by sex would be another possible explanation for the stronger EtO effect in women. However, the adjustment specification addressing susceptibility

TABLE 3 Standardized mortality ratio for nonmalignant respiratory disease (by Poisson regression, as log(SMR)) on sex, race, employment duration, and cumulative EtO (NMRD deaths: 131)

(Table 4; model 2) fit less well than the specification relating to selection on other risk factors, like smoking (Table 4; model 3).

Previous analyses of female breast cancer in EtO populations have observed positive, nonlinear associations with lagged cumulative EtO exposures. There was a statistically significant, apparently supralinear, association of incidence of breast cancer with EtO in a categorical, internally standardized analysis of Swedish workers¹⁶ based on unlagged cumulative exposures. In the present U.S. cohort, with a 20 year lag, Steenland et al¹⁰ using Cox regression, reported essentially uniformly elevated breast cancer mortality across three lower strata of cumulative exposure and a significantly higher odds ratio in the highest exposure strata (OR = 3.76; 95% CI, 1.03-13.6). Reproductive history was not available for this Swedish or U.S. study. After identification of more than 200 additional, incident cases of breast cancer in the U.S. cohort by questionnaire survey,¹⁸ analyses of incidence exposure-response, with Cox regression and a 15-year lag and controlling for reproductive parity, produced significant trends on both cum. EtO and log(cum. EtO) metrics ($P = .02$); a stronger association was observed with *duration* of EtO exposure itself (lagged 15 years;

TABLE 4 Standardized mortality ratio for lung cancer (by Poisson regression) on sex, race, employment duration, and cumulative EtO (lung cancer deaths: 247)

Duration and cumulative EtO (lag = 10 y)	β	SE $_{\beta}$	95% CL ^a	Δ -2lnL ^b X ² (df)	P ^b
1 Model: deaths = $\exp(a_0 + a_1 \times \text{rac0} + a_2 \times \text{sex0} + a_3 \times \text{rac0} \times \text{sex0}) \times (1 + c_1 \times \text{cumEtO} + c_3 \times \text{Sceto} + c_4 \times \text{RSceto}) \times n_{\text{expected}}$					
intercept	.0890			3.47 (3)	.32
Cum EtO All men	-.0002	0.0007	-0.002, 0.001		
Cum EtO iWhite women ^c	.0013	0.0024	-0.003, 0.006		
Cum EtO iBlack women ^c	.0241	0.0347	-0.044, 0.092		
2 Model: deaths = $\exp(a_0 + a_1 \times \text{rac0} + a_2 \times \text{sex0} + a_3 \times \text{rac0} \times \text{sex0} + b_1 \times \text{dur}) \times (1 + c_1 \times \text{cumEtO} + c_3 \times \text{Sceto} + c_4 \times \text{RSceto}) \times n_{\text{expected}}$					
intercept	.2721			4.60 (3)	.20
Duration	-.0206	0.0077	-0.036, -0.006		
Cum EtO All men	.0008	0.0012	-0.002, 0.003		
Cum EtO iWhite women	.0025	0.0035	-0.004, 0.009		
Cum EtO iBlack women	.0308	0.0433	-0.054, 0.116		
3 Model: deaths = $\exp(a_0 + a_1 \times \text{rac0} + a_2 \times \text{sex0} + a_3 \times \text{rac0} \times \text{sex0}) \times (\exp(b_1 \times \text{dur}) + c_1 \times \text{cumEtO} + c_3 \times \text{Sceto} + c_4 \times \text{RSceto}) \times n_{\text{expected}}$					
intercept	.3251			6.98 (3)	.07
Duration	-.0264	0.0086	-0.043, -0.010		
Cum EtO All men	.0005	0.0006	-0.001, 0.002		
Cum EtO iWhite women	.0025	0.0022	-0.002, 0.007		
Cum EtO iBlack women	.0215	0.0293	-0.036, 0.079		
4 Model: deaths = $\exp(a_0 + a_1 \times \text{rac0} + a_2 \times \text{sex0} + a_3 \times \text{rac0} \times \text{sex0}) \times (\exp(b_1 \times \text{dur}) + c_3 \times \text{Sceto} + c_4 \times \text{RSceto}) \times n_{\text{expected}}$					
intercept	.3270			6.13 (2)	.047
Duration	-.0228	0.0074	-0.037, -0.008		
Cum EtO iWhite women	.0028	0.0021	-0.001, 0.007		
Cum EtO iBlack women	.0217	0.0299	-0.037, 0.080		

Note: n_{expected} , number of deaths expected based on U.S. rates; rac0–race coded as 0 = white, 1 = nonwhite; sex0, sex coded as 0 = men, 1 = women; duration, time-dependent employment duration, yrs; Cum EtO, cumulative EtO exposure, lagged 10 y, as ppm-yrs EtO; Sceto, cumEtO \times sex0; RSceto, Sceto \times rac0.

^aCL – Wald confidence limits.

^bChange in 2ln(Likelihood) with addition of cumulative EtO terms and associated p.

^cincremental increase in log(SMR): for white women vs men (iWhite women); for black women vs white women and men (iBlack women).

$P = .006$). All of the Cox regression models assumed a log-linear relationship: $\log(\text{OR}) = a + bX$ which would under-estimate response at low exposures for a carcinogen which actually has a linear exposure-response. Observing here the improvement with a 20-yr vs. 10-yr lag suggests that early exposures may have been important, possibly related to reproductive status such as at the age of first live birth. However, an EtO cumulative exposure metric restricted to exposures occurring up to age 35, with a 10-yr lag, did not predict risk well for premenopausal or all breast cancer (data not shown).

For all haematopoietic cancer incidence,¹⁶ Mikoczy et al (17 incident cases) found no significant increases using unlagged cumulative EtO exposure. Steenland et al¹⁰ in the present mortality cohort (with Cox regression and a 15 year lag) observed increasing odds ratios with log(cum. EtO) but only in men (LRT: $P = .02$); stratification of analyses by race was not reported.

4.2 | Limitations

This study demonstrates a method of adjustment for survivor effects, a need that was suggested long ago by Gilbert¹⁹ and has

been applied using employment duration in other studies.^{20–23} As applied here, the method constrains the baseline risk in the form of an exponential decline based on employment duration. The risk factors contributing to this decline are not known nor is the optimum form of this duration-association. It offers a partial correction and appears to increase statistical power for outcomes affected by survivor bias. Other selection effects related to employment status or health effects causing changes in exposure status, may be poorly or inappropriately controlled using employment duration. Some have posited that If work status is both a mediator and a confounder (or proxy thereof) of the exposure-outcome relation, then adjustment by employment duration (as done here) may result in a biased estimate of the dose-response.^{2,24,25} Therefore, more sophisticated methods (eg, g-estimation) may be required. Methods based on directed acyclic graph-derived regression structures and g-estimation of failure time attempt to address these issues but face similar unknowns, and have difficulties accommodating continuous time-dependent exposures.^{2,6} A parallel treatment of the EtO data by such methods would be informative.

	Cumulative EtO (lag = 10 y)	β	SE $_{\beta}$	95% CI ^a	Δ -2lnL ² (df) ^b	P ^b
With lag=10 y						
1	Model: deaths = $\exp(a_0 + a_1 \times \text{rac}0) \times (1 + c_3 \times \text{Sceto} + c_4 \times \text{RSceto}) \times n_{\text{expected}}$					
	intercept	-.0630			0.97 (2)	0.61
	Cum EtO White women	.0025	0.0032	-0.0037, 0.0087		
	Cum EtO iBlack women ^c	-.0035	0.0110	-0.025, 0.018		
2	Model: deaths = $\exp(a_0 + a_1 \times \text{rac}0) \times (1 + c_3 \times \text{Sceto}) \times n_{\text{expected}}$					
	intercept	-.0616			0.93 (1)	.33
	Cum EtO All women	.0024	0.0031	-0.0036, 0.0084		
3	Model: deaths = $\exp(a_0 + a_1 \times \text{rac}0 + b_1 \times \text{dur}) \times (1 + c_3 \times \text{Sceto}) \times n_{\text{expected}}$					
	intercept	.0239			1.47 (1)	.23
	Duration	-.0105	0.0135	-0.037, 0.016		
	Cum EtO All women	.0030	0.0030	-0.0028, 0.0087		
4	Model: deaths = $\exp(a_0 + a_1 \times \text{rac}0) \times (\exp(b_1 \times \text{dur}) + c_3 \times \text{Sceto}) \times n_{\text{expected}}$					
	intercept	.0212			1.55 (1)	.21
	Duration	-.0107	0.0128	-0.036, 0.014		
	Cum EtO All women	.0039	0.0043	-0.0045, 0.012		
With lag=20 y						
5	Model: deaths = $\exp(a_0 + a_1 \times \text{rac}0) \times (1 + c_3 \times \text{Sceto} + c_4 \times \text{RSceto}) \times n_{\text{expected}}$					
	intercept	-.1067			4.17 (2)	.12
	Cum EtO White women	.0099	0.0062	-0.0022, 0.022		
	Cum EtO iBlack women	-.0101	0.0234	-0.056, 0.036		
6	Model: deaths = $\exp(a_0 + a_1 \times \text{rac}0) \times (1 + c_3 \times \text{Sceto}) \times n_{\text{expected}}$					
	intercept	-.1031			4.06 (1)	0.04
	Cum EtO All women	.0094	0.0059	-0.0022, 0.021		
7	Model: deaths = $\exp(a_0 + a_1 \times \text{rac}0 + b_1 \times \text{dur}) \times (1 + c_3 \times \text{Sceto}) \times n_{\text{expected}}$					
	intercept	.0311			6.04 (1)	0.014
	Duration	-.0181	0.0125	-0.043, 0.0063		
	Cum EtO All women	.0166	0.0096	-0.0023, 0.035		
8	Model: deaths = $\exp(a_0 + a_1 \times \text{rac}0) \times (\exp(b_1 \times \text{dur}) + c_3 \times \text{Sceto}) \times n_{\text{expected}}$					
	intercept	.0242			5.29 (1)	0.02
	Duration	-.0151	0.0137	-0.042, 0.012		
	Cum EtO All women	.0097	0.0053	-0.0006, 0.020		

Note: n_{expected} , number of deaths expected based on U.S. rates; rac0, race coded as 0 = white, 1 = nonwhite; sex0, sex coded as 0 = men, 1 = women; duration-time-dependent employment duration, yrs; cumEtO, cumulative EtO exposure, lagged 10 y, as ppm-yrs EtO; Sceto, cumEtO \times sex0; RSceto, Sceto \times rac0.

^aCL - Wald confidence limits.

^bChange in 2lnL with addition of cumulative EtO terms and associated p.

^ciBlack women... - incremental increase in log(SMR) for black women vs white women.

TABLE 5 Standardized mortality ratio for female breast cancer (by Poisson regression) on sex, race, employment duration, and cumulative EtO (breast cancer deaths: 102)

5 | CONCLUSIONS

Many occupational exposures may play a role in the termination of employment because of irritant or other adverse health effects whether or not manifest as symptoms and whether or not perceived as work-related. In the case of EtO, the threshold for odor is quite high (about 250 ppm), and acute symptoms occur above 200 ppm, exposures far higher than in most of the jobs in this study (Table 1). Besides EtO, examples might include toluene di-isocyanate and other isocyanates

(sensitizers), formaldehyde, glutaraldehyde, and other aldehydes, diacetyl, and other α -diketones, acrylamide, silica, irritant metal compounds, for example, hexavalent chromium, titanium dioxide, and innumerable other agents with irritancy potential. If the population affected and leaving employment or avoiding exposure differs from those remaining on unmeasured risk factors or modifiers of determinants for the end-point understudy, important bias could result. Thus survivors in exposure might have lower inherent susceptibility and should be compared to similar populations without exposure. If smokers are differ-

TABLE 6 Standardized mortality ratio for all lymphopietic cancer (by Poisson regression) on sex, race, employment duration, and cumulative EtO (cancer deaths: 73)

	Cumulative EtO (lag = 10 y)	β	SE $_{\beta}$	95% CL ^a	Δ -2lnL ^b /X ² (1 df)	P ^b
1	Model: deaths = exp(a ₀ + a ₂ × sex0) × (1 + c ₂ *Rceto) × n _{expected}					
	intercept	-.113	0.1831	-0.47, 0.25	6.53	.011
	Cum EtO all Black workers	.0129	0.0079	-0.003, 0.028		
2	Model: deaths = exp(a ₀ + a ₂ × sex0 + b ₁ × dur) × (1 + c ₂ *Rceto) × n _{expected}					
	intercept	-.0007	0.2160	-0.42, 0.42	7.27	.007
	Duration	-.0116	0.0125	-0.036, 0.013		
	Cum EtO all Black workers	.0153	0.0093	-0.003, 0.034		
3	Model: deaths = exp(a ₀ + a ₂ × sex0) × (exp(b ₁ × dur) + c ₂ *Rceto) × n _{expected}					
	intercept	-.0063	0.2203	-0.44, 0.43	7.06	.008
	Duration	-.0105	0.0131	-0.036, 0.015		
	Cum EtO all Black workers	.0118	0.0071	-0.002, 0.026		

Note: n_{expected}, number of deaths expected based on U.S. rates; rac0, race coded as 0 = white, 1 = nonwhite; sex0, sex coded as 0 = men; 1 = women; duration, time-dependent employment duration, yrs; cumEtO, cumulative EtO exposure, lagged 2.5 y, as ppm-yrs EtO; Rceto, cumEtO×rac0.
^aCL, Wald confidence limits.

^bChange in 2lnL with addition of cumulative EtO terms.

entially affected (more likely or less likely to leave) that could have a large impact of estimates of exposure effects for any smoking-related disease. If the rate of smokers leaving employment is enhanced by exposure, then even stronger bias would result. As suggested here for NMRD, the magnitude of survivor bias can be very large, potentially obscuring important exposure risks.

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CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

DISCLOSURE BY AJIM EDITOR OF RECORD

John D. Meyer declares that he has no conflict of interest in the review and publication decision regarding this article.

ETHICS APPROVAL AND INFORMED CONSENT

This work utilized deidentified data that had been previously collected, analyzed, and published under CDC/NIOSH policies for protection of human subjects.

DISCLAIMER

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the National Institute for Occupational Safety and Health.

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APPENDIX A

Example of SAS *proc countreg* model specification for employment termination rate model

Model: $\text{expectation}(\text{quits}) = p\text{-yrs} \times \exp(a + b_i \times (\text{indicators of age strata } i) + c \times \text{sex} + d \times \text{race} + e \times \text{sex} \times \text{race} + f \times \text{duration} + g \times (\text{unlagged cumulative EtO exposure}) + \dots$

[This model does not allow duration effect to depend on race or sex.]

```
proc countreg data=etoaf32_f2; class IA;
```

```
model cNQ= IA SEX RAC RS aCNLDUR aCNLETO Rceto Sceto RSceto/offset=lnPY;
```

```
run;
```

where: cNQ: no. of quits in classification cell (usually 0); IA: age strata 1 to 9; SEX: 0=men 1=women; RAC: 0=white, 1=nonwhite; RS=SEX*RAC; aCNLDUR = duration of employment; aCNLETO = unlagged cumulative EtO exposure; Rceto = aCNLETO×RAC; Sceto = aCNLETO×SEX; RSceto = aCNLETO×RS; lnPY = log(person-years) (durations and cumulative exposures as p-yr-weighted cell means)

Parameter	DF	Parameter estimates		t Value	Approx Pr > t
		Estimate	SE		
Intercept	1	-1.482120	0.071386	-20.76	<.0001
IA 1	1	0.026156	0.072656	0.36	0.7188
IA 2	1	-0.077633	0.072023	-1.08	0.2811
IA 3	1	-0.337052	0.073389	-4.59	<.0001
IA 4	1	-0.475046	0.074432	-6.38	<.0001
IA 5	1	-0.474857	0.075147	-6.32	<.0001
IA 6	1	-0.386475	0.075789	-5.10	<.0001
IA 7	1	-0.313229	0.078456	-3.99	<.0001
IA 8	1	-0.252783	0.083565	-3.03	0.0025
IA 9	0	0	.	.	.
sex	1	0.044432	0.020833	2.13	0.0329
rac	1	-0.057120	0.034405	-1.66	0.0969
RS	1	-0.133694	0.049346	-2.71	0.0067
aCNLDUR	1	-0.095984	0.002352	-40.81	<.0001
aCNLETO	1	0.001659	0.000190	8.75	<.0001
Rceto	1	-0.000028954	0.000388	-0.07	0.9404
Sceto	1	0.000611	0.000374	1.63	0.1022
RSceto	1	-0.003591	0.001511	-2.38	0.0174

Example SAS *proc nlin* model specification for employment termination rate model

Model specific for each demographic group (sex, race):

$$\text{expectation}(\text{quits}) = p\text{-yrs} \times \exp(a + b \times (\text{age}-40) + c \times (\text{age}-40)^2 + d \times \text{duration} + e \times (\text{unlagged cumulative EtO exposure}))$$

[These models allow duration effect to depend on race or sex.]

```
proc nlin data=eto.etoaf32_f1 nohalve method=gauss eformat sigsq=1;
  where rac=1 and sex=1;

  parameters a0=0.25 a1=0 a2=0 b3=0 b4=0;
  age40=5*(IA-5.5); * IA = 6 ~ age 40-44;

  model.cNQ = exp(a0 + a1*age40 + a2*age40**2 + b3*aCNLDUR
    +b4*aCNLETO) * nPY;

  _weight_ = 1/model.cNQ;
  dev = Deviance('Poisson', cNQ, Model.cNQ);
  _loss_ = dev/_weight_;

  * output out=fitdata (label = 'Dataset containing additional results of
  the Poisson regression')

  Residual=Res Predicted=Predict_cNQ;

run;
```

where: cNQ: no. of quits in classification cell (usually 0);
 age40 = age-40; strata 1 to 9; aCNLDUR = duration of employ-
 ment; aCNLETO = unlagged cumulative EtO exposure; nPY =
 person-years

(durations and cumulative exposures as p-yr-weighted cell means)

Parameter	Estimate	Approx. SE	Approximate 95% Confidence Limits	
a0	-1.9848	0.0544	-2.0915	-1.8782
a1	0.0155	0.00502	0.00562	0.0253
a2	0.00172	0.000265	0.00120	0.00224
b3	-0.1290	0.00974	-0.1481	-0.1099
b4	0.00274	0.00180	-0.00080	0.00627

Example SAS *proc nlin* model specification for mortality outcome (lymphopoietic cancer death) with linear relative rate model for exposure to Eto in nonwhite workers

$$\text{Model: expectation(LP deaths)} = \text{expected no.} \times \exp(a + b \times \text{sex}) \times (c \times \text{duration} + d \times \text{race}) \times (\text{lagged cumulative EtO exposure})$$

```
proc nlin data=EtoAF45_fLPallR nohalve method=gauss eformat sigsq=1;

  parameters a0 = 0.104 a2 = 0.01 a3 = -0.01 c2 = 0;

  termA=exp(a0 + a2*sex0);

  model.cD = termA * (exp(a3*aDure) + c2*Rceto) * expt;

  _weight_ = 1/model.cD;

  dev = Deviance('Poisson', cD, Model.cD);

  _loss_ = dev/_weight_;

  * output out=fitdata (label = 'Dataset containing additional results of
  the Poisson regression');

run;
```

where: cD = number of observed deaths from lymphopoietic cancer in each classification cell;

sex0 = sex(0 = men, 1 = women); race: 0 = white, 1 = nonwhite; aDure = duration of employment;

Rceto = lagged cumulative EtO exposure in nonwhite workers; expt = expected number of deaths in each classification cell (based on national rates)

Parameter	Estimate	Approx. SE	Approximate 95% Confidence Limits	
a0	-0.00630	0.2203	-0.4381	0.4255
a2	-0.0153	0.2414	-0.4885	0.4579
a3	-0.0105	0.0131	-0.0361	0.0151
c2	0.0118	0.00709	-0.00207	0.0257

Rationale for model specifications regarding HWSE

Scenario 1

This specification assumes a population surviving in employment to dur has diminishing average susceptibility to Eto effect compared to population at dur=0 (could be due, eg, to depletion of high risk individuals).

$$\text{pred deaths} = \exp(a_0 + a_1 \times \text{rac0} + a_2 \times \text{sex0} + a_3 \times \text{rac0} \times \text{sex0} + b_1 \times \text{dur}) \times (1 + c_1 \times \text{cumEto}) \times n_{\text{expected}}$$

where $b_1 < 0$, i.e. a declining background risk

Dividing by p-yrs:

$$\text{pred rate} = \exp(a_0 + a_1 \times \text{rac0} + a_2 \times \text{sex0} + a_3 \times \text{rac0} \times \text{sex0} + b_1 \times \text{dur}) \times (1 + c_1 \times \text{cumEto}) \times \text{expected rate}$$

Dividing by expected rate:

$$\text{pred rate ratio} = \exp(a_0 + a_1 \times \text{rac0} + a_2 \times \text{sex0} + a_3 \times \text{rac0} \times \text{sex0} + b_1 \times \text{dur}) \times (1 + c_1 \times \text{cumEto})$$

$$\text{excess rate ratio} = \text{ERR} = \exp(a_0 + a_1 \times \text{rac0} + a_2 \times \text{sex0} + a_3 \times \text{rac0} \times \text{sex0} + b_1 \times \text{dur}) \times c_1 \times \text{cumEto}$$

Scenario 2

This specification assumes a population surviving to dur has no diminishing susceptibility to Eto effect but that other causes of the outcome are diminishing resulting in a smaller contribution of non-attributable cases (by a factor $\exp(b_1 \times \text{dur})$ where $b_1 < 0$). This could happen if smokers are leaving employment faster and the outcome is smoking-related.

$$\text{pred deaths} = \exp(a_0 + a_1 \times \text{rac0} + a_2 \times \text{sex0} + a_3 \times \text{rac0} \times \text{sex0}) \times (\exp(b_1 \times \text{dur}) + c_1 \times \text{cumEto}) \times n_{\text{expected}}$$

Dividing by p-yrs:

$$\text{pred rate} = \exp(a_0 + a_1 \times \text{rac0} + a_2 \times \text{sex0} + a_3 \times \text{rac0} \times \text{sex0}) \times (\exp(b_1 \times \text{dur}) + c_1 \times \text{cumEto}) \times \text{expected rate}$$

Dividing by expected rate:

$$\text{pred rate ratio} = \exp(a_0 + a_1 \times \text{rac0} + a_2 \times \text{sex0} + a_3 \times \text{rac0} \times \text{sex0}) \times (\exp(b_1 \times \text{dur}) + c_1 \times \text{cumEto})$$

$$\text{excess rate ratio} = \text{ERR} = \exp(a_0 + a_1 \times \text{rac0} + a_2 \times \text{sex0} + a_3 \times \text{rac0} \times \text{sex0}) \times c_1 \times \text{cumEto}$$

A typical study where HWSE is present may not be able to statistically distinguish these two options.