ORIGINAL ARTICLE

Mortality analyses in a cohort of 18 235 ethylene oxide exposed workers: follow up extended from 1987 to 1998

K Steenland, L Stayner, J Deddens

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See end of article for authors' affiliations

Correspondence to: Dr N K Steenland, Rollins School of Public Health, Emory University, 1518 Clifton Road, Atlanta, GA 30322, USA; nsteenl@sph.emory.edu

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Aims: To extend mortality follow up from 1987 to 1998 for cohort of 18 235 men and women exposed to ethylene oxide.
Methods: Standard mortality follow up, life table and Cox regression analysis.
Results: There were 2852 deaths, compared with 1177 in the earlier 1987 follow up. There was no overall excess of haematopoietic cancers combined or of non-Hodgkin's lymphoma. However, internal exposure-response analyses found positive trends for haematopoietic cancers which were limited to males (15 year lag). The trend in haematopoietic cancer was driven by lymphoid tumours (non-Hodgkin's lymphoma, myeloma, lymphocytic leukaemia), which also have a positive trend with cumulative exposure for males with a 15 year lag. Haematopoietic cancer trends were somewhat weaker in this analysis than trends in the earlier follow up, and analyses restricted to the post-1987 data did not show any significant positive trends (exposure levels dropped sharply in the early 1980s). Breast cancer did not show any overall excess, although there was an excess in the highest cumulative exposure quartile using a 20 year lag. Internal exposure-response analyses found positive trend for breast cancer using the log of cumulative exposure with a 20 year lag.
Conclusions: There was little evidence of any excess cancer mortality for the cohort as a whole, with the exception of bone cancer based on small numbers. Positive exposure-response trends for lymphoid tumours were found for males only. Reasons for the sex specificity of this effect are not known. There was also some evidence of a positive exposure-response for breast cancer mortality.

Ethylene oxide (ETO) is widely used as a sterilant gas and an industrial chemical. NIOSH has estimated that approximately 270 000 people were exposed in the USA in the 1980s, principally in hospitals (96 000) and commercial sterilisation (21 000).[1] ETO is a direct alkylating agent which causes increased chromosomal aberrations and sister chromatid exchange.[2] Inhaled ETO is quickly absorbed in the lungs and distributed rapidly throughout all tissues; it forms dose related haemoglobin adducts in people and rodents, and dose related DNA adducts have been measured in rodents.[2] The International Agency for Research on Cancer (IARC) determined in 1994 that ETO was a definite (group 1) human carcinogen, based on limited evidence from epidemiological studies showing increased haematopoietic cancers which was supported by positive human cytogenetic evidence, and on sufficient evidence from animal studies for haematopoietic and other cancers.[2]

Ethylene oxide has been studied in 10 cohort studies with over 33 000 workers. The largest component is the cohort studied here (18 000). Results of these studies as of 1998 were reviewed by Teta and colleagues.[3] Generally cancer findings were unremarkable in comparisons of exposed workers to the general population for most of these studies, with the notable exception of large excesses of haematopoietic cancer (particularly leukaemia) in several early small studies from Sweden. However, a meta-analysis of all 10 studies did show an increase in non-Hodgkin's lymphoma (1.34, 95% CI 0.96 to 1.89), based on 33 deaths.

Besides haematopoietic cancer, more recently there has been concern that ETO might also be linked to breast cancer, based on limited evidence. Norman and colleagues[4] found a statistically significant twofold increase in breast cancer incidence based on 12 observed cases among women exposed at a plant doing commercial sterilisation of medical products. A cluster of breast cancers was observed among Hungarian hospital workers exposed to ETO.[5] Furthermore, animal data indicated that ETO caused mammary tumours in mice,[2] although not in rats. However, two other small incidence studies (together based on fewer than 10 cases) did not show an excess of breast cancer.[6 7] Two mortality studies, one small[8] (four breast cancer deaths) and one large[9] (the present cohort, 42 breast cancer deaths as of 1987) also failed to show an excess.

In the mid 1980s the National Institute for Occupational Safety and Health (NIOSH) assembled a cohort of 18 235 workers exposed to ethylene oxide.[9 10] Results of the original follow up through 1987 showed no overall excess of haematopoietic cancer, but did find a significant excess among men (SMR 1.55, 1.02–2.26), concentrated in non-Hodgkin's lymphoma (NHL).[9] Exposure-response analyses showed a significant positive trend with cumulative exposure for lymphoid cancers (non-Hodgkin's lymphoma and lymphocytic leukaemia, ICD 9th revision codes, 200, 202, 204), particularly among men.

We have updated the vital status of this cohort from 1987 to 1998. This resulted in 2852 deaths, a 140% increase over the 1177 deaths in the earlier follow up. Analyses focused on haematopoietic and breast cancer mortality. A study of breast cancer incidence is the subject of a different paper.[11]

METHODS

Vital status follow up was conducted through 1998 via the National Death Index (NDI), which provided cause of death, and via the Social Security Administration and the Internal Revenue Service (IRS). Person-time for each subject began

Abbreviations: ETO, ethylene oxide; NHL, non-Hodgkin's lymphoma; SMR, standardised mortality ratio

Main messages

- There was little evidence of cancer excesses for the ethylene oxide exposed workers versus the general population in this 11 year update of the largest existing cohort of ETO workers.
- However, positive exposure-response trends were found for males for lymphoid cancer mortality, and for females for breast cancer mortality.
- Male and female workers of each sex with the highest cumulative exposures and longest latency had statistically significant excesses for these two cancers, respectively.
- There is priori evidence from other studies, both animal and human, associating these cancers with ETO.

90 days after first exposure (due to a three month minimum for cohort eligibility), and continued until 31 December 1998, date of death, or date of loss to follow up, whichever was earlier. Life table analyses were conducted using the NIOSH life table program (Steenland *et al*, 1998), which allows for calculations of standardised mortality ratios (SMRs) for 99 causes of death for the years 1960–99. Deaths and person-time prior to 1960 were not included in this analysis, but there were only eight deaths before 1960 (0.2% of all deaths).

Exposure data over time for this cohort had been developed previously, based on a large number of measurements coupled with data of historical process changes, making it possible to quantitatively estimate cumulative exposure to ethylene oxide.[12] One small plant in the study (n = 705, 4% of the cohort) lacked exposure estimates, and was excluded from exposure-response analyses. Exposure levels generally diminished sharply in the early 1980s after the reports of a haematopoietic cancer effect in animals and humans.

Work history data had been gathered originally in the mid-1980s. Some plants in the study continued using ETO after this point. For those plants, we gathered additional information on the date last employed for those who had been employed and exposed at the time work history was collected (25% of the cohort). Work history for these individuals was extended until the date last employed at the plant; it was assumed that they did not change jobs and that the level of ETO exposure remained the same as in their last job in the mid-1980s. This represented a compromise between an expensive and time consuming effort to update all work histories in detail, and ignoring the incomplete histories altogether. In practice when we compared cumulative exposure calculated with and without the extended work histories, they differed little, largely because exposures were very low by the mid-1980s, so that the largest proportion of cumulative exposure came before those years.

Life table analyses were conducted for the entire cohort (n = 18 235), using the US population as the referent population.[13] Categorical analyses were done after categorising the data by quartiles of cumulative exposure, based on distribution of cumulative exposure for either the deaths from either haematopoietic cancer or from breast cancer. The goal was to have approximately equal numbers of deaths from the principal causes of interest (haematopoietic and breast cancer) in each quartile, in unlagged analyses, thereby ensuring approximately equal precision of rate ratios. Life table analyses were conducted using no lag, a 10 year lag for haematopoietic cancer, or a 20 year lag for breast cancer, prostate cancer, and kidney cancer. A 20 year lag discounts all exposure occurring with the last 20 years, and in some instances results in a case having no exposure (''lagged out''). These lags were chosen a priori as typical for haematopoietic tumours and solid tumours. Prostate and kidney cancer analyses were conducted based on finding slight excesses in the overall exposed versus non-exposed analysis, rather than an a priori hypothesis; the same cut points were used in categorical analyses of cumulative exposure as were used for breast cancer, another solid tumour.

Internal exposure-response analyses were conducted using Cox regression for haematopoietic and breast cancer. Cox regression analyses were done using the SAS PHREG procedure.[14] In these analyses the time variable was age (effectively matching on age), and risk sets were constructed in which 100 randomly selected controls were chosen for each case from the pool of all those who survived without haematopoietic or breast cancer to at least the age of the index case. Use of 100 controls has been shown to result in virtually the identical rate ratio with all possible controls (the full risk set), with approximately the same precision,[15] while making possible more rapid computer runs. We refer to the measures of effect from the nested case-control approach (equivalent to a conditional logistic regression analysis) as odds ratios, which estimate that hazard or rate ratio expected from a full Cox regression. Cases and controls were matched on race (white/non-white), sex, and date of birth (within five years), and only exposure variables were included in models. Matching on date of birth, in combination with the use of age as the time variable to form risk set, was equivalent to matching on calendar time. Exposure in these analyses was time dependent, and was truncated if it extended beyond the age of the case failure. Internal analyses focused on cancers of a priori interest—that is, all haematopoietic cancers and breast cancer. We also analysed lymphoid cell line tumours as a group, under the hypothesis that these tumours might share a common aetiology. In previous analyses[10] we had included as lymphoid tumours both non-Hodgkin's lymphoma and lymphocytic leukaemia (9th revision ICD codes 200, 202, and 204), and we again have provided some results for that original grouping. However, we have now also conducted analyses after adding myeloma (ICD code 203) to the lymphoid group, based on current thinking on this issue[16 17] (personal communication, Bernard Goldstein, University of Pittsburgh, 2002). Another complication was that 4/25 (16%) leukaemias in the exposure-response analyses were classified as ''not specified'', some of which might have been lymphocytic leukaemia. Finally, a separate analysis was also done of Hodgkin's disease (ICD 201), although numbers for this cause were quite small.

Exposure-response analyses focused on cumulative exposure or the log of cumulative exposure, with or without a lag for exposure (5, 10, 15, and 20 year lags were tried). A lag period is a period before death or end of follow up during which any exposure is ignored; its use is similar to requiring a latency period. We added 1 ppm-day to cumulative exposure in lagged analyses to avoid taking the log of 0. In the results we present only the lagged model with the best fit to the data, as judged by the likelihood ratio test. We also tried models using peak exposure, average exposure, and duration of exposure, with no lag or different lags. Test of significance for the coefficients of continuous exposure variables (tests for trend) were based on the likelihood ratio statistic rather than the Wald statistic.

RESULTS

Cumulative exposure averaged 26.9 ppm-years in this cohort (SD 65.7), with a highly skewed distribution (median 5.6 ppm-years). Exposure for males (mean 37.8, SD 87.6, median 7.6) was higher than for females (mean 18.2, SD 38.2, median 4.6), largely because of their more frequent

Table 1 Mortality in the ETO cohort (n = 18 235*)

Cause (ICD-9 code)	Observed deaths	SMR (95% CI)	Male SMR (95% CI)	Female SMR (95% CI)
All causes	2852	0.90 (0.88–0.93)	0.94 (0.89–0.99)	0.86 (0.81–0.91)
Coronary heart disease (410–414)	669	0.92 (0.86–0.98)	1.04 (0.85–1.04)	0.87 (0.78–0.99)
All cancers (140–208)	860	0.98 (0.92–1.03)	0.94 (0.95–1.16)	0.92 (0.84–1.01)
Stomach (151)	25	1.07 (0.74–1.49)	0.87 (0.44–1.52)	1.34 (0.71–2.29)
Pancreas (157)	38	0.92 (0.69–1.21)	1.03 (0.64–1.61)	0.82 (0.45–1.30)
Lung (162)	258	1.05 (0.95–1.17)	1.05 (0.89–1.23)	1.05 (0.86–1.27)
Prostate (185)	37	1.29 (0.91–1.78)	1.29 (0.91–1.78)	n.a.
Kidney (189.0–189.2)	21	1.19 (0.80–1.72)	1.51 (0.85–2.49)	0.78 (0.281.28)
Brain (191–192)	14	0.59 (0.36–0.91)	0.52 (0.19–1.13)	0.65 (0.25–7.37)
Bone (170)	6	2.82 (1.23–5.56)	3.51 (0.96–8.98)	2.04 (0.25–7.37)
Breast cancer (174)	103	0.99 (0.84–1.17)	2.04 (0.05–11.37)	0.99 (0.81–1.20)
All haematopoietic (200–208)	79	1.00 (0.79–1.24)	1.09 (0.79–1.47)	0.91 (0.84–1.25)
Non-Hodgkin's lymphoma (200, 202)	31	1.00 (0.72–1.35)	1.29 (0.78–2.01)	0.73 (0.38–1.29)
Hodgkin's disease (201)	6	1.24 (0.53–2.43)	1.83 (0.59–4.27)	0.47 (0.05–11.87)
Myeloma (203)	13	0.92 (0.54–0.87)	0.61 (0.17–1.56)	1.19 (0.54–2.26)
Leukaemia (204–208)	29	0.99 (0.71–1.36)	0.97 (0.52–1.63)	1.02 (0.57–1.68)

*These analyses include the entire cohort. Subsequent exposure-response analyses are based on a reduced cohort in which one small plant (4% of cohort) without adequate exposure data was not included.

employment in high exposure jobs such as steriliser operator or warehouse employee. There were 461 000 person years of follow up; mean follow up time from first employment was 26.8 years (SD 8.5). Sixteen per cent of the cohort died during follow up, which ended on 31 December 1998. Of the decedents, 1.5% (n = 44) were missing cause of death.

Table 1 gives the overall mortality results for the entire cohort, compared to the US population. No cancer site showed a significant excess at the 0.05 level, with the exception of bone cancer, for which there were only six deaths. Neither all haematopoietic cancer nor non-Hodgkin's lymphoma show any increase. In sex specific analyses, the rate ratios for men for all haematopoietic cancer, leukaemia, and non-Hodgkin's lymphoma were 1.09 (0.79–1.47), 0.97 (0.53–1.63), and 1.29 (0.78–2.01) respectively, while the corresponding rate ratios for women were 0.90 (0.64–1.25), 1.02 (0.57–1.68), and 0.73 (0.38–1.28). Brain cancer mortality, which was of some a priori interest due to positive animal studies, was significantly reduced in this update, similar to findings in our prior follow up. Prostate and kidney cancer showed slight increases (SMR 1.29 (95% CI 0.96 to 1.70, 37 deaths) and 1.19 (95% CI 0.80 to 1.72, 21 deaths), respectively), motivating further life table exposure-response analyses.

Exposure-response analyses were of limited value for bone cancer due to the small number of deaths (n = 6). Life table analyses of bone cancer by quartiles of cumulative exposure (not shown) were not supportive of a positive exposure-response.

Table 2 shows the analyses by quartile of cumulative exposure for all haematopoietic cancer, with the quartiles chosen in order to approximately distribute the haematopoietic deaths equally by quartile. There is no suggestion of a trend for all haematopoietic cancers combined or any specific category, with the exception of Hodgkin's disease where inference is limited by the small number of deaths. Table 3 shows the same analyses with a 10 year lag. Here the highest quartile of cumulative exposure shows a somewhat increased rate ratio for non-Hodgkin's lymphoma, based on nine deaths.

Table 4 shows the data for haematopoietic cancer by sex, with a 10 year lag. The only statistically significant excess, at the 0.05 level, is the SMR for males for non-Hodgkin's lymphoma in the uppermost exposure quartile with a 10 year lag (SMR 2.37, 95% CI 1.02 to 4.67, eight deaths). Five of the six Hodgkin's disease deaths occurred among males, and this outcome again shows a positive exposure-response based on very small numbers. Complementary analyses by 10+ years latency gave similar results. For NHL, the SMRs by quartile were 0.34, 0.78, 1.16, and 2.15 based on 1, 2, 3, and 8 cases, respectively.

Table 5 shows the data for cumulative exposure and breast, prostate, and kidney cancer mortality. The quartiles for these analyses used the quartile cut points which allocated breast cancers equally by quartile. In this analysis there is an indication of excess risk for breast cancer in the uppermost quartile, which is 2.20 (95% CI 1.57 to 2.98) using a 20 year lag. There was little or no suggestion of positive exposure-response trends for prostate or kidney cancer.

Table 6 shows the results of internal Cox regression analyses for all haematopoietic cancers combined, for both sexes combined and for men and women separately. It indicates that only males show positive trends. The best fitting model shows a positive trend (p = 0.02) for males using the log of cumulative exposure with a 15 year lag. The log transformation tends to give less influence in the model to very high exposures typical of skewed exposure distributions, which may improve model fit. It also usually implies that rate ratios tend to flatten out or plateau at higher exposures, rather than increasing in a linear fashion, which is

Table 2 SMRs (observed deaths) by cumulative exposure for haematopoietic cancer (ICD 9th revision 200–208), no lag (n = 17 530)

Cause	0–1199 ppm-days	1200–3679 ppm-days	3680–13499 ppm-days	13500+ ppm-days
All haematopoietic	0.77 (18)	1.31 (20)	1.10 (18)	0.94 (18)
NHL	0.76 (7)	1.34 (8)	0.85 (6)	1.21 (9)
Hodgkin's	0 (0)	0.99 (1)	2.97 (3)	2.20 (2)
Leukaemia	1.15 (10)	1.06 (6)	0.93 (6)	0.43 (3)
Myeloma	0.26 (1)	1.89 (5)	0.92 (3)	1.03 (4)

Table 3 SMRs (observed deaths) by cumulative exposure for haematopoietic cancer, 10 year lag* (n = 17 530)

Cause	0 (lagged out)	>0–1199 ppm-days	1200–3679 ppm-days	3680–13499 ppm-days	13500+ ppm-days
All haematopoietic	0.72 (9)	0.88 (18)	1.16 (15)	1.08 (16)	1.04 (16)
NHL	1.31 (5)	0.71 (6)	1.13 (6)	0.66 (4)	1.47 (9)
Hodgkin's	0.41 (1)	0 (0)	1.75 (1)	3.57 (2)	3.77 (2)
Leukaemia	0.40 (2)	1.35 (10)	0.85 (4)	1.33 (7)	0.36 (2)
Myeloma	1.36 (1)	3.65 (2)	2.44 (4)	1.03 (3)	0.92 (3)

*A 10 year lag ignores any exposure which occurs in the ten years prior to death or end of follow up.

Table 4 SMRs (observed deaths) by cumulative exposure, for haematopoietic cancer mortality, by sex, 10 year lag

Cause	0 (lagged out)	>0–1199 ppm-days	1200–3679 ppm-days	3680–13499 ppm-days	13500+ ppm-days
Males (n = 7645)					
All haematopoietic	1.15 (7)	0.63 (5)	0.87 (5)	1.10 (7)	1.46 (13)
NHL	2.09 (4)	0.61 (2)	0.88 (2)	0.79 (2)	2.37* (8)
Hodgkin's	1.07 (1)	0 (0)	3.44 (1)	3.44 (1)	5.71 (2)
Leukaemia	0.41 (1)	1.01 (3)	0.0 (0	1.70 (4)	0.60 (2)
Myeloma	1.56 (1)	0 (0)	1.94 (2)	0 (0)	0.54 (1)
Females (n = 9885)					
All haematopoietic	0.31 (2)	1.04 13)	1.38 (10)	1.06 (9)	0.46 (3)
NHL	1.88 (1)	0.78 (4)	1.32 (4)	0.56 (2)	0.37 (1)
Hodgkin's	0 (0)	0 (0)	0 (0)	3.70 (1)	0 (0
Leukaemia	0.49 (1)	1.57 (7)	1.56 (4)	1.02 (3)	0 (0)
Myeloma	0 (0)	0.85 (2)	1.42 (2)	1.76 (3)	1.43 (2)

*95 % CI 1.02 to 4.67.

Table 5 SMRs (observed deaths) by cumulative exposure, for breast cancer, prostate cancer, and kidney cancer, no lag and 20 year lag

Cause	0 (lagged out)	>0–646 ppm-days	647–2779 ppm-days	2780–12321 ppm-days	12322+ ppm-days
Breast—no lag (females only)		1.00 (26)	0.85(24)	0.92 (26)	1.27 (26)
Prostate—no lag		1.74 (6)	1.47 (8)	0.77 (5)	1.33 (15)
Kidney—no lag		0.88 (3)	0.74 (3)	1.36 (6)	1.06 (5)
Breast—20 year lag (females only)	0.80 (42)	1.05 (17)	1.01 (15)	1.15 (15)	2.07* (13)
Prostate—20 year lag	1.08 (8)	1.43 (5)	1.44 (6)	1.75 (8)	1.00 (7)
Kidney—20 year lag	0.70 (2)	0.28 (1)	1.62 (6)	2.11 (8)	0.99 (5)

*95% CI 1.10 to 3.54.

apparent in our own data here for males. Categorical analyses by quartile for males indicated that all three upper quartiles were increased compared to the lowest category. Categorical analyses using cumulative exposure with a 15 year lag shows a more monotonically increasing trend.

Although not shown, models using duration of exposure, peak exposure, and average exposure did not predict haematopoietic cancer as well as models using cumulative exposure.

Table 7 shows result for lymphoid tumours. There is a positive trend for lymphoid tumours (non-Hodgkin's lymphoma, myeloma, and lymphocytic leukaemia) with cumulative exposure for both sexes combined ($p = 0.08$), which was again concentrated in for males ($p = 0.06$ for cumulative exposure and $p = 0.02$ for log cumulative exposure, 15 year lag, the latter being the best fitting model). Although not shown, models using duration of exposure, peak exposure, and average exposure did not predict haematopoietic cancer as well as models using cumulative exposure.

Additional analyses (not shown) were conducted using a more restricted definition of lymphoid tumours (non-Hodgkin's lymphoma and lymphocytic leukaemia, $n = 40$, 23 male and 17 female deaths) to conform to our earlier analysis of this cohort.[10] The coefficient for cumulative exposure with no lag was 5.6×10^{-6} (SE 2.3×10^{-6}, $p = 0.04$, based on change in likelihood), decreased from 9.0×10^{-6} in our earlier follow up which ended in 1987. ETO exposure levels dropped sharply in the 1980s following reports of leukaemia, and this may have contributed to decreased haematopoietic cancer after 1987.

Additional regression analyses, not shown, were restricted to the period following 1987, the end of the prior follow up. In these post-1987 analyses there were no significant positive trends for all haematopoietic cancer ($n = 41$), male haematopoietic cancer ($n = 13$), lymphoid cancers ($n = 31$), or male lymphoid cancers ($n = 10$). The analyses restricted to males did show a suggestion of increased haematopoietic cancer, but analyses were limited by small numbers. The coefficient for male haematopoietic cancer for log cumulative exposure with a 15 year lag was 0.11 (SE 0.12, $p = 0.35$), about the same value as that for the entire follow up period (table 7).

Additional analyses (not shown) were conducted for Hodgkin's disease, based on only six deaths. A positive trend ($p = 0.08$) was found for the log of cumulative exposure with a lag of 10 years, for both sexes combined. This excess also was concentrated in males (five of six deaths).

Table 8 gives the results for internal Cox regression analyses for breast cancer. The best model using a continuous exposure variable was that using the log of cumulative exposure with a 20 year lag ($p = 0.01$). Cumulative exposure itself did not show a strong trend ($p = 0.16$). Categorical analysis of lagged data (20 year lag) showed an increased rate in the highest quartile (3.13, 95% CI 1.42 to 6.92).

Table 6 Cox regression* results for all haematopoietic cancer mortality

Analysis, exposure variable	Model likelihood, df, p value†	Coefficient (SE)	Odds ratios by category‡
Both sexes, cumulative exposure	1.62, 1 df, p=0.20	0.0000033 (0.0000023)	
Males, cumulative exposure	2.45, 1 df, p=0.12	0.0000040 (0.0000022)	
Males, categorical cumulative exposure	2.53, 3 df, p=0.46	na	1.00, 2.07 (0.67–6.41), 2.02 (0.68–5.98), 2.06 (0.72–5.91)
Females, cumulative exposure	0.87, 1 df, p=0.34	−0.000011 (0.000014)	
Females, categorical cumulative exposure	3.78, 3 df, p=0.29	na	1.00, 1.51 (0.69–3.34), 0.93 (0.38–2.30), 0.52 (0.16–1.66)
Males, log cumulative exposure, 15 year lag	5.29, 1 df, p=0.02	0.119 (0.052)	
Males, categorical cumulative exposure, 15 year lag	6.81, df=4 p=0.15	na	1.00, 1.23 (0.32–4.73), 2.52 (0.69–9.22), 3.13 (0.95–10.37, 3.42 (1.09–10.73)

*Cases and controls matched on age, race (white/non-white), date of birth within five years, 74 cases (37 male, 37 female).
†Model likelihood is difference in −2 log likelihoods between model with and without covariates; the only covariate in these models was exposure, so the p value of the model serves as a test of significance of the exposure coefficient, and as a test of exposure-response trend.
‡Categories for cumulative exposure are the same as in tables 2–5.

Table 7 Cox regression results for lymphoid cell line tumours*

Analysis, exposure variable	Model likelihood, df, p value†	Coefficient (SE)	Odds ratios by category‡
Both sexes, cumulative exposure	3.16, 1 df, p=0.08	0.0000046 (0.0000022)	na
Males, cumulative exposure	3.62 1 df, p=0.06	0.0000050 (0.0000022)	na
Males, categorical cumulative exposure	2.43, 3 df, p=0.49	na	1.00, 2.45 (0.61–9.92, 1.85 (0.46–7.48), 2.44 (0.67–8.87)
Females, cumulative exposure	0.08, 1 df, p=0.78	−0.0000034 (0.000012)	na
Females, categorical, cumulative exposure	2.81, 3 df, p=0.42	na	1.00, 2.05 (0.76–5.56), 1.25 (0.40–3.76), 0.87 (0.24–3.10)
Males, log cumulative exposure, 15 year lag	5.39, 1df, p=0.02	0.138 (0.061)	na
Males, categorical cumulative exposure, 15 year lag	6.62, 4 df, p=0.13	na	1.00, 0.90 (0.16–5.24), 2.89 (0.65–12.86) 2.74 (0.65–11.55), 3.76 (1.03–13.64)

*Lymphoid cell line tumours include NHL, myeloma, and lymphocytic leukaemia (ICD 9th revision codes 200, 202, 203, 204 (53 cases, 27 male, 26 female). Cox regression, cases and controls matched on age, race (white/non-white), date of birth within five years.
†Model likelihood is difference in −2 log likelihoods between model with and without covariates; the only covariate in these models was exposure, so the p value of the model serves as a test of significance of the exposure coefficient, and as a test of exposure-response trend.
‡Categories for cumulative exposure are the same as in tables 2–5.

Table 8 Cox regression results for breast cancer mortality*

Analysis, exposure variable	Model likelihood, df, p value†	Coefficient (SE)	Odds ratios by category‡
Cumulative exposure	0.88, 1 df, p=0.34	0.0000049 (0.0000048)	na
Log cumulative exposure, 20 year lag	5.69, 1df, p=.01	0.084 (0.035)	na
Categorical cumulative exposure lagged 20 years (quartiles)	8.69, 4 df, p=0.07	na	1.00, 1.76 (0.91–3.43), 1.77 (0.88–3.56), 1.97 (0.94–4.06), 3.13 (1.42–6.92)

*There were 103 cases of breast cancer (ICD 9th 174, 175). In Cox regression, cases and controls were matched on age, race (white/non-white), and date of birth within five years.
†Model likelihood is difference in −2 log likelihoods between model with and without covariates; the only covariate in these models was exposure, so the p value of the model serves as a test of significance of the exposure coefficient, and as a test of exposure-response trend.
‡Categories for cumulative exposure are the same as in table 6.

DISCUSSION

We have now updated mortality follow up for the large NIOSH cohort of 18 000 workers exposed to ethylene oxide, adding 11 more years of follow up and more than doubling the number of deaths. There was no evidence of cancer excesses in exposed versus non-exposed comparisons, with the exception of bone cancer. The healthy worker effect has diminished (all cause mortality was up to an SMR of 0.90 from the prior SMR of 0.81), as would be expected with increased follow up. The healthy worker effect would seem an unlikely explanation for the lack of cancer excesses in the exposed versus non-exposed comparisons.

There was a significant excess of bone cancer compared to the US population, based on only six deaths, but this excess did not show an increase with increasing exposure. There is some supporting animal evidence in that mice injected subcutaneously developed local sarcomas,[2] which share the mesenchymal cell origin of bone tumours. However, due the small number of bone cancer deaths, and the lack of exposure-response, no conclusions can be drawn from this excess. No other cancer site was in excess in the cohort.

Regarding haematopoietic cancer, we did not find an overall excess of haematopoietic cancer or any specific type of haematopoietic cancer. However, we did find statistically

significant exposure-response trends for male haematopoietic cancer, particularly lymphoid tumours. These findings are consistent with analyses of this cohort with earlier follow up.[10] Exposure-response coefficients were somewhat smaller than we found in our earlier analyses (analyses restricted to recent years did not show significant positive exposure-response trends). This suggests that any ETO damage to the haematopoietic system may be decreasing over time.

It is not known why we find an association for males and not females for haematopoietic cancer. While males on average did have higher exposure than females because they were over-represented in high exposure jobs (for example, steriliser operator), there was sufficient variation in the exposure of women to have observed an exposure-response if one existed. Animal data do not support a sex-specific effect for leukaemia.

The increasing trends in rate ratios for haematopoietic or lymphoid cancer for males, and breast cancer for females, were fit best by a model using a log transformation of cumulative exposure rather than untransformed cumulative exposure. Use of the log gives less weight to extremely high exposures which often occur in log-normal distribution typical of occupational studies, and a log transformation tends to fit better when rate ratios tail off or plateau at very high exposures. This phenomenon has been seen in other occupational carcinogens such as dioxin,[18] silica,[19] and diesel fumes,[20] and has been discussed in detail in relation to arsenic.[21] Possible reasons for this phenomenon include, among others: (1) a depletion of susceptibles at high exposures, (2) the healthy worker survivor effect, (3) misclassification of high exposures, and (4) a saturation of metabolic pathways.

While we considered a large number of models in our exposure-response analyses, we believe that this type of extensive search for the best model is appropriate in this situation—that is, it is not an example of ''data dredging'' or the perils of multiple hypothesis testing. For example, we knew from previous experience that a latency period is likely to be required for cancer (hence the lagging), and that the log of cumulative exposure often fits better than cumulative exposure itself in occupational cancer studies. Hence we believe it was appropriate to search for the best fitting lag and to try the log of cumulative exposure.

We found no overall excess of breast cancer mortality, but we did find a suggestive positive trend with increasing cumulative exposure, particularly after taking into account a 20 year lag period. Mortality is a less sensitive endpoint than incidence for breast cancer. We have also recently completed a study of breast cancer incidence in this cohort, results of which confirm a positive trend of increased breast cancer with increased cumulative exposure.[11]

Our study had a number of limitations, including the reliance on small numbers to make inferences about haematopoietic cancers, uncertainties in the retrospective estimation of exposure, and the use of mortality data rather than incidence data for evaluation of cancer risk. On the other hand, this is by far the largest existing cohort of ETO workers, the 11 year update has added substantially more deaths, and retrospective exposure estimation for this study was based on a large number of observed industrial hygiene samples and a well validated model to estimate past exposures. Mortality data for haematopoietic cancer might be expected to give similar results to incidence data, as these cancers are often fatal.

In conclusion, we found no overall evidence of excess cancer mortality in this cohort, with the exception of bone cancer based on small numbers. However, in exposure-response analyses we found evidence of an association between increased exposure and some types of haematopoietic cancer, particularly for males. There is also some evidence for a positive exposure-response for breast cancer mortality.

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Authors' affiliations

K Steenland, Rollins School of Public Health, Emory University, Atlanta, Georgia, USA

L Stayner, J Deddens, National Institute for Occupational Safety and Health (NIOSH), Cincinnati, Ohio, USA

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