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Mortality Among Workers Exposed to Toluene Diisocyanate in the US Polyurethane Foam Industry: Update and Exposure-Response Analyses

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Abstract

Background—Mortality among 4,545 toluene diisocyante (TDI)-exposed workers was updated through 2011. The primary outcome of interest was lung cancer.

Methods—Life table analyses, including internal analyses by exposure duration and cumulative TDI exposure, were conducted.

Results—Compared with the US population, all cause and all cancer mortality was increased. Lung cancer mortality was increased but was not associated with exposure duration or cumulative TDI exposure. In post hoc analyses, lung cancer mortality was associated with employment duration in finishing jobs, but not in finishing jobs involving cutting polyurethane foam.

Conclusions—Dermal exposure, in contrast to inhalational exposure, to TDI is expected to be greater in finishing jobs and may play a role in the observed increase in lung cancer mortality. Limitations include the lack of smoking data, uncertainty in the exposure estimates, and exposure estimates that reflected inhalational exposure only.

Keywords

toluene diisocyanate; mortality; cancer; cohort studies; exposure-response

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AUTHORS' CONTRIBUTIONS

All authors meet the authorship criteria.

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The authors report no conflicts of interest.

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INTRODUCTION

Toluene diisocyanate (TDI) is used to make polyurethane foam, elastomers, coatings, adhesives, binders, and sealants. In 2012, the US demand for TDI was 478.3 million pounds [American Chemistry Council, 2013]. TDI is a well-known sensitizer and cause of occupational asthma. TDI may also be carcinogenic [IARC, 1999; NTP, 2014]. The International Agency for Research on Cancer classifies TDI as a possible human carcinogen based on sufficient evidence in experimental animals and inadequate evidence in humans [IARC, 1999]. Similarly, the US National Toxicology Program concluded that TDI is reasonably anticipated to be a human carcinogen based on experimental animals [NTP, 2014]. Tumors observed in experimental animal studies include hepatocellular adenomas, benign mammary gland fibroadenomas, pancreatic acinar cell adenomas, fibromas, fibrosarcomas, hemangiomas, and hemangiosarcomas [NTP, 2014].

Cancer mortality and/or incidence have been evaluated in three cohorts of TDI-exposed workers [Hagmar et al., 1993a,b; Sorahan and Pope, 1993; Schnorr et al., 1996; Sorahan and Nichols, 2002; Mikoczy et al., 2004]. Workers in two of the cohorts, the Swedish and UK cohorts, were exposed to TDI and/or methylene diphenyl diisocyanate (MDI) [Sorahan and Nichols, 2002; Mikoczy et al., 2004]. Workers in the third cohort, the US cohort, were exposed to TDI but had minimal potential for exposure to MDI [Schnorr et al., 1996]. There are few consistent findings in studies of these cohorts except for an increase in lung cancer among women, which was statistically significant in the most recent analyses of both the Swedish and UK cohorts [Schnorr et al., 1996; Sorahan and Nichols, 2002; Mikoczy et al., 2004]. The reason for the observed increase in lung cancer among women is unclear [Mikoczy et al., 2004]. There was no evidence of an association with TDI or MDI exposure in the Swedish or UK cohorts, but the power to detect an exposure-response relation in the Swedish cohort was low. Exposure was not estimated in the US cohort. Data on smoking were not available for any of these cohorts, but other data suggest that smoking is unlikely to fully explain excess lung cancer among women [Sorahan and Pope, 1993; Mikoczy et al., 2004].

We extended follow-up of the US cohort of TDI-exposed workers by 18 years to further evaluate the carcinogenicity of TDI and non-cancer mortality. In this update, we also estimated exposure to TDI and examined exposure-response relations. When mortality was previously assessed in this cohort, the cohort was relatively young, and 7% of the cohort was deceased [Schnorr et al., 1996].

MATERIALS AND METHODS

Cohort Description

The cohort included workers employed in four polyurethane foam plants for at least 3 months in an exposed department or job between the date polyurethane production began (between 1958 and 1965) and the date the plant closed (1982 for plant D) or the date of data collection (1984 for plants A, B, and C) [Schnorr et al., 1996]. Some employees who did not meet the cohort criteria were inadvertently included in the original study cohort of 4,611

workers. After these errors were corrected the cohort included 4,595 workers. One additional worker was excluded from the analysis because the date of death was before 1960 when the mortality rate files began; 49 were excluded because of unknown race.

Exposure Assessment

Three of the plants (plants A, B, and D) manufactured molded polyurethane foam car cushions [Schnorr et al., 1996]. Plant C, which comprised over half of the cohort, produced slab foam for the furniture and carpet industries.

During the original study, historical TDI air concentrations were obtained from company and state records; these data existed primarily for production (i.e., pouring line) and finishing workers. In addition, National Institute for Occupational Safety and Health (NIOSH) investigators conducted exposure surveys in 1984–1985 at each of the three plants that were still operating. Briefly, 189 personal breathing zone samples were collected for randomly selected workers among the various departments. TDI air concentrations varied between plants and between departments, but were, in general, higher for production workers than finishing workers [Boeniger, 1991a; Schnorr et al., 1996]. Additional details about these exposure data can be found elsewhere [Boeniger, 1991a; Schnorr et al., 1996]. MDI was used by a few workers to patch foam in plants A and B. A few quality control personnel in plant C were also potentially exposed to MDI.

NIOSH industrial hygienists developed an exposure matrix using available TDI air concentration data stratified by plant, era, department, and/or operation. Air concentrations at all four plants declined appreciably over time. For example, in plant A, average TDI concentrations declined from 360 $\mu g/m^3$ in 1968 to 15–20 $\mu g/m^3$ in 1985. Actual reductions in plant A may have been greater because the historical data reflect 2,4-TDI only whereas the 1985 NIOSH exposure survey data reflect both 2,4-TDI and 2,6-TDI [Schnorr et al., 1996]. The trend in exposures over time and information from the exposure surveys in 1984–1985 were used along with professional judgment to develop exposure estimates for the exposure matrix. Exposure estimates were operation-specific for plants B and D and department-specific for plant C. For these plants, unique operations or departments in work histories were collapsed into four to six broad categories (production, finishing, maintenance, quality control, unexposed, and/or unknown), depending on the plant. For plant A, past exposure data indicated that exposure levels were approximately the same throughout the plant, so everyone was considered exposed and exposure estimates were based on era only. Exposure duration was based on the duration of employment in jobs with exposure potential. Cumulative exposure to TDI (in $\mu g/m^3$-days) was estimated by combining the estimates in the exposure matrix with the work history data. Work history data for most workers allowed us to clearly link exposure estimates with individuals; however, in some instances, expert judgment was used in making those links. Some cohort members (n = 376) had at least one job for which we could not estimate exposure because operation (plants B and D) or department (plant C) was unknown, and so cumulative exposure to TDI was not estimated. For plants B, C, and D, work history records were also examined to identify workers who worked in finishing jobs and workers in finishing jobs who performed cutting, slitting, or grinding fabrication techniques. Employment duration in

these jobs was also calculated. We could not determine if one or more jobs were in finishing or not for 980 workers (including all workers at Plant A, for whom detailed work history records were not available), and duration was not calculated for these workers.

Follow-Up

Vital status was updated through December 31, 2011 using linkages to the Social Security Administration, Internal Revenue Service, and National Death Index (NDI). Causes of death for newly ascertained deaths were obtained from NDI Plus. Cohort members known to be alive in 1979 (when NDI began) or later with a social security number not known to be invalid and not identified as deceased were assumed to be alive as of December 31, 2011 because the sensitivity of the NDI is over 95% when social security numbers are available [Cowper et al., 2002].

Although vital status was updated for the workers in the cohort, the work histories were not. We assumed that exposure ceased in 1984 (i.e., when the work histories were obtained for the original study) for 530 workers employed in an exposed job when the work history data were obtained.

Analysis

The mortality experience of the cohort was analyzed with the NIOSH LTAS.NET, a modified person-time analysis program [Schubauer-Berigan et al., 2011]. In LTAS.NET, International Classification of Diseases codes for the underlying causes of death were mapped to 119 cause of death categories as described on the NIOSH website (http://www.cdc.gov/niosh/ltas/pdf/niosh-119-table-2007.pdf). For each cohort member, person-years-at-risk (PYAR) began on January 1, 1960 (when the rate files begin) or the completion of the 3-month eligibility period, whichever was later, and ended on the earliest of the date of death, the date last observed, or the study end date (December 31, 2011). PYAR were stratified into 5-year intervals by age and calendar time and then multiplied by the appropriate US general population gender, race, and cause-specific mortality rates to calculate the expected number of deaths for that stratum. The resulting expected numbers were summed across strata to obtain cause-specific and total expected number of deaths. The standardized mortality ratio (SMR) was calculated as the ratio of the observed to expected number of deaths. Ninety-five percent confidence intervals (CI) were computed for the SMRs assuming a Poisson distribution for observed deaths.

SMRs were stratified by duration of exposure and cumulative exposure to TDI for (i) specific outcomes of a priori interest with five or more observed deaths; (ii) cancer causes of death that were elevated (SMR > 1.10) with five or more observed deaths; and (iii) non-cancer causes of death that were significantly elevated. Standardized rate ratios (SRRs) for the subset of these outcomes with eight or more observed deaths among cohort members with cumulative TDI exposure estimates were calculated in LTAS.NET as the ratio of standardized rates for higher exposure categories compared to the lowest exposure category. When less than two deaths were observed in the lowest exposure category, the lowest two categories combined served as the referent group. Trend slopes were calculated for the standardized rates across exposure duration and cumulative TDI exposure categories. The

statistical significance of each trend was determined using a two-tailed Z-test with $\alpha = 0.05$ [Rothman, 1986]. Cut-points for both exposure duration and cumulative exposure were selected by dividing the subset of the cohort with cumulative TDI exposure estimates into four groups with an approximately equal number of observed deaths from all causes.

Sensitivity analyses were conducted to (i) generate SMRs based on state general population mortality rates (OH for plant A, PA for plant B, VA for plant C, and CA for plant D); (ii) generate SMRs based on US mortality rates and SRRs excluding short-term workers (i.e., workers employed for less than 1 year at the study plants in jobs with or without exposure to TDI); and (iii) assume workers who were employed in an exposed job when the records were obtained continued to work in an exposed job until age 65, the date last observed, or the date the plant closed, whichever came first. In the third sensitivity analysis, the same cut-points were used as in the main analysis. In analyses excluding short-term workers, cut-points were selected to obtain an approximately equal number of observed deaths from all causes in each quartile.

Exposure duration and cumulative TDI exposure were lagged 10 years in all exposure-response analyses. Analyses by exposure duration were restricted to cohort members with cumulative TDI exposure estimates for comparability with analyses by cumulative TDI exposure.

Finally, post hoc analyses were conducted to obtain SRRs for lung cancer by employment duration in finishing and by employment duration in finishing jobs involving cutting and similar tasks using a lag period of 10 years. Cut-points were selected to obtain four groups with an approximately equal number of lung cancer deaths in each group with an employment duration greater than zero.

Based on previous studies, the primary a priori outcome of interest was lung cancer among women. Mortality from other cancers, chronic obstructive pulmonary disease (COPD), and asthma were also of interest.

RESULTS

A total of 4,545 workers contributing 158,898 person-years were included in the analysis. Compared with the original study, the update included 810 more deaths and 68,505 more person-years. Characteristics of the analysis cohort are shown in Table I. At the study end date, 25% of the cohort was deceased. Causes of death were obtained for 1,114 (99%) of 1,126 cohort members known to have died.

The median employment and exposure durations before the work history records were obtained in 1984 were short (0.93 and 0.87 years, respectively) with 55% of the cohort exposed for less than 1 year. Employment and exposure durations may be underestimated for 530 (12%) of the 4,545 cohort members in the analysis because they were still employed at the study plants when the work history records were obtained. Cumulative TDI exposure may also be underestimated for 502 of these workers. Cumulative TDI exposure was not estimated for the other 28 workers because they were a subset of the 376 workers with at least one job for which TDI exposure could not be estimated. Among workers who only held

jobs that we could determine if were in finishing or not (n = 3,565), women were more likely to have worked in finishing than men (98.0% vs. 65.3%); they were also more likely to have held a finishing job involving cutting and similar tasks (60.7% vs. 27.3%) (data not shown).

Mortality in the Overall Cohort

The results of the analysis of underlying causes of death in the overall cohort and by sex, based on US general population mortality rates, are shown in Table II. Mortality from all causes (SMR 1.16; 95% CI 1.10–1.23) and all cancer (SMR 1.27; 95% CI 1.14–1.42) was significantly elevated. Among cancer causes of death, mortality from larynx (SMR 4.00; 95% CI 1.99–7.16; 11 deaths), lung (SMR 1.59; 95% CI 1.32–1.89; 124 deaths), and other and unspecified cancer (SMR 1.51; 95% CI 1.00–2.18; 28 deaths) was significantly increased. Of the 28 deaths from other and unspecified cancer, 24 were secondary or unspecified cancers. Non-statistically significant elevations in mortality were observed for several other cancers including Hodgkin disease (SMR 3.17; 95% CI 0.86–8.10; 4 deaths), non-Hodgkin lymphoma (NHL) (SMR 1.45; 95% CI 0.77–2.48; 13 deaths) and cancers of the intestine (SMR 1.36; 95% CI 0.90–1.98; 27 deaths), rectum (SMR 1.14; 95% CI 0.37–2.67; 5 deaths), peritoneum (SMR 2.36; 95% CI 0.29–8.53; 2 deaths), breast (SMR 1.12; 95% CI 0.71–1.68; 23 deaths), cervix (SMR 2.02; 95% CI 0.74–4.40; 6 deaths), uterus (SMR 1.54; 95% CI 0.42–3.95; 4 deaths), kidney (SMR 1.33; 95% CI 0.58–2.63; 8 deaths), brain (SMR 1.13; 95% CI 0.49–2.22; 8 deaths), and thyroid (SMR 1.76; 95% CI 0.04–9.82; 1 death); however, some of these findings are based on very few observed deaths.

Among nonmalignant causes of death, mortality from diabetes mellitus (SMR 1.40; 95% CI 1.00–1.90), COPD (SMR 1.93; 95% CI 1.47–2.49), and intentional self-harm (SMR 1.69; 95% CI 1.21–2.30) was significantly elevated. Only one death from asthma was observed (SMR 0.38; 95% CI 0.01–2.14).

Mortality by Sex

Mortality from all causes, all cancers, larynx cancer, lung cancer, and COPD was significantly elevated in both men and women. The SMRs for larynx cancer, lung cancer, and COPD were higher in women than men. Mortality from musculoskeletal and connective tissue diseases and other non-malignant digestive diseases was significantly elevated among women, but not men. The underlying cause of death for deaths in these two categories varied without a predominant underlying cause. Mortality from intentional self-harm was significantly elevated in men, but not women.

Mortality Based on State General Population Mortality Rates

Mortality results for the overall cohort based on state general population mortality rates are shown in Supplemental Table SI. Results for cancer causes of death were very similar to those based on US mortality rates, although the increased SMR for other and unspecified cancer based on state rates was slightly lower and not statistically significant. Results for non-cancer causes of death, in general, were also similar to those based on US mortality rates.

Mortality Excluding Short-Term Workers

When short-term workers were excluded, mortality from all causes (SMR 1.11; 95% CI 1.02–1.20), all cancers (SMR 1.34; 95% CI 1.16–1.54), larynx cancer (SMR 3.20; 95% CI 1.04–7.47; 5 deaths), lung cancer (SMR 1.78; 95% CI 1.41–2.21; 80 deaths), and COPD (SMR 1.62; 95% CI 1.09–2.32; 30 deaths) remained significantly elevated compared to the US general population (Supplemental Table SII). In addition, mortality from musculoskeletal and connective tissue diseases was significantly elevated (SMR 2.86; 95% CI 1.15–5.89; 7 deaths). SMRs for other and unspecified cancer, diabetes mellitus, and intentional self-harm remained elevated but were no longer statistically significant. SMRs for most cancers that were elevated but not statistically significant in the main analysis remained elevated.

Exposure-Response Analyses Among All Cohort Members With Cumulative TDI Estimates

SMRs and SRRs for selected outcomes stratified by 10-year lagged exposure duration and cumulative TDI exposure estimates are shown in Tables III and IV, respectively. Of the 4,545 workers in the analysis cohort, 4,169 (92%) were included in these analyses; TDI exposure could not be estimated for one or more jobs held by the other 376 workers.

We did not observe a monotonically increasing exposure-response relation of larynx cancer, lung cancer, or lung cancer in women with exposure duration or cumulative TDI exposure. For these outcomes, SMRs increased across the first three exposure duration categories and then decreased in the fourth category. There was not a clear trend between breast cancer mortality and exposure duration. However, SMRs and SRRs for breast cancer were highest in the top 2 exposure duration categories, and a statistically significant positive trend in breast cancer mortality with cumulative TDI exposure was observed. For brain cancer mortality, a significant positive trend was observed with exposure duration, but not with cumulative TDI exposure. However, the SMR and SRR were highest and statistically significant in the top cumulative TDI exposure category. These results were based on few brain cancer deaths, and the confidence intervals for the SRRs were very wide. SMRs for NHL were highest in the top two exposure duration categories, and the trend in NHL mortality with exposure duration approached statistical significance. NHL mortality was significantly associated with cumulative TDI exposure, but the increase in SRRs across exposure categories was small (SRR = 1.11 for the top exposure category). Mortality from intestinal cancer, diabetes mellitus, COPD, and intentional self-harm was highest in the lowest exposure duration category, and a significant negative trend in mortality from COPD with exposure duration was observed. Mortality from COPD and intentional self-harm was also highest in the lowest cumulative TDI exposure category, but a significant negative trend with cumulative TDI exposure was only observed for intentional self-harm. In contrast, a significant positive trend in intestinal cancer mortality with cumulative TDI exposure was observed.

The 10-year lagged exposure duration category remained unchanged for 4,035 (96.8%) of the 4,169 workers included in the exposure-response analyses when we assumed that workers who were employed in an exposed job when the records were obtained continued to work in an exposed job until age 65, the date last observed, or the date the plant closed,

whichever came first. No substantive changes in the results by exposure duration were observed under this assumption (data not shown).

Exposure-Response Analyses Excluding Short-Term Workers

The results of exposure-response analyses excluding short-term workers are shown in Supplemental Tables SIII and SIV. In contrast to the main analysis, we observed a significant, negative association between all cause mortality and exposure duration. SMRs for larynx cancer decreased with increasing cumulative TDI exposure category; SRRs for larynx cancer were not evaluated because of the small number of deaths from larynx cancer in these analyses. Mortality from lung cancer overall and lung cancer among women was not associated with exposure duration or cumulative TDI exposure. There was a negative trend in lung cancer mortality among men with both exposure duration and cumulative TDI exposure, although the trends were not statistically significant. In contrast to the main analysis, breast cancer was not associated with exposure duration or cumulative TDI exposure. Brain cancer mortality was highest in the highest cumulative TDI exposure categories, but SRRs were not evaluated because of the small number of brain cancer deaths in these analyses. Significant, positive associations of intestinal cancer mortality were observed with both exposure duration and cumulative TDI exposure. A positive trend in COPD mortality with cumulative TDI exposure was observed, but the trend was not statistically significant. A significant, negative trend in mortality from intentional self-harm was observed with cumulative TDI exposure, but not with exposure duration.

Post Hoc Analyses of Lung Cancer

A significant positive association was observed for lung cancer with employment duration in finishing jobs (Table V). In contrast, a significant negative association was observed for lung cancer with employment duration in finishing jobs involving cutting and similar tasks. Gender-specific analyses are not reported because almost all female lung cancer decedents worked in finishing jobs and few male lung cancer decedents ever worked in finishing jobs involving cutting and similar tasks.

DISCUSSION

Overall Mortality

All cause and all cancer mortality were significantly increased among TDI-exposed workers compared to the general population with or without inclusion of short-term workers; thus, there is little evidence of a strong healthy worker hire effect in this cohort. However, we observed a healthy worker survivor effect as evidenced by decreasing risk across exposure duration categories for some outcomes (e.g., COPD) and for all cause mortality when excluding short-term workers. All cause mortality was also elevated in the UK cohort [Sorahan and Nichols, 2002], but not the Swedish cohort [Mikoczy et al., 2004].

Cancers of the Larynx and Lung

Cancers of the larynx and lung were significantly elevated in this cohort compared to the general population. The overall SMR for other smoking-related cancers (buccal, pharyngeal, esophagus, colorectal [i.e., intestine and rectum], stomach, liver, pancreas, cervix, bladder,

and kidney [USDHHS, 2014]) was 1.06; non-significant increases in mortality were observed only for colorectal, cervical, and kidney cancers. This suggests there is relatively little bias in the SMRs for larynx and lung cancer in the overall cohort due to smoking. The excess in laryngeal cancer mortality compared with the general population was large and unlikely to be explained by smoking alone [Siemiatycki et al., 1988].

SMRs for larynx and lung cancer increased across the first three exposure duration categories, and then decreased in the top exposure duration category. Exposure-response relations that are attenuated or become negative at higher exposure have been observed in many occupational studies, and may be attributable to healthy worker survivorship or other factors [Stayner et al., 2003]; however, similar trends were not observed in the SRRs, in analyses excluding short-term workers, or in analyses of cumulative TDI exposure. Lung cancer mortality compared with the US population was greater among women than men. Because women were more likely to work in finishing than men, we conducted post hoc analyses to evaluate whether lung cancer mortality was associated with work in finishing. A positive association with employment duration in finishing and a negative association with employment duration in finishing jobs involving cutting and similar tasks were observed. These findings suggest that dermal exposure to TDI may play a role in the observed excess in lung cancer mortality. If polyurethane foam contained residual unreacted TDI, finishing workers would be expected to have higher dermal exposure to TDI than most other workers. In contrast, TDI air concentrations were, in general, higher for production workers than finishing workers [Boeniger, 1991a; Schnorr et al., 1996]. Animal studies have shown that TDI can be absorbed through skin and that dermal absorption can lead to respiratory sensitization [Karol et al., 1981; Yeh et al., 2008]. In addition, an occupational exposure study found substantially higher urinary levels of TDI metabolites in workers who directly handled uncured polyurethane foam than in other workers at the same plant with similar inhalation exposures [Austin, 2007]. However, our cumulative TDI exposure estimates did not account for potential dermal exposure to TDI, and other skin-absorptive compounds besides TDI could be present in newly formed foam. Inadvertent ingestion exposure from hand to mouth activity is also a possibility; however, the rapid permeation and reactivity of TDI with macromolecules in skin or evaporation of TDI from skin would make much of the TDI contacting hands unavailable for ingestion [Hoffmann et al., 2010].

Finishing workers may also be exposed to polyurethane dust. However, we observed a negative association between lung cancer mortality and employment duration in the finishing jobs that would be expected to have the highest polyurethane dust exposures. This negative association is difficult to explain unless susceptible workers developed acute effects and self-selected out of these jobs or workers in these jobs had less dermal exposure because of personal protective equipment use or automation of some cutting operations.

The lack of observed associations of cumulative TDI exposure with lung and laryngeal cancer mortality may reflect our reliance on exposure estimates that reflected inhalational exposure but not dermal exposure. Our ability to detect an exposure response relation for laryngeal cancer was also limited by the relatively small number of observed laryngeal cancer deaths. In addition, our exposure-response analyses did not account for smoking or bias from a healthy worker survivor effect. The negative trend in COPD mortality with

exposure duration suggests the potential for negative confounding by smoking. Alternatively, COPD mortality may be higher among workers with shorter exposure durations because workers sensitive to respiratory effects of TDI self-selected out of employment involving TDI exposure. We have no data on smoking; thus, we were unable to examine exposure-response relations adjusted for smoking.

Laryngeal cancer incidence was elevated in the UK cohort, but there were relatively few (n = 13) cases observed and patterns with exposure were not reported [Sorahan and Nichols, 2002]. Results for laryngeal cancer in the Swedish cohort were not reported [Mikoczy et al., 2004]. Lung cancer incidence was elevated among women, but not men, in the UK and Swedish cohorts [Sorahan and Nichols, 2002; Mikoczy et al., 2004]. In the UK cohort, no lung cancer cases occurred in women with isocyanate exposure, and there was no association of lung cancer with exposure duration categories in the overall cohort. In the Swedish cohort, there was no association with exposure duration or a crude assessment of polyurethane dust exposure. However, there was low statistical power to detect an exposure-response relation and limitations in the exposure assessment which likely biased the results toward the null. Smoking data were not available for either cohort, but other data suggested that smoking was unlikely to fully explain the excess in lung cancer observed in these cohorts [Sorahan and Pope, 1993; Mikoczy et al., 2004].

Breast, Intestinal, and Brain Cancers and NHL

Mortality from cancers of the breast, intestine, and brain, and NHL was elevated in the cohort, although not significantly, and significantly associated with exposure duration or cumulative TDI exposure estimates. Breast cancer was associated with cumulative TDI exposure in the main analysis, but not in analyses excluding short-term workers. An increased incidence of fibroadenomas of the mammary gland in female rats has been observed with administration of TDI by gavage [NTP, 1986], but other data in humans are not suggestive of an association between breast cancer and TDI exposure. Breast cancer mortality and/or incidence was elevated in men, but not in women in the most recent updates of the UK and Swedish cohorts, and the findings in men were based on very few observed cases and not statistically significant [Sorahan and Nichols, 2002; Mikoczy et al., 2004].

Intestinal cancer was associated with cumulative TDI exposure in the main analysis and analyses excluding short-term workers. Little other data exists suggesting an association between intestinal cancer and TDI exposure. Non-significant increases in mortality from cancers of the small intestine and colon were observed among men, but not women, in the UK cohort [Sorahan and Nichols, 2002]. Colon cancer incidence was not elevated among men in the UK cohort or in the Swedish cohort [Sorahan and Nichols, 2002; Mikoczy et al., 2004]. The incidence of small intestinal cancer was not reported for the Swedish cohort [Mikoczy et al., 2004], and no cases were observed in the UK cohort [Sorahan and Nichols, 2002].

In the main analysis, brain cancer mortality was associated with exposure duration, and the SMR and SRR were highest and significantly elevated in the highest cumulative TDI exposure category. SRRs for brain cancer were not evaluated in analyses excluding short-term workers because few brain cancer deaths were observed. Brain cancer incidence was

non-significantly elevated in the Swedish cohort, but the patterns with exposure and duration categories were not suggestive of an exposure-response relation [Mikoczy et al., 2004]. Brain cancer mortality and incidence was not elevated in the UK cohort [Sorahan and Nichols, 2002].

NHL mortality was associated with cumulative TDI exposure in the main analyses, but the magnitude of the association was small. SRRs were not evaluated in analyses excluding short-term workers because few deaths were observed; in these analyses, there was no clear trend in the SMRs. The incidence of NHL was not elevated in the Swedish cohort [Mikoczy et al., 2004] or the UK cohort [Sorahan and Nichols, 2002].

Strengths and Limitations

Strengths of the current study include the addition of quantitative estimates of exposure and the long follow-up period. However, our assessment of mortality and not cancer incidence is a limitation, especially for cancers with relatively good survival rates (e.g., breast and bladder cancers). Other limitations include the relatively small cohort size, the short employment duration of most workers, and the lack of data on smoking and non-occupational risk factors for cancers that were elevated in the cohort or associated with cumulative TDI exposure. In addition, as with all retrospective studies, exposure misclassification is possible. The level of detail for the air concentration measurements varied for each plant and by era. Generally, operational level exposure data (plants B and D) should result in more accurate exposure matrices than department level (plant C) or plant level (plant A) data. Even so, a great deal of between-worker exposure variability can be expected for workers in the same department or doing the same operation. Some air concentration data were missing in the early years, particularly for plant C, and had to be imputed based on declining exposures over time, information gathered in the 1984–1985 surveys, and professional judgment. Exposure measurements for this cohort were primarily for 2,4-TDI only and thus would have underestimated the total TDI exposure, which is typically an 80:20 mixture of 2,4-TDI and 2,6-TDI [NIOSH, 1989]. The proportion of these compounds in air will vary according to the process. According to the 1984–1985 surveys, for most processes, 2,6-TDI was present in air at higher concentrations than 2,4-TDI (up to twofold difference) [Boeniger, 1991a]. This TDI mixture has a high vapor pressure (0.01 mmHg at 25°C) [NIOSH, 2007]; therefore, the main route of exposure would have been inhalation. Exposure misclassification could result if appropriate respiratory protection had been used. However, according to the 1984–1985 surveys as well as company records, respirator use was either voluntary or non-existent during the exposure period for this study and available respirators were often not appropriate for isocyanates. Despite these limitations in the assessment of exposure, we would expect that most workers were placed in the appropriate quartile of cumulative TDI exposure and that this provides a more reliable estimate of inhalational exposure than exposure duration alone. Workers in this cohort generally did not wear gloves so dermal absorption was also possible for workers who directly handled uncured products. Our exposure estimates, however, did not consider the dermal route. We did not update the work histories to capture work after 1984; however, a sensitivity analysis suggests that this had little impact on the findings. Finally, some workers may have been exposed to methylene chloride, aliphatic amines, nitrogen dioxide, acrolein,

or acrylonitrile [Boeniger, 1991b; Schnorr et al., 1996]. However, none of these chemicals are known to cause the cancers that were elevated or associated with exposure duration or cumulative TDI in humans [NTP, 2014; IARC, 2015]. Based on the NIOSH exposure surveys conducted in 1984–1985, finishing workers using glues had higher inhalation exposures to methylene chloride, on average, than production workers in plant A, but the reverse was observed in plant C [Boeniger, 1991b]. Thus, it seems unlikely the observed association between employment duration in finishing jobs and lung cancer mortality is due to methylene chloride because over half of the cohort members (and over half of the lung cancer decedents) worked at plant C. Some data suggest that acrylonitrile may cause lung cancer [NTP, 2014], but personal exposures to acrylonitrile in the study plants were expected to be extremely low to nondetectable [Boeniger, 1991b].

CONCLUSIONS

We found a statistically significant increase in all cause and all cancer mortality as well as laryngeal and lung cancer mortality. Lung cancer mortality was not related to exposure duration or cumulative TDI exposure, but was associated with employment duration in finishing jobs, which suggests that dermal exposure may play a role. Our ability to detect an association with cumulative TDI exposure may have been hampered by the lack of smoking data, a healthy worker survivor effect, uncertainty in the exposure estimates, and the use of exposure estimates that reflected inhalational exposure only. The excess in laryngeal cancer mortality was large and unlikely to be explained by smoking alone.

Mortality from breast, intestine, and brain cancers and NHL were slightly increased, although not significantly, and associated with exposure duration or cumulative TDI exposure. The limited other data in humans do not suggest an association between these cancers and TDI exposure.

The UK and Swedish cohorts were both relatively young when last updated [Sorahan and Nichols, 2002; Mikoczy et al., 2004]. Additional follow-up and evaluation of these cohorts may be helpful, as previously recommended by Mikoczy et al. [2004], especially if the exposure assessment can be improved or smoking data collected.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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TABLE I

Characteristics of the Study Population

	Total[a]
Number of workers in analysis	4,545
Sex, race	
Male,white	1,662 (37%)
Male, other than white	1,009 (22%)
Female,white	1,281 (28%)
Female, other than white	593 (13%)
Vital status[b] (as of December 31, 2011)	
Alive	3,337 (73%)
Deceased	1,126 (25%)
Unknown	82 (2%)
Plant	
A	212 (5%)
B	701 (15%)
C	2,905 (64%)
D	727 (16%)
Year of birth	
Median (range)	1948 (1894–1965)
Year of first employment	
Median (range)	1972 (1948–1984)
Duration of employment (years)	
<1	2,378 (52%)
1–<3	1,225 (27%)
3–<6	410 (9%)
≥6	532 (12%)
Duration in exposed jobs (years)	
<1	2,489 (55%)
1–<3	1,202 (26%)
3–<6	397 (9%)
≥6	457 (10%)
Time since first exposure (years)	
<10	163 (4%)
10–<20	186 (4%)
≥20	4,196 (92%)

[a] Number (%) or median (range).

[b] Cohort members known to be alive in 1979 (when the NDI began) or later with a social security number not known to be invalid and not identified as deceased were assumed to be alive as of December 31, 2011.

TABLE II

Mortality Among a Cohort of TDI-Exposed Workers (1960–2011, U.S. Referent Rates)[a]

	Men (n = 2,871)			Women (n = 1,874)			Overall (n = 4,545)		
	OBS	SMR	95% CI	OBS	SMR	95% CI	OBS	SMR	95% CI
All deaths	750	1.12	1.04–1.20	376	1.26	1.14–1.39	1,126	1.16	1.10–1.23
All cancers	193	1.18	1.02–1.36	140	1.43	1.21–1.69	333	1.27	1.14–1.42
Buccal and pharyngeal cancer	2	0.41	0.05–1.50	0	0.00	0.00–3.57	2	0.34	0.04–1.23
All digestive cancer	44	0.99	0.72–1.33	24	1.26	0.81–1.88	68	1.07	0.83–1.36
Esophagus	3	0.45	0.09–1.30	1	0.95	0.02–5.27	4	0.51	0.14–1.31
Stomach	5	0.97	0.31–2.26	1	0.56	0.01–3.14	6	0.86	0.32–1.88
Intestine (except rectum)	14	1.11	0.61–1.86	13	1.81	0.96–3.09	27	1.36	0.90–1.98
Rectum	5	1.67	0.54–3.90	0	0.00	0.00–2.68	5	1.14	0.37–2.67
Liver and biliary	6	0.81	0.30–1.76	4	1.65	0.45–4.22	10	1.01	0.49–1.87
Pancreas	11	1.23	0.61–2.20	3	0.63	0.13–1.83	14	1.02	0.56–1.71
Peritoneum, other, and unspecified	0	0.00	0.00–7.75	2	5.39	0.65–19.5	2	2.36	0.29–8.53
All respiratory cancer	78	1.36	1.07–1.69	57	2.38	1.80–3.09	135	1.66	1.39–1.96
Larynx	7	2.93	1.18–6.04	4	11.1	3.03–28.4	11	4.00	1.99–7.16
Trachea, bronchus, and lung	71	1.30	1.01–1.64	53	2.27	1.70–2.96	124	1.59	1.32–1.89
Breast cancer	1	4.33	0.11–24.1	22	1.08	0.68–1.64	23	1.12	0.71–1.68
Female genital cancer	—	—	—	14	1.21	0.66–2.02	14	1.21	0.66–2.02
Cervix	—	—	—	6	2.02	0.74–4.40	6	2.02	0.74–4.40
Uterus	—	—	—	4	1.54	0.42–3.95	4	1.54	0.42–3.95
Ovary	—	—	—	3	0.53	0.11–1.55	3	0.53	0.11–1.55
Other	—	—	—	1	2.65	0.07–14.8	1	2.65	0.07–14.8
Male genital cancer	10	0.98	0.47–1.80	—	—	—	10	0.98	0.47–1.80
Prostate	10	1.02	0.49–1.88	—	—	—	10	1.02	0.49–1.88
All urinary cancer	9	1.20	0.55–2.27	3	1.23	0.25–3.61	12	1.21	0.62–2.11
Kidney	6	1.34	0.49–2.92	2	1.30	0.16–4.71	8	1.33	0.58–2.63
Bladder	3	0.99	0.20–2.88	1	1.11	0.03–6.21	4	1.02	0.28–2.60
Lymphatic and hematopoietic cancer	17	1.07	0.62–1.72	8	1.02	0.44–2.02	25	1.06	0.68–1.56
Hodgkin disease	2	2.21	0.27–7.99	2	5.57	0.67–20.1	4	3.17	0.86–8.10

	Men (n = 2,871)			Women (n = 1,874)			Overall (n = 4,545)		
	OBS	SMR	95% CI	OBS	SMR	95% CI	OBS	SMR	95% CI
Non-Hodgkin lymphoma	10	1.65	0.79–3.04	3	1.03	0.21–3.00	13	1.45	0.77–2.48
Multiple myeloma	1	0.32	0.01–1.80	2	1.21	0.15–4.39	3	0.63	0.13–1.85
Leukemia and aleukemia	4	0.69	0.19–1.76	1	0.35	0.01–1.93	5	0.57	0.19–1.34
All other and unspecified cancer	32	1.39	0.95–1.96	12	1.05	0.54–1.83	44	1.27	0.93–1.71
Melanoma	3	1.11	0.23–3.23	0	0.00	0.00–3.18	3	0.77	0.16–2.26
Non-melanoma skin	1	1.05	0.03–5.85	0	0.00	0.00–19.5	1	0.88	0.02–4.88
Connective tissue	2	1.72	0.21–6.22	0	0.00	0.00–4.56	2	1.01	0.12–3.66
Brain	6	1.29	0.47–2.80	2	0.83	0.10–2.98	8	1.13	0.49–2.22
Thyroid	0	0.00	0.00–11.9	1	3.90	0.10–21.7	1	1.76	0.04–9.82
Other and unspecified (excludes cancers of the bone and eye and mesothelioma)	19	1.55	0.93–2.42	9	1.42	0.65–2.70	28	1.51	1.00–2.18
Benign/unspecified neoplasms	1	0.50	0.01–2.79	3	2.35	0.49–6.88	4	1.22	0.33–3.13
Tuberculosis and HIV related diseases	14	0.69	0.38–1.16	3	1.00	0.21–2.91	17	0.73	0.42–1.17
Diseases of the blood	2	0.73	0.09–2.64	2	1.24	0.15–4.47	4	0.92	0.25–2.35
Diabetes mellitus	29	1.56	1.05–2.24	12	1.12	0.58–1.95	41	1.40	1.00–1.90
Mental disorders	6	0.49	0.18–1.06	3	0.60	0.12–1.75	9	0.52	0.24–0.99
Alcoholism	4	0.58	0.16–1.49	0	0.00	0.00–3.16	4	0.50	0.14–1.28
Nonmalignant nervous system diseases	16	1.38	0.79–2.24	7	0.80	0.32–1.64	23	1.13	0.71–1.69
Heart diseases	186	1.10	0.95–1.27	66	1.09	0.84–1.38	252	1.10	0.97–1.24
Ischemic heart disease	136	1.09	0.91–1.28	44	1.08	0.78–1.45	180	1.08	0.93–1.25
Circulatory system diseases	49	1.12	0.83–1.48	22	0.86	0.54–1.30	71	1.02	0.80–1.29
Nonmalignant respiratory diseases	53	1.36	1.02–1.78	36	1.61	1.13–2.23	89	1.45	1.17–1.79
Chronic obstructive pulmonary disease	31	1.66	1.13–2.35	28	2.37	1.57–3.42	59	1.93	1.47–2.49
Asthma	1	0.75	0.02–4.18	0	0.00	0.00–2.90	1	0.38	0.01–2.14
Nonmalignant digestive diseases	26	0.76	0.50–1.12	19	1.41	0.85–2.20	45	0.94	0.69–1.26
Cirrhosis and other chronic liver diseases	12	0.61	0.31–1.06	5	0.83	0.27–1.93	17	0.66	0.38–1.06
Other (excludes diseases of stomach and duodenum, hernia, and intestinal obstruction)	10	0.85	0.41–1.57	12	1.97	1.02–3.44	22	1.24	0.77–1.87
Musculoskeletal and connective tissue diseases	1	0.55	0.01–3.06	7	2.72	1.09–5.60	8	1.82	0.79–3.59
Nonmalignant genitourinary diseases	12	1.08	0.56–1.89	7	1.06	0.43–2.19	19	1.08	0.65–1.68
Acute glomerulonephritis, nephrotic syndrome and acute renal failure	2	1.74	0.21–6.28	3	4.79	0.99–14.0	5	2.81	0.91–6.57
Chronic/unspecified nephritis and renal failure and other renal sclerosis	6	0.83	0.31–1.81	2	0.50	0.06–1.82	8	0.71	0.31–1.41

	Men (n = 2,871)			Women (n = 1,874)			Overall (n = 4,545)		
	OBS	SMR	95% CI	OBS	SMR	95% CI	OBS	SMR	95% CI
Ill-defined conditions	12	1.18	0.61–2.07	4	1.05	0.28–2.68	16	1.14	0.65–1.86
Transportation injuries	27	0.85	0.56–1.24	13	1.88	1.00–3.21	40	1.03	0.74–1.41
Falls	3	0.64	0.13–1.87	1	0.73	0.02–4.05	4	0.66	0.18–1.69
Other injury	36	1.35	0.94–1.86	6	0.95	0.35–2.08	42	1.27	0.92–1.72
Violence	53	1.21	0.90–1.58	12	1.58	0.81–2.75	65	1.26	0.97–1.61
Intentional self-harm	35	1.80	1.25–2.50	5	1.18	0.38–2.76	40	1.69	1.21–2.30
Assault and homicide	18	0.74	0.44–1.16	7	2.07	0.83–4.27	25	0.90	0.58–1.33
Other causes	23	1.05	0.66–1.57	9	0.74	0.34–1.41	32	0.94	0.64–1.33
Unknown cause of death	8			4			12		

OBS, observed number of deaths; SMR, standardized mortality ratio; CI, confidence interval.

[a] International Classification of Diseases codes were mapped to 119 cause of death categories as described on the NIOSH website at http://www.cdc.gov/niosh/ltas/pdf/niosh-119-table-2007.pdf. One major category (nonmalignant skin diseases) was omitted because no deaths occurred; some minor categories were also omitted.

TABLE III

Standardized Mortality Ratios and Standardized Rate Ratios for Selected Causes of Death Stratified by Quartiles of 10-Year Lagged Exposure Duration[a,b]

	Exposure duration (days)												
	0–<142			142–<334			334–<913			≥913			
Cause of death	**OBS**	**SMR Referent**	**95% CI**	**OBS**	**SMR SRR**	**95% CI**	**OBS**	**SMR SRR**	**95% CI**	**OBS**	**SMR SRR**	**95%CI**	**Trend slope, *P*-value**
All causes	250	1.11	0.97–1.25	254	1.25	1.10–1.42	252	1.34	1.18–1.52	252	1.02	0.90–1.16	
		Referent			1.12	0.89–1.41		1.18	0.94–1.48		0.85	0.69–1.05	−1.10E–06, 0.16
All cancers	52	1.03	0.77–1.35	70	1.24	0.97–1.57	87	1.61	1.29–1.98	88	1.24	1.00–1.53	
		Referent			1.37	0.82–2.28		1.33	0.92–1.94		1.20	0.81–1.76	1.61 E–07, 0.61
Intestinal cancer	7	1.92	0.77–3.95	4	0.95	0.26–2.43	3	0.73	0.15–2.14	9	1.60	0.73–3.03	
		Referent			0.35	0.10–1.26		0.34	0.08–1.37		0.80	0.28–2.30	5.16E–08, 0.55
Rectal cancer	3	3.56	0.73–10.4	2	2.05	0.25–7.40	0	0.00	0.00–4.05	0	0.00	0.00–3.21	
		—			—	—		—	—		—	—	
Larynx cancer	1	2.01	0.05–11.2	3	4.85	1.00–14.2	4	7.21	1.96–18.5	1	1.36	0.03–7.59	
		Referent[c]						1.49	0.37–6.05		0.36	0.04–3.24	−4.41E–08, 0.16
All lung cancer[d]	16	1.16	0.66–1.88	30	1.79	1.21–2.56	39	2.40	1.71–3.28	32	1.46	1.00–2.06	
		Referent			2.08	0.85–5.08		1.82	0.98–3.38		1.12	0.59–2.13	−3.73E–08, 0.89
Male lung cancer[d]	11	1.17	0.58–2.10	16	1.38	0.79–2.24	18	1.66	0.98–2.63	20	1.32	0.81–2.04	
		Referent			1.06	0.48–2.35		1.28	0.58–2.81		0.94	0.43–2.05	−6.44E–08, 0.56
Female lung cancer[d]	5	1.13	0.37–2.65	14	2.75	1.50–4.61	21	3.89	2.40–5.94	12	1.76	0.91–3.07	
		Referent			4.55	1.02–20.4		3.14	1.04–9.51		1.57	0.49–5.04	8.58E–08, 0.84
Breast cancer	3	0.62	0.13–1.82	2	0.43	0.05–1.56	11	2.36	1.18–4.23	7	1.38	0.55–2.84	
		Referent			0.48	0.08–2.94		2.67	0.73–9.74		2.09	0.51–8.46	1.40E–07, 0.17
Cervical cancer	3	3.34	0.69–9.76	0	0.00	0.00–5.72	2	3.10	0.38–11.2	1	1.66	0.04–9.26	
		—			—	—		—	—		—	—	
Kidney cancer	0	0.00	0.00–3.36	2	1.49	0.18–5.38	2	1.58	0.19–5.72	1	0.63	0.02–3.51	
		—			—	—		—	—		—	—	
NHL	2	1.10	0.13–3.99	2	1.03	0.13–3.73	3	1.62	0.33–4.74	4	1.70	0.46–4.34	
		Referent			0.56	0.08–4.05		1.06	0.17–6.41		1.48	0.27–8.30	5.19E–08, 0.052
Brain cancer	1	0.60	0.02–3.33	2	1.25	0.15–4.50	2	1.37	0.17–4.96	3	1.90	0.39–5.56	

	Exposure duration (days)												
	0–<142			142–<334			334–<913			≥913			
Cause of death	OBS	SMR Referent	95% CI	OBS	SMR SRR	95% CI	OBS	SMR SRR	95% CI	OBS	SMR SRR	95%CI	Trend slope, *P*-value
		Referent[c]						1.48	0.24–8.97		2.16	0.43–10.9	3.20E–08, <0.0001
Other/unspecified cancer[e]	3	0.85	0.18–2.49	9	2.21	1.01–4.20	5	1.30	0.42–3.02	9	1.77	0.81–3.37	
		Referent			3.65	0.89–14.9		1.89	0.40–8.81		2.77	0.67–11.5	9.20E–08, 0.30
Diabetes mellitus	9	1.69	0.77–3.21	9	1.38	0.63–2.63	8	1.29	0.56–2.54	11	1.34	0.67–2.40	
		Referent			0.60	0.23–1.60		0.70	0.26–1.91		0.70	0.27–1.86	−6.71E–09, 0.90
COPD	13	2.72	1.45–4.65	15	2.53	1.41–4.17	11	1.77	0.88–3.17	18	1.81	1.07–2.86	
		Referent			0.78	0.31–1.95		0.75	0.28–2.02		0.63	0.26–1.56	−9.38E–08, 0.0068
Intentional self-harm	19	2.08	1.25–3.25	5	1.01	0.33–2.35	7	1.77	0.71–3.64	3	0.93	0.19–2.71	
		Referent			0.42	0.13–1.36		0.45	0.18–1.10		0.34	0.08–1.47	−1.39E–07, 0.23

OBS, observed deaths; SMR, standardized mortality ratio; CI, confidence interval; SRR, standardized rate ratio; NHL, non-Hodgkin lymphoma; COPD, chronic obstructive pulmonary disease.

[a]Analysis is restricted to cohort members with cumulative TDI exposure estimates. SRRs are not reported when the total number of observed deaths was less than eight in this analysis.

[b]Quartiles of exposure duration are based on the exposure distribution among all decedents with cumulative TDI exposure estimates.

[c]The referent category was 0–<334 days (i.e., the lowest two exposure categories combined).

[d]Includes trachea, bronchus, and lung cancer.

[e]Excludes cancers of the bone and eye and mesothelioma.

TABLE IV

Standardized Mortality Ratios and Standardized Rate Ratios for Selected Causes of Death Stratified by Quartiles of 10-Year Lagged Cumulative TDI Exposure[a,b]

	Cumulative TDI exposure (in μg/m^3-days)												
	0–< 1,270			1,270–<3,800			3,800–<14,280			≥14,280			
Cause of death	**OBS**	**SMR Referent**	**95% CI**	**OBS**	**SMR SRR**	**95% CI**	**OBS**	**SMR SRR**	**95% CI**	**OBS**	**SMR SRR**	**95% CI**	**Trend slope, *P*-value**
All causes	248	1.04	0.91–1.17	256	1.35	1.19–1.52	252	1.19	1.05–1.35	252	1.13	1.00–1.28	
		Referent			1.49	1.12–1.99		1.13	0.91–1.41		1.08	0.87–1.35	2.74E-09, 0.96
All cancers	53	1.00	0.75–1.30	80	1.46	1.16–1.81	78	1.29	1.02–1.61	86	1.35	1.08–1.67	
		Referent			1.77	1.12–2.81		1.31	0.88–1.95		1.49	1.00–2.24	2.60E-08, 0.34
Intestinal cancer	5	1.31	0.42–3.05	5	1.22	0.40–2.85	4	0.86	0.24–2.21	9	1.78	0.81–3.38	
		Referent			1.30	0.33–5.16		1.11	0.26–4.74		1.95	0.55–6.91	4.16E-09, 0.014
Rectal cancer	2	2.21	0.27–7.98	2	2.17	0.26–7.83	1	0.99	0.02–5.50	0	0.00	0.00–3.55	
		—			—	—		—	—		—	—	
Larynx cancer	1	2.09	0.05–11.6	5	8.43	2.74–19.7	2	3.08	0.37–11.1	1	1.47	0.04–8.18	
		Referent[c]						0.38	0.08–1.87		0.28	0.03–2.36	−3.04E-09, 0.21
All lung cancer[d]	20	1.45	0.89–2.25	31	1.87	1.27–2.65	33	1.78	1.23–2.50	33	1.66	1.14–2.34	
		Referent			1.46	0.79–2.71		1.31	0.71–2.42		1.30	0.70–2.42	3.69E-09, 0.66
Male lung cancer[d]	7	0.82	0.33–1.68	17	1.48	0.86–2.37	22	1.69	1.06–2.56	19	1.37	0.82–2.14	
		Referent			1.77	0.70–4.45		1.95	0.80–4.75		1.51	0.60–3.80	5.32E-09, 0.71
Female lung cancer[d]	13	2.51	1.34–4.30	14	2.76	1.51–4.63	11	1.99	0.99–3.57	14	2.34	1.28–3.93	
		Referent			1.21	0.52–2.80		0.80	0.33–1.94		1.13	0.49–2.63	1.57E-09, 0.90
Breast cancer	4	0.68	0.18–1.73	6	1.36	0.50–2.96	7	1.56	0.63–3.21	6	1.38	0.51–3.00	
		Referent			2.08	0.54–8.04		2.72	0.63–11.7		3.34	0.73–15.3	1.12E-08, 0.021
Cervical cancer	4	3.62	0.99–9.26	1	1.70	0.04–9.46	0	0.00	0.00–6.22	1	1.99	0.05–11.1	
		—			—	—		—	—		—	—	
Kidney cancer	0	0.00	0.00–3.27	1	0.78	0.02–4.32	3	2.10	0.43–6.13	1	0.69	0.02–3.87	
		—			—	—		—	—		—	—	
NHL	0	0.00	0.00–1.95	5	2.70	0.88–6.29	3	1.45	0.30–4.23	3	1.40	0.29–4.11	
		Referent[c]						1.04	0.24–4.46		1.11	0.26–4.80,	3.90E-10, <0.0001

	Cumulative TDI exposure (in μg/m^3-days)												
	0–< 1,270			1,270–<3,800			3,800–<14,280			≥14,280			
Cause of death	**OBS**	**SMR Referent**	**95% CI**	**OBS**	**SMR SRR**	**95% CI**	**OBS**	**SMR SRR**	**95% CI**	**OBS**	**SMR SRR**	**95% CI**	**Trend slope, *P*-value**
Brain cancer	1	0.55	0.01–3.08	1	0.67	0.02–3.74	1	0.64	0.02–3.54	5	3.47	1.13–8.10	
		Referent[c]						1.09	0.10–12.2		7.08	1.35–37.1	3.77E-09, 0.29
Other/unspecified cancer[e]	3	0.82	0.17–2.39	7	1.79	0.72–3.68	9	2.07	0.95–3.94	7	1.52	0.61–3.14	
		Referent			2.38	0.46–12.4		2.66	0.53–13.3		2.09	0.39–11.1	2.79E-09, 0.51
Diabetes mellitus	8	1.39	0.60–2.73	7	1.14	0.46–2.35	12	1.74	0.90–3.03	10	1.35	0.65–2.48	
		Referent			0.73	0.24–2.22		1.13	0.42–3.05		1.00	0.35–2.85	2.35E-09, 0.47
COPD	13	2.80	1.49–4.79	14	2.26	1.24–3.80	12	1.65	0.85–2.89	18	2.04	1.21–3.23	
		Referent			0.60	0.23–1.59		0.60	0.22–1.65		0.64	0.26–1.59	–1.2E-09, 0.81
Intentional self-harm	18	1.81	1.07–2.86	5	1.22	0.40–2.85	9	2.18	1.00–4.13	2	0.64	0.08–2.31	
		Referent			0.50	0.16–1.56		0.69	0.29–1.62		0.17	0.04–0.75	−1.10E-08, 0.0016

OBS, observed deaths; SMR, standardized mortality ratio; CI, confidence interval; SRR, standardized rate ratio; NHL, non-Hodgkin lymphoma; COPD, chronic obstructive pulmonary disease.

[a] Analysis is restricted to cohort members with cumulative TDI exposure estimates; SRRs are not reported when the total number of observed deaths was less than eight.

[b] Quartiles of cumulative exposure are based on the exposure distribution among all decedents with cumulative TDI exposure estimates.

[c] The referent category was 0–<3,800 μg/m^3-days (i.e., the lowest two exposure categories combined).

[d] Includes trachea, bronchus, and lung cancer.

[e] Excludes cancers of the bone and eye and mesothelioma.

TABLE V

Standardized Rate Ratios for Lung Cancer Stratified by Categories of 10-Year Lagged Employment Duration in Finishing Jobs and in Finishing Jobs Involving Cutting and Similar Activities[a,b]

Finishing jobs					Finishing jobs involving cutting and similar activities				
Employment duration (days)[c]	**Obs**	**SRR**	**95% CI**	**Trend slope, *P*-value**	**Employment duration (days)[c]**	**Obs**	**SRR**	**95% CI**	**Trend slope, *P*-value**
0	32	Referent			0	72	Referent		
1–<227	24	1.96	0.72–5.32		1–<110	11	1.28	0.46–3.51	
227–<525	24	1.92	1.04–3.53		110–<275	11	1.01	0.34–3.02	
≥525	25	3.22	0.95–11.0	1.51E-06, <0.0001	≥275	11	0.60	0.30–1.18	−8.64E-07, <0.0001

OBS, observed deaths; SRR, standardized rate ratio; CI, confidence interval.

[a] Includes trachea, bronchus, and lung cancer.

[b] Analysis is restricted to cohort members who only held jobs that we could determine if were in finishing.

[c] Cut-points were selected to obtain four categories with an approximately equal number of lung cancer deaths in each category with an employment duration greater than zero.