Cancer, Heart Disease, and Diabetes in Workers Exposed to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin

Kyle Steenland, Laurie Piacitelli, James Deddens, Marilyn Fingerhut, Lih Ing Chang

Background: **In 1997, the International Agency for Research on Cancer classified 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) as a group 1 human carcinogen, based largely on four highly exposed industrial cohorts that showed an excess of all cancers combined. In this study, we extended the follow-up period for the largest of these cohorts by 6 years and developed a job-exposure matrix.** ***Methods:*** **We did cohort mortality analyses involving 5132 chemical workers at 12 U.S. plants by use of life table techniques (U.S. population referent) and Cox regression (internal referent). We conducted exposure-response analyses for 69% of the cohort with adequate work history data and adequate plant data on TCDD contamination. All *P* values are two-sided.** ***Results:*** **The standardized mortality ratio (SMR) for all cancers combined was 1.13 (95% confidence interval = 1.02–1.25). We found statistically significant positive linear trends in SMRs with increasing exposure for all cancers combined and for lung cancer. The SMR for all cancers combined for the highest exposure group was 1.60 (95% confidence interval = 1.15–1.82). SMRs for heart disease showed a weak increasing trend with higher exposure (*P* = .14). Diabetes (any mention on the death certificate) showed a negative exposure–response trend. Internal analyses with Cox regression found statistically significant trends for cancer (15-year lag time) and heart disease (no lag).** ***Conclusions:*** **Our analyses suggest that high TCDD exposure results in an excess of all cancers combined, without any marked specificity. However, excess cancer was limited to the highest exposed workers, with exposures that were likely to have been 100–1000 times higher than those experienced by the general population and similar to the TCDD levels used in animal studies.** **[J Natl Cancer Inst 1999;91:779–86]**

In 1997, the International Agency for Research on Cancer (IARC) classified 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) as a human carcinogen (group 1) based on limited human epidemiology data, sufficient animal data, and supplementary information on biologic mechanism *(1)*. The human epidemiologic evidence was not consistent for all studies but did point to a generalized excess of all cancer mortality (without any pronounced site specificity) in four highly exposed industrial cohorts with well-documented exposure *(2–5)*. Furthermore, in three of these cohorts, mortality from all cancers combined increased with higher estimated serum TCDD levels in a statistically significant manner *(3–5)*. In the fourth cohort, the cancer excess was confined to those individuals with the longest duration of exposure *(2)*.

TCDD is a multisite carcinogen in animals. However, it is not directly genotoxic and is thought to induce tumors in animals indirectly. TCDD operates via an Ah (aryl hydrocarbon) receptor that is present in many tissues in both animals and humans. In animals, the affinity of TCDD for the Ah receptor is correlated with carcinogenic potential *(1)*. Animal carcinogenesis is thought to arise from Ah receptor-mediated alteration of gene expression, although other possible mechanisms, such as increased oxidative DNA damage or immune suppression, have been proposed *(1,6)*. TCDD is also known to act as a promoter of other carcinogens *(1)*. Body burdens of TCDD among the more highly exposed workers in the industrial cohorts were similar in magnitude to body burdens that produced cancer in rodent studies *(1)*.

The largest of the four industrial cohorts considered by the IARC is the U.S. cohort of 5172 workers (5132 after exclusions) at 12 plants that produced chemicals contaminated with TCDD. These workers were exposed to high levels of TCDD. Blood drawn from a sample of these workers (n = 253) indicated an estimated mean serum level of 2000 parts per trillion in lipids at the time of last exposure compared with six to eight parts per trillion for the general population *(7)*. From the earlier follow-up data through 1987, this cohort had a 15% excess of mortality from all cancers combined (standardized mortality ratio [SMR] = 1.15; 95% confidence interval [CI] = 1.02–1.30) compared with the general population, increasing to a 46% excess of mortality in the subcohort of these workers who had an exposure of more than 1 year and a first exposure that occurred at least 20 years previously (SMR = 1.46; 95% CI = 1.21–1.76) *(2)*. No quantitative estimate of exposure over time was available for the cohort at the time of the original analysis. This cohort is the subject of this report; existing data have now been assembled enabling quantitative exposure estimates.

Beside cancer, in recent years, TCDD has been implicated as a possible cause of heart disease. Elevated rate ratios for mortality from ischemic heart disease were found in a large multicountry cohort (rate ratio = 1.67; 95% CI = 1.23–2.26) *(8)*, in a heavily exposed Dutch cohort (rate ratio = 1.9; 95% CI = 0.9–3.6) *(5)*, in men in the high-exposure zone at Seveso (rate ratio = 1.6; 95% CI = 1.1–2.5) *(9)*, in those with the highest estimated TCDD levels in a German industrial cohort (rate ratio = 1.4; 95% CI = 0.71–2.76) *(3)*, and in U.S. Air Force Ranch Hand personnel (nonflying personnel) with the highest estimated TCDD exposure (rate ratio = 1.5; 95% CI = 1.0–2.2) *(10)*. On the other hand, two cross-sectional medical studies of U.S. industrial workers (a subset of this cohort) and U.S. Air Force Ranch Hand personnel have been largely negative for cardiovascular morbidity *(11,12)*.

Plausible mechanisms exist for an effect of TCDD on cardiovascular disease, primarily by an alteration of lipid metabolism, although other mechanisms such as an effect on inflammation affecting atherothrombosis have also been suggested *(13)*. Two cross-sectional studies *(12,14)* have shown an inverse relationship between serum TCDD level and high density lipoprotein, and one of these studies also showed a positive relationship with total cholesterol *(12)*.

A recent cross-sectional medical study *(15)* of the Operation Ranch Hand cohort found a 50% higher prevalence of diabe-

Affiliation of authors: National Institute for Occupational Safety and Health, Cincinnati, OH.

Correspondence to: Kyle Steenland, Ph.D., International Agency for Research on Cancer, 150 Cours Albert Thomas, 69372 Lyon, France (e-mail: steenland@iarc.fr).

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tes (prevalence ratio = 1.5; 95% CI = 1.2–2.0) among those individuals with the highest levels of TCDD in serum compared with nonexposed referents. One other cross-sectional medical survey of U.S. industrial workers provided some supporting evidence for these findings [*(16);* Calvert G, Sweeney M, Deddens J, Wall D: manuscript submitted for publication], but another cross-sectional medical study of German industrial workers was negative *(17).* Animal studies have shown that TCDD reduces glucose transport in adipose and other tissues *(15).*

Thus, there have been reasonably consistent findings of an excess of all cancers combined among those individuals with the highest TCDD exposure in four industrial cohorts, although site-specific findings have not always been consistent. Cancer excesses have not been consistently observed in TCDD-exposed cohorts with lower exposures. There are a number of findings of increased amounts of heart disease and diabetes associated with TCDD exposure, but the data are inconsistent. To further investigate the issues raised above, we have extended the follow-up of the U.S. cohort through 1993 (6 more years), with a 37% increase in the number of deaths observed. In addition, we have conducted exposure–response analyses after estimating past TCDD exposures for 69% of the cohort by using historic data on TCDD contamination of process materials and detailed work histories.

Subjects and Methods

Cohort Definition

The cohort has been described previously *(2).* Briefly, 5172 male workers from all 12 U.S. plants that produced TCDD-contaminated products (including Agent Orange) from 1942 through 1984 were included in the study. Documentation of ever having worked in a TCDD-exposed job was required for inclusion. TCDD was generated primarily as a contaminant in the production of 2,4,5-trichlorophenol. The National Institute for Occupational Safety and Health conducted a review of industrial hygiene records and production processes at all plants.

For the present study, we rereviewed all of the data and eliminated 40 workers who were found to be female or to have never worked in TCDD-exposed departments or whose record was missing a date of birth. Of the remaining 5132 workers, 238 lacked adequate data to characterize duration of exposure and could not be used in the "exposure-level" subcohort for exposure–response analyses.

The exposure-level subcohort was further restricted to eight plants because four plants (with 591 workers) lacked records on the degree of TCDD contamination of their work processes or lacked detailed work history required to estimate the level of TCDD exposure by job. Another 38 workers at the remaining eight plants were eliminated because they worked in a process in which TCDD contamination could not be estimated. Finally, another 727 workers with exposure to both pentachlorophenol and TCDD were eliminated to avoid possible confounding of any TCDD effects by pentachlorophenol. Pentachlorophenol is contaminated with the higher chlorinated dioxins. These dioxins and TCDD are thought to act similarly with regard to the Ah receptor and gene expression, although they are considered less toxic *(1).* These restrictions led to an exposure-level subcohort of 3538 workers (69% of the overall cohort). All restrictions were made *a priori* without knowledge of their effect on disease outcome.

We also analyzed another subcohort of 608 workers (taken from all 12 plants) who had chloracne (a skin disorder that can result from TCDD exposure) and who also had not had any exposure to pentachlorophenol [which is also a chloracnegen *(18)*]. Workers in this subcohort were classified as having had chloracne based on historic plant medical records. The motivation for this analysis was in part because these workers were likely to have had higher TCDD exposures and in part for comparison with other studies of TCDD-exposed workers with chloracne.

Job-Exposure Matrix

The job-exposure matrix is described in a separate publication *(19).* Briefly, the matrix assigns each worker a quantitative exposure score for each day he worked. The score is based on the following three factors: 1) the concentration of TCDD (μg/g) present in process materials, 2) the fraction of the day the worker worked on the specific process, and 3) a qualitative contact level (0.01–1.5) based on estimates of the amount of TCDD contamination reaching exposed skin areas or the potential for inhalation of TCDD-contaminated dust. Data on TCDD concentration in process materials were available for all plants from the 1960s through 1983 (production contaminated by TCDD had stopped in all plants by 1984). Supplemental data on the chloracnegenic potential of contaminated processes were also available for earlier periods at the largest plant in the cohort. Data on any changes in process across time were also known, allowing adjustment of the concentration factor over time. Contact level was related to the job category; for example, in general, production workers were assigned higher contact levels than chemists or engineers. The three factors (concentration, fraction of day exposed, and contact level) were multiplied together to form a daily exposure score. For example, a full-time production worker producing 2,4,5-trichlorophenoxyacetic acid on a specific day in 1966 at a specific plant might be assigned the estimated 1966 concentration of TCDD in the 2,4,5-trichlorophenoxyacetic acid (e.g., 0.66 μg/g), a fraction of the day equal to 1.0 (full-time worker), and a contact level of 1.0 (assigned to most production workers), resulting in an exposure score for that day of 0.66. For each worker, these scores in turn were accumulated over time to give a cumulative exposure score.

The exposure scores cannot be interpreted in units of external exposure, such as parts per million or mg/m^3 in the air, in part because exposure was primarily dermal and in part because the scores represent a quantitative exposure ranking of workers across different jobs and plants rather than an assignment of a specific dose of TCDD. Nonetheless, the scores should reflect the relative exposure level to TCDD among workers.

Follow-up and Data Analysis

Follow-up through 1993 was conducted via Social Security death files, the National Death Index, and the Internal Revenue Service. Cause-of-death data were obtained for 98% of the decedents. Life table analyses, stratified for race, age, and calendar time and, using the U.S. population as a comparison, were conducted for the entire cohort for 92 underlying causes of death by using a National Institute for Occupational Safety and Health life table program *(20).* Person-years at risk (1 person-year at risk = 1 person followed for 1 year) began at the time of first exposure to TCDD and continued until date of death, date last observed, or date of the study's end, whichever came first. Only 0.6% of the cohort could not be followed until death or the end of the study.

Life table analyses were also run on the exposure-level subcohort of 3538 workers. Categorical analyses used seven cumulative exposure cut points, the maximum permitted by the life table program. Cut points were chosen before analysis based on the septiles of cumulative exposure of all observed deaths, with the aim of creating categories so that the resulting cause-specific SMRs would have similar variances across septiles. In addition, lagged life table analyses were also run, in which it is assumed that cancer cannot result from exposure until after a lag or latency period. In the analyses with a 15-year lag period, for example, person-years at risk due to exposure began 15 years after exposure. A person is viewed as nonexposed until 15 years has passed since his first exposure. In his 16th year after first exposure, his cumulative exposure equals that received in his first year of exposure, and in his 30th year after exposure, his cumulative exposure equals that received in his first 15 years of exposure. The lag discounts any exposure received during the prior 15 years. Deaths and person-years occurring during the lag period (e.g., during the first 15 years of follow-up) were considered nonexposed and were included in the lowest exposure category. Tests for trend in SMRs with cumulative dose and logarithm of cumulative dose were calculated by the method suggested by Breslow et al. *(21).* The mid-points of exposure categories were used in this test; for the uppermost exposure category (which has no midpoint), we used the median cumulative exposure of those workers who were in that category.

Cox regression analyses were also conducted with the exposure-level subcohort for death (underlying cause) from ischemic heart disease (International Classification of Diseases [ICD] 410–414, 9th Revision), all cancers, and some subsets of cancers. In addition, a Cox regression analysis was conducted for diabetes, based on any mention on the death certificate (multiple cause). Unlike SMR analyses using the U.S. population as the nonexposed referent group, Cox regression analyses are internal analyses that use the low-exposure group as the referent group for higher exposure groups. Compared with SMR analyses, Cox regression analyses permitted more flexible modeling of the exposure–response curve, exploration of various lag times, and explo-

ration of possible interactions. Because internal analyses compare workers with other workers likely to share some lifestyle characteristics, such analyses may also help avoid potential confounding by unmeasured variables, such as smoking or other chemical exposures. They may also help avoid a possible healthy worker effect that can occur (especially for heart disease) when workers are compared with the general population. The time variable for Cox regression was age, which had the effect of matching on age; risk sets were also matched on race, and year of birth was included in all models. The SAS program package (PHREG program) was used *(22)*. Cumulative exposure was a time-dependent variable. We considered several exposure metrics, including cumulative exposure score, logarithm of cumulative exposure score (with 0.001 added to each subject's exposure scores to avoid taking the logarithm of 0 in lagged analyses), average exposure score (cumulative exposure score divided by duration), and categorized exposure scores divided into septiles. Lag times of 5, 10, 15, and 20 years were used, with the change in likelihood as the criteria for a better fit. Individuals who only had exposure during the lag period (e.g., during their last 15 years of follow-up) were considered nonexposed and were combined with the lowest exposure category. Tests for trend in the categorized data (septiles of cumulative exposure) from a Cox regression analysis were done with an inverse-variance weighted regression analysis of the logarithm of the categorical rate ratios on the mid-points of the exposure categories *(23)*. For the uppermost category, which has no mid-point, the median exposure was used. The regression line was forced through zero, so that the nonexposed were assumed to have a rate ratio of 1.0.

Cox regression analyses were also conducted for smoking-related cancers and non-smoking-related cancers. Smoking-related cancers were defined as those most strongly related to smoking (i.e., lung, larynx, esophagus, oral, pharyngeal, and bladder cancers), whereas non-smoking-related cancers were the remainder. These analyses were motivated by analyses of other investigators *(4)*, suggesting that TCDD increased the risk of cancer only in smokers. Our data did not include information on the smoking history of our subjects. However, if this hypothesis were true, then by inference one might expect to detect a TCDD effect reflected in increased numbers of smoking-related cancers.

All reported *P* values are two-sided. No adjustment of *P* values was made for multiple comparisons; instead, we sought to interpret positive findings in light of biologic and epidemiologic consistency.

RESULTS

Fig. 1 shows that plants in the exposure matrix differed considerably by median cumulative exposure of the workers. The principal reason for the large differences between plants was the degree to which dioxin contaminated the products produced, which would have led to workers at different plants having different intensities of exposure. The cumulative exposure scores permit analyses that take the duration and level of exposure into account. There exists no gold standard to validate the job-exposure matrix and its estimated exposure scores. However, in general, those workers with chloracne would be expected to have had higher exposures to TCDD, although chloracne is an imperfect marker of high exposure. In our cohort, those workers with chloracne (n = 393) had a markedly higher median cumulative exposure score (11546) than those workers without chloracne (n = 3145), whose median score was 77. This marked difference persisted when the average exposure scores rather than cumulative exposure scores were considered (median 10.3 versus 0.3). Both serum TCDD levels and exposure scores were available for 193 workers at one of the plants in the exposure-level cohort (Fig. 1, plant 1). However, this plant unfortunately had relatively poor-quality work history information compared with other plants, making estimation of exposure level there particularly difficult. Many workers in this plant had the same job title and worked during the same period, so that estimated intensity of exposure was similar for many workers. The Spearman correlation coefficient between cumulative exposure score and serum level back-extrapolated to the last exposure for this sample of workers was .70. The correlation coefficient between the duration of exposure and the serum level of dioxin was .74 and between the cumulative exposure score and the duration was .91.

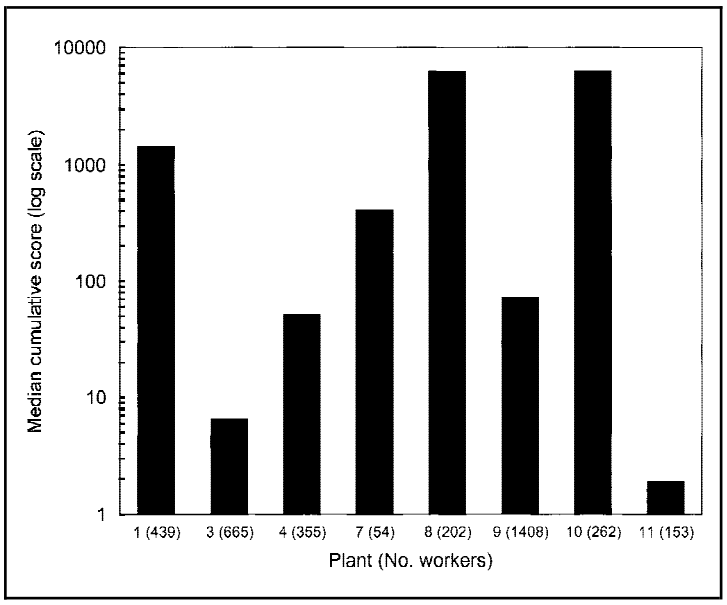

Fig. 1. Median cumulative exposure score by plant.

Table 1 presents the life table results for the entire cohort (n = 5132) for a variety of causes. Results were unremarkable for all cancers combined, ischemic heart disease, and diabetes, the causes of *a priori* interest. Heart disease might have been expected to be in deficit due to the healthy-worker effect. The slight excess observed could be related to TCDD toxicity or to the fact that most of this cohort has been followed past retirement age, diminishing the healthy-worker effect. Larynx cancer and myeloma were statistically significantly elevated based on small numbers of cases. Bladder cancer was also statistically significantly elevated, but this elevation was largely due to an excess at one plant that was caused by exposure to 4-aminobiphenyl (this plant accounted for 10 cases of bladder cancer). When the data were restricted to those workers with more than 1 year of TCDD exposure and analyzed for the period of 20 years or more of potential latency, the SMR for all cancers was 1.29 (95% CI = 1.10–1.51), a decrease from the SMR of 1.46, which was observed for this group in the earlier follow-up.

Table 1 presents the data for 608 men who had chloracne, as noted in plant medical records. This group had an excess risk of 25% for all cancers (SMR = 1.25; 95% CI = 0.98–1.57) and an excess risk of 17% for heart disease (SMR = 1.17; 95% CI = 0.94–1.44), whereas this group had no excess risk for diabetes. They had an excess risk of 45% for lung cancer that had borderline statistical significance and a risk for soft tissue sarcoma that was statistically significantly elevated, based on only three cases. A number of men in this chloracne subcohort (215 of 608 men) were identified in prior studies of men

Table 1. Cohort mortality results: selective causes*

Death category (ICD-9 code)	No. of deaths†	SMR (95% CI)
Total cohort (n = 5132)		
All cancers (140–208)	377	1.13 (1.02–1.25)
Esophagus (150)	13	1.46 (0.77–2.49)
Stomach (151)	13	1.04 (0.55–1.78)
Small intestine, colon (152–153)	34	1.16 (0.80–1.61)
Rectum (154)	6	0.85 (0.31–1.85)
Liver and biliary (155–156)	7	0.88 (0.44–1.57)
Pancreas (157)	16	0.96 (0.55–1.56)
Peritoneum and unspecified (158–159)	3	2.19 (0.45–6.41)
Larynx (161)	10	2.22 (1.06–4.08)
Lung (162)	125	1.06 (0.88–1.26)
Prostate (185)	28	1.17 (0.78–1.69)
Kidney (189.0–189.2)	13	1.56 (0.82–2.66)
Bladder (188, 189.3–189.9)	16	1.99 (1.13–3.23)
Lymphatic and hematopoietic (200–208)	35	1.11 (0.78–1.54)
Hodgkin's disease (201)	3	1.09 (0.22–3.19)
Non-Hodgkin's lymphoma (200, 202)‡	12	1.10 (0.56–1.91)
Multiple myeloma (203)‡	10	2.07 (0.99–3.80)
Leukemia and aleukemia (204–208)	10	0.81 (0.38–1.48)
Brain and nervous system (191–192)	8	0.81 (0.35–1.60)
Connective tissue and soft tissue (171)	4	2.32 (0.63–5.93)
Nonmalignant respiratory disease (460–519)	86	0.91 (0.73–1.12)
Ischemic heart disease (410–414)	456	1.09 (1.00–1.20)
Cerebrovascular disease (430–438)	69	0.96 (0.74–1.21)
Diabetes (250) (underlying cause)	26	1.18 (0.77–1.73)
Diabetes, multiple causes,§ 1960 and beyond	89	1.08 (0.87–1.33)
Accidents (800–930)	117	1.25 (1.03–1.50)
All causes (total)	1444	1.03 (0.97–1.08)
Mortality results for chloracne subcohort (n = 608); selective causes‖		
All cancers (140–208)	73	1.25 (0.98–1.57)¶
All digestive organs (150–159)	11	0.74 (0.36–1.33)
Larynx (161)	2	2.52 (0.30–9.10)
Lung (162)	30	1.45 (0.98–2.07)
Bladder (188, 189.3–189.9)	6	3.02 (1.43–8.52)
Lymphatic and hematopoietic (200–208)	6	1.13 (0.41–2.46)
Connective tissue and soft tissue (171)	3	11.32 (2.33–33.10)
Ischemic heart disease (410–414)	92	1.17 (0.94–1.44)
Diabetes (250)	4	1.06 (0.29–2.71)
All causes (total)	271	1.11 (0.98–1.25)

*ICD-9 = International Classification of Diseases, 9th Revision; SMR = standardized mortality ratio; and CI = confidence interval.

†Numbers do not necessarily add up to the expected totals because data on some diseases are not included.

‡Comparison rates were available only since 1960.

§Multiple causes based on any mention on the death certificate, not just underlying cause.

‖Person-years at risk (one person-year at risk = one person followed for 1 year) began at time of diagnosis of chloracne. Of the 608 men with chloracne, 393 were also in the exposure-level subcohort.

¶The 393 men with chloracne also in the exposure-level subcohort had an overall cancer SMR of 1.36 (95% CI = 0.98–1.84), increasing to 1.68 (95% CI = 1.19–2.30) in the two highest septiles of cumulative exposure (exposure score >5740).

with chloracne but lacked detailed work history and, hence, were not in the exposure-level subcohort. These men may have been exposed only briefly during cleanup of accidents. For those who had detailed work history and were in the exposure subcohort (n = 393), the SMR for all cancers combined was 1.36 (95% CI = 0.98–1.84), increasing to 1.68 (95% CI = 1.19–2.30) for those in the two highest cumulative exposure septiles (cumulative exposure score >5740). A test for trend in SMR for all cancers combined with increasing exposure for these men was not statistically significant ($P = .12$) with untransformed cumulative exposure but was statistically significant when the logarithm of cumulative exposure was used ($P = .02$).

Table 2 presents the life table results by estimated cumulative exposure level in the exposure-level subcohort. Statistically significant positive linear trends of increasing disease with increasing exposure occur for all cancers ($P = .02$) and lung cancer ($P = .05$). The SMR trend for heart disease fell short of statistical significance ($P = .14$). These trends are not monotonic (they do not show a steady increase in rate ratio with each increasing category of increasing exposure), but the higher SMRs generally do occur in the highest exposure categories. All cancers with a 15-year lag time also showed a statistically significant positive trend ($P = .02$) with cumulative exposure and an even stronger trend with the logarithm of cumulative exposure ($P = .002$).

Excess cancer risk was confined largely to those with the highest estimated cumulative exposure (top two septiles, cumulative exposure score >5740) and was not specific to particular sites. The SMR for all cancers in this group was 1.46 (95% CI = 1.15–1.82), based on 78 cancers. The two largest categories of cancers, respiratory cancers (ICD 161–165) and digestive cancers (ICD 150–159), showed similar elevations (SMR = 1.67 [95% CI = 1.16–2.34] and SMR = 1.41 [95% CI = 0.85–2.20]), based on 19 and 34 cancers, respectively. Hematopoietic cancers did not show an elevation, but there were few deaths in this category (three observed and 4.8 expected).

SMRs for all cancers in this exposure-level subcohort also showed increasing trends with simple duration of exposure, although these trends were somewhat less monotonic than those with increasing cumulative exposure. The SMRs for all cancers by increasing septile of duration of exposure were 1.10, 0.86, 1.01 1.11, 1.48, 1.15, and 1.56 (P for linear trend = .01). For duration with a 15-year lag time, the SMRs by septile of duration of exposure were 1.09, 0.86, 1.14, 1.14, 2.03, 1.27, and 1.39 (P for linear trend = .16).

Table 3 presents results for a Cox regression analysis using an internal referent group. These analyses again indicated higher rate ratios for cancer (no lag) and heart disease in the higher exposure categories, with tests for trend based on the categorical data giving values of $P = .10$ and $P = .05$, respectively. The trend for heart disease was strengthened with the use of the logarithm of cumulative exposure. There was a statistically significant negative trend between diabetes risk (any

Table 2. Life table results for the exposure-level subcohort: standardized mortality ratios (SMRs) (No. of observed deaths in parentheses) by cumulative exposure scores (in brackets) for selected causes, with the U.S. population in general as referent*

Death category	SMR (No. of observed deaths) Septile 1 [0 to <19]	Septile 2 [19 to <139]	Septile 3 [139 to <581]	Septile 4 [581 to <1650]	Septile 5 [1650 to <5740]	Septile 6 [5740 to <20 200]	Septile 7 [⩾20 200]	Two-sided *P* for trend CE	LCE
Cumulative exposure score, analyses with no lag									
All cancers	1.14 (34)	1.15 (39)	0.85 (29)	1.10 (36)	1.15 (40)	1.34 (38)	1.60† (40)	.02	.10
Lung cancer	1.06 (11)	1.07 (13)	0.82 (10)	0.78 (9)	1.12 (14)	1.47 (15)	1.65 (15)	.05	.14
Ischemic heart disease	0.93 (29)	1.00 (39)	1.05 (45)	0.97 (42)	1.10 (48)	1.20 (44)	1.28 (43)	.14	.12
Diabetes (underlying cause)	1.87 (4)	2.17 (5)	1.36 (3)	0.92 (2)	1.33 (3)	1.10 (2)	0 (0)	.10	.09
	SMR (No. of observed deaths)							Two-sided *P* for trend	
Death category	Septile 1 [0 to <39]	Septile 2 [39 to <224]	Septile 3 [224 to <791]	Septile 4 [791 to <2120]	Septile 5 [2120 to <6140]	Septile 6 [6140 to <15 800]	Septile 7 [⩾15 800]	CE	LCE
Cumulative exposure score, analysis with 15-y lag time‡									
All cancers	0.98 (67)	0.90 (27)	1.14 (31)	1.18 (30)	1.33 (34)	1.69§ (33)	1.54‖ (34)	.02	.002
Lung cancer	1.02 (23)	0.62 (7)	0.99 (10)	1.30 (12)	0.95 (9)	2.08¶ (15)	1.33 (11)	.20	.08

*CE = cumulative exposure, and LCE = logarithm of cumulative exposure; trend tests based on categorical data.

†Two-sided $P = .003$.

‡For the analyses after a 15-year lag time, a number of subjects were assigned 0 exposure due to the lag; these subjects were included in the lowest exposure category. For all cancers, their SMR was 0.82 (33 observed), and for lung cancer, their SMR was 1.06 (13 observed). Cut points for the analyses after a lag time were based on septiles of cumulative exposure after a 15-year lag time for all decedents with a dose above 0.

§Two-sided $P = .003$.

‖Two-sided $P = .01$.

¶Two-sided $P = .007$.

Table 3. Cox regression results for the exposure–level subcohort: rate ratios (95% confidence interval [CI]) by cumulative exposure score category (in brackets), with an internal referent*,†

Death category	Rate ratio (95% CI) Septile 1 [0 to <19]	Septile 2 [19 to 139]	Septile 3 [139 to <581]	Septile 4 [581 to <1650]	Septile 5 [1650 to <5740]	Septile 6 [5740 to <20 200]	Septile 7 [⩾20 200]	Two-sided *P* for trend CE	LCE
Unlagged cumulative exposure score									
All cancers	1.00‡	0.99 (0.62–1.58)	0.71 (0.43–1.19)	0.93 (0.57–1.51)	0.96 (0.60–1.53)	1.12 (0.69–1.81)	1.33 (0.82–2.13)	.10	.71
Ischemic heart disease	1.00‡	1.23 (0.75–2.00)	1.34 (0.83–2.18)	1.30 (0.79–2.13)	1.39 (0.86–2.24)	1.57 (0.96–2.56)	1.75 (1.07–2.87)	.05	<.001
Diabetes (multiple causes) (n = 55)	1.00‡	1.27 (0.49–3.33)	0.92 (0.33–2.53)	0.81 (0.28–2.30)	0.98 (0.36–2.65)	0.72 (0.23–2.21)	0.54 (0.15–1.89)	.02	.12
	Rate ratio (95% CI)							Two-sided *P* for trend	
Death category	Septile 1 [0 to <39]	Septile 2 [39 to <224]	Septile 3 [224 to <791]	Septile 4 [791 to <2120]	Septile 5 [2120 to <6140]	Septile 6 [6140 to <15 800]	Septile 7 [⩾15 800]	CE	LCE
Cumulative exposure score, after a 15-y lag time									
All cancers	1.00‡	1.00 (0.62–1.59)	1.29 (0.83–2.00)	1.38 (0.89–2.14)	1.43 (0.92–2.20)	1.88 (1.22–2.91)	1.76 (1.14–2.72)	.05	<.001
Lung cancer	1.00‡	0.75 (0.31–1.81)	1.20 (0.56–2.57)	1.56 (0.75–3.22)	1.12 (0.51–2.46)	2.55 (1.29–5.03)	1.62 (0.76–3.44)	.15	.03
Smoking-related cancer	1.00‡	0.87 (0.41–1.81)	1.16 (0.58–2.32)	1.58 (0.82–3.01)	1.19 (0.59–2.40)	2.43 (1.31–4.49)	1.65 (0.85–3.22)	.12	.02
All other cancers	1.00‡	1.09 (0.60–1.97)	1.39 (0.78–2.46)	1.24 (0.67–2.26)	1.61 (0.92–2.81)	1.49 (0.80–2.76)	1.85 (1.04–3.27)	.04	<.001

*All models were controlled for year of birth (quartiles) and age (the time variable). Cut points for categorical analyses were based on septiles of unlagged or lagged cumulative exposure of decedents (decedents with >0 dose for lagged analyses). For lagged analyses, the referent includes those with 0 exposure due to lag. The trend test was based on categorical data.

†CE = cumulative exposure, and LCE = logarithm of cumulative exposure.

‡Referent.

mention on the death certificate) and cumulative exposure.

When the cancer data were analyzed after a 15-year lag time, there were statistically significant positive trends in the categorical data between both cumulative exposure and the logarithm of cumulative exposure for all cancers and all cancers not related to smoking. Trends were more pronounced with the logarithm of cumulative exposure compared with untransformed cumulative exposure.

The best fitting model for all cancers used a lag time of 15 years, whereas the best fitting model for heart disease used no lag time. The best fit for both cancer and heart disease that used a continuous exposure variable was provided by the logarithm of cumulative exposure compared with cumulative exposure itself, average cumulative exposure (cumulative exposure divided by duration), or a quadratic model with cumulative exposure. The coefficients for logarithm cumulative exposure were statistically significant for heart disease, all cancers (15-year lag time), smoking-related cancers (15-year lag time), and non-smoking-related cancers (15-year lag time) ($P = .01$, $<.001$, .004, and .005, respectively), whereas the coefficients for cumulative exposure itself were not ($P = .33$, .60, .56, and .24, respectively).

The lack of apparent linear trend in cancer with untransformed cumulative exposure, as a continuous variable, was largely a product of the extreme skewness of the data. The cumulative exposure score ranged from 0.002 to more than 1 558 400; the median was 125, the mean was 10 019, and the coefficient of variation was 6.1. Without a logarithmic transformation, those workers with the very highest exposures would have to have a very high cancer risk so that a linear trend with cumulative exposure would not be flattened. A stronger trend with the logarithm of cumulative exposure indicates a sublinear trend with cumulative exposure at high levels of exposure. To examine the cancer risk at higher exposures, we subdivided the upper septile into two parts by the median exposure in an analysis of all cancers (15-year lag time). Both halves of the upper septile showed an elevated cancer risk (rate ratio = 1.65 [95% CI = 0.93–2.94] for the lower half and rate ratio = 1.86 [95% CI = 1.09–3.15] for the upper half), indicating no drop in risk for those with the highest exposure (the top 7%). To explore the influence of those workers with the very highest exposures on the statistical significance of cumulative exposure as a continuous variable, we also analyzed the data after deleting those with highest 1% of exposure values (exposure score >185 000). With these subjects deleted from the analysis, for example, the coefficient for cumulative exposure was statistically significant for all cancers and for all cancers analyzed after 15 years ($P = .006$ and $P = .02$, respectively). These subjects with the very highest doses were generally those who worked with highly contaminated waste products, and these untypical exposures may have been more subject to exposure misclassification.

Findings for smoking-related cancers were unchanged when subjects with bladder cancers (known to be at excess at one plant due to 4-aminobiphenyl exposure) were omitted. Models using duration of exposure fit the data about as well as logarithm of cumulative exposure for cancer but considerably less well for heart disease.

To investigate plant-specific exposure–response trends, we fit a model with a term for the exposure–response relationship at each plant. For all cancers, this model statistically significantly improved the fit ($P = .05$) over a model with a single estimated exposure–response relationship, indicating that there was evidence for interaction between plant and exposure–response relationship (some of this interaction was due to plant 11, which did not show a positive dose–response relationship but in which virtually all subjects had very low exposure). We therefore calculated a random-effects measure *(24)*, a weighted average of plant-specific exposure–response coefficients that included a variance component for heterogeneity across plants. The point estimate for the random-effects measure (0.0422; 95% CI = 0.0181–0.0661) was virtually the same as the overall estimated exposure–response coefficient (0.0453; 95% CI = 0.0198 to 0.0708).

We also ran some models stratified on plant, considering plant as a confounder. These models led to virtually no change in the effect of logarithm of cumulative exposure (15-year lag time) on all cancers ($P<.001$). For heart disease (no lag time and logarithmic-transformed exposure), stratification on plant led to a 35% decrease in the exposure–response coefficient and a corresponding higher P value ($P = .15$). However, the plant is a surrogate for exposure level (Fig. 1 shows large differences in exposure levels across plants), and it might be expected that stratification on plant might decrease estimated exposure–response trends for this reason. Therefore, we believe it is preferable to not stratify on plant.

DISCUSSION

This study is, to our knowledge, the first time that quantitative exposure–response trends have been estimated for the largest and most highly exposed cohort of workers exposed to TCDD. The development of a job-exposure matrix permitted us to quantitatively estimate cumulative exposure. Our results show that workers with the highest estimated levels of TCDD exposure had a higher rate of all cancers combined, due to a generalized increase rather than an excess at one or two specific sites. Our results also support other recent results in the literature for three other cohorts of industrial workers with high exposures to TCDD.

Lung cancer has been associated with TCDD exposure in other highly exposed cohorts, as well as this one *(1)*. Smoking is likely to partly confound an overall lung cancer association comparing our cohort with the U.S. population; limited smoking data on a sample of 223 workers from two plants suggested that expected lung cancers should be increased about 5% based on increased smoking by the workers versus the U.S. comparison population *(7)*. However, such confounding is less likely to be important in exposure–response analyses in which workers with a high exposure are compared with workers with a low exposure. Asbestos, present in most industrial settings, likewise might be expected to have some confounding effect on an overall association (particularly for maintenance workers) but again less in an exposure–response analysis. We found no deaths from asbestosis in the cohort. Inspection of death certificates coded as cancer did reveal three subjects with mesotheliomas; two subjects were pipefitters with long-term employment (with presumed asbestos exposure) and one subject was a chemical packer/dispatcher who worked 13 years in our cohort (and who may have had asbestos exposure elsewhere).

It is possible that other chemicals acted as confounders and were responsible for increases in cancer rates in this cohort, given that workers in chemical plants can be exposed to a wide range of toxic substances. However, this would require a high correlation between these unspecified chemical exposures and the cumulative exposure to TCDD across many different plants, a rather stringent requirement that is unlikely to be fulfilled. In the entire cohort, the correlation between the duration of employment (a possible marker of cumulative exposure to other chemicals) and the cumulative TCDD exposure score was only .42, which is not extremely high (some corre-

lation is expected because the duration of TCDD exposure is a component of the cumulative exposure score).

Cox regression, using an internal comparison group with low exposure, found a statistically significant positive trend between all cancers (after a 15-year lag time) and cumulative exposure. Similar trends were present both for smoking-related cancers and non-smoking-related cancers, suggesting that the cancer findings were not limited to an interaction between TCDD and smoking. The finding of stronger trends with the logarithm of cumulative exposure rather than cumulative exposure itself indicates that the exposure–response trend is sublinear at very high doses, which in our data was probably a reflection of the extreme skewness of the exposure data.

The finding that the best lag time was 15 years (marginally better than a 10-year lag time) is consistent with current views that TCDD acts as both an initiator and promoter *(25)*. Were TCDD to act as an initiator only, one might expect a longer lag of 20 years or more before the development of most tumors. Were TCDD to act as a promoter only, one might expect little or no lag. Because 1) there is still uncertainty about the basic biology of TCDD carcinogenesis, 2) our epidemiologic estimates of exposure are crude approximations of biologically relevant dose, and 3) statistical evidence is weak for favoring one lag time over another, we suggest that not too much interpretative weight be given to a finding that one particular lag period versus another provides a slightly better model.

For ischemic heart disease, there was only a modest trend of increasing SMRs with increasing exposure; the SMR for the highest category was 1.28 (95% CI = 0.92–1.72). However, internal analyses using Cox regression found statistically significant exposure–response trends. No lag time for heart disease was indicated in the Cox regression analysis, suggesting that any possible mechanism (e.g., an alteration of lipid profiles) occurred simultaneously with exposure. Because TCDD persists for a long time in the tissues [half-life, 8.7 years *(26)*], TCDD would be present for many years after exposure ceased, possibly resulting in a long-term effect.

We found no excess mortality from diabetes in the cohort and found a negative exposure–response trend for diabetes in the exposure-level subcohort. This finding conflicts with some recent studies of morbidity from diabetes, particularly the positive findings for diabetes in the Operation Ranch Hand cohort *(15)*, which was less heavily exposed than the cohort in our study. Death certificate data, even including contributory causes, may be inadequate to study diabetes *(27)*, and we had less power to detect exposure–response trends for this outcome than for our other outcomes. Alternatively, diabetes may in fact be unrelated to TCDD exposure.

In summary, we have extended follow-up of this TCDD-exposed cohort for 6 years. No new soft tissue sarcomas were observed. Mortality from non-Hodgkin's lymphoma, another cancer thought to be related to TCDD exposure, was unremarkable. SMR analyses using an external referent showed a statistically significant positive trend for cancer mortality with increasing exposure, with a 60% excess of mortality for all cancers combined in the highest exposure group. The excess of all cancers in those subjects with highest exposure was not specific for any type of cancer, paralleling other recent studies. Internal exposure–response analyses confirmed the positive exposure–response trend for cancer and also showed a statistically significant positive trend in risk of death from ischemic heart disease with increasing exposure, in conformity with the recent literature. We did not find a positive exposure-response trend with diabetes, which has been associated with TCDD in some studies. With regard to the excess of all cancers combined observed in the workers with the highest exposure, it should be noted that these workers had serum TCDD levels that were likely to have been two to three orders of magnitude higher than serum levels of the general public and, thus, similar to the levels that caused cancer in animals.

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