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Original Contribution

Mortality Rates Among Trichlorophenol Workers With Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin

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The authors examined 1,615 workers exposed to dioxins in trichlorophenol production in Midland, Michigan, to determine if there were increased mortality rates from exposure. Historical dioxin levels were estimated by a serum survey of workers. Vital status was followed from 1942 to 2003, and cause-specific death rates and trends with exposure were evaluated. All cancers combined (standardized mortality ratio (SMR) = 1.0, 95% confidence interval (CI): 0.8, 1.1), lung cancers (SMR = 0.7, 95% CI: 0.5, 0.9), and nonmalignant respiratory disease (SMR = 0.8, 95% CI: 0.6, 1.0) were at or below expected levels. Observed deaths for leukemia (SMR = 1.9, 95% CI: 1.0, 3.2), non-Hodgkin lymphoma (SMR = 1.3, 95% CI: 0.6, 2.5), diabetes (SMR = 1.1, 95% CI: 0.6, 1.8), and ischemic heart disease (SMR = 1.1, 95% CI: 0.9, 1.2) were slightly greater than expected. No trend was observed with exposure for these causes of death. However, for 4 deaths of soft tissue sarcoma (SMR = 4.1, 95% CI: 1.1, 10.5), the mortality rates increased with exposure. The small number of deaths and the uncertainty in both diagnosis and nosology coding make interpretation of this finding tenuous. With the exception of soft tissue sarcoma, the authors found little evidence of increased disease risk from exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin.

dioxins; neoplasms; phenols; sarcoma; tetrachlorodibenzodioxin

Abbreviations: CI, confidence interval; IARC, International Agency for Research on Cancer; SMR, standardized mortality ratio; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TCP, 2,4,5-trichlorophenol.

The dioxin, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), is classified by the International Agency for Research on Cancer (IARC) as a known human carcinogen on the basis of animal studies and mechanistic information, but the epidemiology data were judged to be limited (1). Increased risk of all cancers combined, lung cancer, non-Hodgkin lymphoma, and soft tissue sarcoma was seen in some epidemiology studies but not in all (1). Some noncancer effects, such as type 2 diabetes, ischemic heart disease, and nonmalignant respiratory disease, have also been associated with human TCDD exposures in some studies (2–5).

Some of the highest measured exposures to TCDD occur among persons exposed to 2,4,5-trichlorophenol (TCP). This dioxin is an unwanted contaminant in TCP that was most often used to make the pesticide, 2,4,5-trichlorophenoxyacetic acid (2,4,5-T). Because of concerns about TCDD in 2,4,5-T, the United States terminated its use, and trade of 2,4,5-T was restricted internationally. Workers at The Dow Chemical Company site in Midland, Michigan, made TCP from 1942 to 1979 and 2,4,5-T from 1948 to 1982. As reported previously, 12% of these workers developed chloracne, an acute skin condition, presumably due to TCDD exposure (6). However, cancer rates were generally at expected levels (7). Recently, we completed an extensive dioxin serum evaluation of these workers (8). In the present study, we used these serum dioxin evaluations to develop historical TCDD exposure estimates for all TCP and 2,4,5-T workers, updated vital status from the previous study, and evaluated the risk of cancer and noncancer mortality with regard to TCDD exposure levels. To our knowledge, this is the largest single-plant group of TCP or 2,4,5-T workers ever studied for the health effects of TCDD, and no other group has been followed so long (1942–2003).

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MATERIALS AND METHODS

We identified 1,615 workers who worked 1 or more days in a department with potential TCDD exposure. Person-years at risk were accumulated from January 1, 1942, or from the date at which a TCP or a 2,4,5-T department assignment first appeared in a worker's job history, whichever was later, and continued to the date of death or through the end of follow-up, December 31, 2003. We subsequently refer to this group of 1,615 as the TCP workers. Death certificates were obtained from the states in which the employees died and coded to the *International Classification of Diseases* revision in effect at the time of death. This study conduct was pursuant to review and oversight by a human subjects review board in Midland, Michigan.

A serum evaluation of a 17% sample (280 of 1,615) of the study population indicated that TCDD levels were greater than those of unexposed workers or the background levels in the community (8). We used these serum dioxin levels to produce a model to estimate historical exposure levels of TCDD for all the 1,615 workers, as described in detail elsewhere (9). Briefly, we used a qualitative exposure characterization from an earlier study to group all TCP-exposed jobs into 1 of 4 similarly exposed groups (10). This qualitative exposure assessment was derived from detailed work history, industrial hygiene monitoring, and the presence of chloracne cases among groups of workers. We selected a sample of workers on the basis of time spent in each group, drew blood from 280 former TCP workers, and measured the levels of dioxins, furans, and polychlorinated biphenyls (8). We used a simple 1-compartment, first-order pharmacokinetic model and assumed elimination rates as previously estimated from a worker population (11). We integrated the pharmacokinetic model with the work history information detailing dates of assignment to jobs in each of the 4 groups and determined the average TCDD dose associated with jobs in each group, after accounting for the presence of background exposures estimated from the residual serum TCDD concentration in the sampled individuals. A pharmacokinetic model applied job-specific dose rates from the sampled workers to the work history of each member of the entire cohort to estimate time-dependent serum concentration profiles for TCDD. The area under the curve for TCDD was used to represent the cumulative workplace dioxin exposure above background at any point in a worker's career.

One hundred and ninety-six of the 1,615 TCP workers also had potential exposure to pentachlorophenol. Although pentachlorophenol does contain dioxin contaminants, significant levels of TCDD are not found in pentachlorophenol (1). We examined the TCP workers with and without the 196 pentachlorophenol workers.

Standardized mortality ratios for cause-specific mortality of the workers compared with the US population were calculated by using the OCMAP program (12). We also examined exposure-response trends in disease through a proportional hazards regression model with SAS PROC PHREG (SAS Institute, Inc., Cary, North Carolina), treating TCDD as a continuous linear predictor (13). For each model parameter, the procedure calculates a regression coefficient and standard error, a Wald chi-square statistic, a *P* value for the test with coefficient 0, and a hazard ratio and 95% confidence interval. Chi-square and *P* values are also provided for tests of linear hypotheses of parameter estimates. The time variable for the proportional hazards model was age, and all models included hire year and year of birth. Exposure was treated as a time-dependent variable. The causes of death for exposure-response analyses were selected on the basis of findings from previous studies or if the standardized mortality ratios were high in our study (3, 5, 14–18).

RESULTS

Vital status follow-up was complete for all but 2 workers (6.6 person-years lost to follow-up), and we obtained 661 death certificates for the 662 known decedents. The mean age at start of follow-up was 29.6 years, and the mean duration of follow-up was 36.4 years. The cumulative exposures in our study ranged from 0.0002 to 112.3 parts per billion-years with a mean of 3.9.

There were 177 cancers (SMR = 1.0, 95% confidence interval (CI): 0.8, 1.1) among the 1,615 TCP workers shown in Table 1. Among the causes of death of a priori interest, there were fewer deaths than expected from lung cancers (SMR = 0.7, 95% CI: 0.5, 0.9) and nonmalignant respiratory disease (SMR = 0.8, 95% CI: 0.6, 1.0). There were more deaths from non-Hodgkin lymphoma (SMR = 1.3, 95% CI: 0.6, 2.5), leukemia (SMR = 1.9, 95% CI: 1.0, 3.2), soft tissue sarcoma (SMR = 4.1, 95% CI: 1.1, 10.5), diabetes (SMR = 1.1, 95% CI: 0.6, 1.8), and ischemic heart disease (SMR = 1.1, 95% CI: 0.9, 1.2) than expected. Table 1 also presents the standardized mortality ratios for trichlorophenol workers excluding the 196 workers who also had exposure to pentachlorophenol. There were 567 deaths (SMR = 0.9, 95% CI: 0.8, 1.0) among these 1,419 workers. The standardized mortality ratios for all causes of death are very similar to those for all TCP workers, so the subset is not further described separately.

Table 2 lists the hazard ratio estimates using the proportional hazards model for a 1-part per billion-year increase in cumulative exposure of TCDD for diseases of a priori interest. None of the causes of death examined showed a significant trend with cumulative TCDD except soft tissue sarcoma. The hazard ratio estimates for soft tissue sarcoma for a 1-part per billion-year increase is 1.060 (95% CI: 1.017, 1.106).

DISCUSSION

Among the strengths of this study are the relative size, the length of follow-up, and the technology used to assess exposures. Our cohort is the largest collection of TCP workers from a single plant ever studied for the health effects of TCDD, and our study has an exceptionally long follow-up period, 62 years, with an average individual follow-up of over 36 years. Exposure measures were derived from the most extensive serum dioxin evaluation ever conducted on industrial workers, coupled with complete work history records and detailed industrial hygiene monitoring data, and

Table 1. Standardized Mortality Ratios and 95% Confidence Intervals for Selected Causes of Death for Workers With Trichlorophenol Exposure, Midland, Michigan, 1942–2003

Death Category (ICD-10 Code)	All Trichlorophenol Workers			Trichlorophenol Workers Excluding 196 Workers Who Also Had Pentachlorophenol Exposure		
	No. of Deaths	Standardized Mortality Ratio	95% Confidence Interval	No. of Deaths	Standardized Mortality Ratio	95% Confidence Interval
All causes (A00–Y89)	662	0.9	0.9, 1.0	567	0.9	0.8, 1.0
All cancers (C00–C97)	177	1.0	0.8, 1.1	154	0.9	0.8, 1.1
Esophagus (C15)	5	1.0	0.3, 2.2	5	1.1	0.4, 2.5
Stomach (C16)	8	1.4	0.6, 2.7	7	1.4	0.6, 2.8
Large intestine (C18)	18	1.2	0.7, 1.8	15	1.1	0.6, 1.8
Rectum (C20, C21)	2	0.6	0.1, 2.1	2	0.7	0.1, 2.4
Biliary passages and liver (C22, C24)	2	0.5	0.1, 1.6	2	0.5	0.1, 1.9
Pancreas (C25)	6	0.7	0.2, 1.4	4	0.5	0.1, 1.3
Other digestive (C17, C19, C23, C26, C48)	2	1.4	0.2, 5.1	2	1.6	0.2, 5.8
Larynx (C32)	3	1.3	0.3, 3.9	3	1.5	0.3, 4.4
Bronchus, trachea, lung (C33, C34)	46	0.7	0.5, 0.9	41	0.7	0.5, 1.0
All other respiratory (C30, C31, C37–C39)	1	1.6	0.0, 9.1	1	1.8	0.0, 10.3
Prostate (C61)	21	1.4	0.9, 2.2	20	1.5	0.9, 2.4
Testes and other male genital (C60, C62, C63)	1	1.6	0.0, 8.9	1	1.8	0.0, 10.1
Kidney (C64, C65)	2	0.4	0.1, 1.5	2	0.5	0.1, 1.7
Bladder and other urinary (C66–C68)	6	1.2	0.5, 2.7	5	1.2	0.4, 2.7
Malignant melanoma (C43)	2	0.6	0.1, 2.3	1	0.4	0.0, 2.0
Central nervous system (C70–C72)	3	0.6	0.1, 1.7	2	0.4	0.1, 1.6
Hodgkin disease (C81)	2	1.8	0.2, 6.4	2	2.0	0.2, 2.3
Non-Hodgkin lymphoma[a] (C81)	9	1.3	0.6, 2.5	8	1.3	0.6, 2.6
Leukemia and aleukemia (C91–C95)	13	1.9	1.0, 3.2	12	1.9	1.0, 3.4
Other lymphopoietic (C88, C90, C96)	2	0.6	0.1, 2.3	2	0.7	0.1, 2.6
Soft tissue sarcoma (C49)	4	4.1	1.1, 10.5	3	3.5	0.7, 10.2
Diabetes mellitus (E10–E14)	16	1.1	0.6, 1.8	15	1.2	0.7, 1.9
Cerebrovascular disease (I60–I69)	37	1.0	0.7, 1.4	29	0.9	0.6, 1.3
Ischemic heart disease (I20–I25)	218	1.1	0.9, 1.2	186	1.0	0.9, 1.2
Nonmalignant respiratory disease (J00–J99)	44	0.8	0.6, 1.0	39	0.8	0.5, 1.1
Ulcer of stomach and duodenum (K25–K27)	2	0.8	0.1, 2.9	1	0.5	0.0, 2.5
Cirrhosis of liver (K70–K74)	6	0.4	0.1, 0.8	6	0.4	0.2, 0.9
Accidents (V01–X59)	35	0.9	0.6, 1.3	29	0.9	0.6, 1.2
	Missing certificates, no.	Persons, no.	Person-years, no.	Missing certificates, no.	Persons, no.	Person-years, no.
	1	1,615	58,743	1	1,419	51,986

Abbreviation: ICD-10, *International Classification of Diseases*, Tenth Revision.
[a] Comparison rates available only since 1960.

Table 2. Hazard Ratio Estimates With 95% Confidence Intervals for a 1 Part Per Billion-Year Increase in Cumulative Exposure to 2,3,7,8-Tertachlorodiphenyl-*p*-dioxin Using a Proportional Hazards Model, Midland, Michigan, 1942–2003

Cause of Death	Parameter Estimate[a]	*P* Value for Chi-Square	Hazard Ratio	95% Confidence Interval
All cancers	0.00161	0.7762	1.002	0.991, 1.013
Lung	−0.00173	0.8853	0.998	0.975, 1.022
Prostate	0.01294	0.2950	1.013	0.989, 1.038
Leukemia and aleukemia	−0.12822	0.3384	0.880	0.677, 1.144
Non-Hodgkin lymphoma	0.01081	0.6773	1.011	0.961, 1.064
Soft tissue sarcoma	0.05872	0.0060	1.060	1.017, 1.106
Diabetes	0.00435	0.7864	1.004	0.973, 1.036
Ischemic heart diseases	−0.00106	0.8402	0.999	0.989, 1.009
Nonmalignant respiratory disease	−0.00357	0.7562	0.996	0.974, 1.019

[a] The time variable was age, and all models included hire year and birth year.

are corroborated by the presence of chloracne cases in the study population (6).

The 2 studies that exceed ours in size are compiled groups from multicentric studies and are not likely to be homogeneous with regard to exposures and other potential disease determinants; hence, they are subject to exposure misclassification and confounding. The exposure measures used in these investigations are either duration of employment (17) or serum dioxin estimates drawn from 2 plants of 8 in the study (3). Though less likely in our study, some exposure misclassification may have been introduced through grouping workers into similar groups or through the assumptions used in the pharmacokinetic modeling of TCDD uptake and elimination. An additional limitation is that our study group is still not large enough to provide precise mortality risk estimates for uncommon diseases. In several instances, such as for non-Hodgkin lymphoma, we cannot rule out the possibility of a small risk from exposure. As an alternative to mortality, we considered incidence analysis as a means to increase the power of detecting less common diseases. For instance, the background incidence of soft tissue sarcoma is almost double the mortality rate, and incidence data are known to be more accurate than death certificate diagnoses. However, because cancer registries are limited both geographically and temporally, accurate disease ascertainment in this cohort is not possible. The Michigan cancer registry, for example, has been in operation for only the last 24 years of our 63-year follow-up period.

Four deaths from soft tissue sarcoma (SMR = 4.1, 95% CI: 1.1, 10.5) were observed in our study. Soft tissue sarcoma is the cause of death initially associated with TCDD exposure (19–21). However, subsequent studies have not consistently found an excess for this cause. Soft tissue sarcoma is a somewhat arbitrary collection of tumors that, when coded from death certificates, often are subject to inadvertent misclassification (22). The coding rules for the *International Classification of Diseases* combine considerations of morphology, behavior, and anatomic site of the tumor origin, so that soft tissue sarcomas that originate in a visceral organ are coded to that organ and not to the soft tissue sarcoma category. Moreover, the accuracy of the death certificate for soft tissue sarcoma diagnoses is poor (22, 23). Of the 4 deaths in our study that specified soft tissue sarcoma as the underlying cause of death, 3 were described as malignant fibrous histiocytomas, and the fourth as an angiosarcoma of the scalp. Two of these deaths were cited in previous studies (7, 24), where it was reported that tissue examinations revealed 1 of these deaths to be a renal clear cell carcinoma and, thus, not in the soft tissue sarcoma category. This death had the highest TCDD exposure among the soft tissue sarcoma deaths. Although it is unlikely that misclassification of this disease occurs differentially in the exposed and the referent populations, reclassification of 1 or 2 deaths could dramatically impact risk estimates and exposure-response trends for uncommon diseases. The small number of soft tissue sarcomas in our study, the potential for misdiagnosis, the uncertainty of nosology coding, the diversity of histologic types, and the lack of similar findings in other studies argue for caution in assessing etiology for this tumor category (5, 14, 22, 25–27).

In contrast to 3 similar studies (3, 14, 25), our study found no overall increase in lung cancer risk among workers exposed to relatively high levels of TCDD. Compared with lung cancer rates in the US population, those in TCP workers were lower overall and displayed a decreasing trend with exposure. The lower standardized mortality ratio estimates could be due to reduced smoking among the TCP workers compared with the US population, which is also consistent with the observed lower risk for nonmalignant respiratory disease. However, it is less likely that the decreasing trends with exposure seen for both causes of death in the internal analyses could be attributed to differential smoking behavior. As with most occupational cohort studies, there was no assessment of smoking behavior for study subjects, so adjustment for potential confounding was not possible. However, given the low rates of lung cancer among these workers, the lack of an exposure response, and the relative homogeneity of the workers, it seems unlikely that confounding from smoking could be masking an effect.

Death rates for non-Hodgkin lymphoma and leukemia were slightly greater than expected in our study. Although non-Hodgkin lymphoma deaths have been greater than expected in some studies of workers exposed to dioxin, leukemia deaths were at expected levels in these same studies (3, 26). We found no association with exposure for either of these causes of death. Ischemic heart disease rates were slightly greater than expected in our study, which is consistent with some studies (3, 26) but not others (14, 28). Likewise, we observed slightly more diabetes deaths than expected, which is consistent with 1 large study (3), yet neither study found an increase in risk with exposure to TCDD. Occupational studies often find decreased rates of heart disease and diabetes as a result of the healthy worker effect, so we should be cautious in our interpretation. Regardless, there is little evidence of an association with TCDD exposure for non-Hodgkin lymphoma, leukemia, ischemic heart disease, or diabetes.

Of the 4 studies of industrial workers that used serum dioxin evaluations to estimate exposures, each found increased total cancer rates associated with increasing exposure to TCDD (14, 25, 26, 29, 30). However, our study found cancer rates at levels slightly less than expected and no trend with exposure. It is unlikely that the exposure levels in our study were lower than in the others, since such a large portion of our study group developed chloracne. Considering individual cancer sites, there seems to be no consistency across the 4 previous studies. For instance, exposure responses were reported for lung cancer and digestive cancer in the study of Ott and Zober (14), lung cancer in the studies of Steenland et al. (3) and Hooiveld et al. (26), and no specific cancer sites in the study of Flesch-Janys et al. (25). In our study, we found a trend with soft tissue sarcoma but no trend with the other cancers or all cancer combined.

A recent IARC evaluation posited a ''pleuripotential'' mode of action manifested as a causal relation between TCDD and all cancers combined in the absence of a consistent finding for any specific cancer site (1). Such an association has no precedent in epidemiology studies (31). Some have argued that dioxin may be a late-stage carcinogen producing excess cancers at many organ sites (32). Although this hypothesis may explain the increased risk with all cancers combined, it does not explain the lack of consistency of specific cancer site findings across studies, because all late-stage carcinogens cause one or more specific cancers (31). Others have speculated that exposures other than dioxins at the various plants in the studies have resulted in different cancer risks at individual plants contributing to increased cancer risk overall (31, 33). This hypothesis has only been rarely studied in industrial workers exposed to TCDD.

The pleuripotential cancer theory of TCDD has led in part to the IARC classification of TCDD as a known human carcinogen (1). New studies and study updates since this evaluation have been judged to be either supportive or not supportive of this IARC assessment (31, 32). In our study, we find cancer rates at expected levels and no trend with exposure, an outcome in common with those of 2 recent studies with high TCDD exposure (5, 27). These new research findings question the IARC 1997 classification of TCDD as a known human carcinogen based on an excess of all cancers combined.

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