MORTALITY IN WOKERS EXPOSED TO 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN AT A TRICHLOROPHENOL PLANT IN NEW ZEALAND

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Introduction

The International Agency for Research on Cancer (IARC) classifies 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) as carcinogenic to humans based on animal studies and mechanistic information. However, the human evidence on carcinogenicity was judged to be limited since increased cancer risk was seen in some but not all studies.[1] Some workers at the Dow AgroSciences site in New Plymouth, New Zealand have been exposed to TCDD from the manufacture of 2,4,5-trichlorophenol (TCP) and 2,4,5-trichlorophenoxy acetic acid (2,4,5-T). An international study of 18,910 phenoxy herbicide sprayers and production workers from 10 countries included workers from the New Plymouth site. The herbicide sprayers and production workers in this study together had total cancer rates at expected levels, but deaths from soft-tissue sarcoma and non-Hodgkin's lymphoma (NHL) were greater than expected.[2,3]

Subsequently, the workers from the New Plymouth site were studied separately with further follow-up to the end of 2000.[4] The authors concluded in that study that there was "excess cancer mortality" among these New Plymouth workers with more multiple myeloma deaths observed than expected (3 deaths observed versus 0.5 expected). However, soft tissue sarcoma deaths (0 observed versus 0.2 expected) and non-Hodgkin's deaths (1 observed versus 1.1 expected) were below expected levels.

Given the on-going debate about whether dioxin increases human cancer risk[5,6] and concerns raised in a previous study about increased cancer risk from dioxin at this site,[4] we expand and update the previous studies by including additional exposed and unexposed workers, constructed exposure estimates based on a serum dioxin evaluation of a sample of both exposed and unexposed workers, and extended vital status follow-up an additional 4 years

Materials and Methods

The work history records were assembled from paper and automated payroll records for current and past worker at the New Plymouth site. The study group includes all men and women working any time between January 1, 1969, the first date of complete work records for the site, and November 1, 1988, the last day 2,4,5-T was used at the site or at the field station. We identified 1,599 individuals working at these two sites who met these criteria. For each worker, vital status follow-up begins on the first day of employment at New Plymouth site or January 1, 1969, whichever came later. Each subject's vital status was then followed until the earliest of the following: the subject is known to have died, the date of the subject's last verifiable living status, the subject emigrated from New Zealand, or the end of the study period, December 31, 2004.. The New Zealand Health Information System (NZHIS) Mortality Collection provided the underlying cause of death for all deaths identified in our study.

We collected serum TCDD from 22% of the 1,599 workers in this study (346/1,599). This serum study has been described in detail elsewhere. We used the current serum TCDD levels to develop TCDD exposure estimates for all 1,599 workers at the New Plymouth site. The exposure estimation process for this study also has been described in detail elsewhere. Standardized mortality ratios (SMRs) and 95% confidence intervals (95%CI) for cause-specific mortality in exposed and unexposed workers compared to the New Zealand population were calculated using OCMAP.[7] The exposure-response analyses were based on 4 categories for cumulative TCDD exposure and were constructed by having equal numbers of total deaths in each category. We also examined trends for diseases using a proportional hazards model with the same exposure cutpoints used in the SMR analyses. The proportion hazards model was applied to the disease categories of all cancers combined, lung cancer, ischemic heart disease and diabetes as was done in a previous TCDD study.[8] The time variable for the proportional hazards model was age.

Results and Discussion

Table 2 presents the SMRs and 95%CIs for 1,134 potentially TCDD exposed workers and the 465 workers with no known workplace exposure. There were 196 deaths among the exposed workers. All cause mortality among exposed workers is similar to the New Zealand population (SMR=1.0, 95%CI 0.9-1.2). For the cancers that have been related to high dioxin exposures in some studies[1,9], cancer of the lung was below expected levels (SMR=0.8, 95%CI 0.4-1.5), while all cancers combined (SMR=1.1, 95%CI 0.9-1.4), soft tissue sarcoma (SMR=3.4, 95%CI 0.1-19.5), and NHL (SMR=1.6, 95%CI 0.3-4.7) were greater than expected. For other cancer sites (not shown) the SMRs were close to expected levels. For other non-cancers that have also been related to high dioxin exposures in some studies,[8,10] diabetes was less than expected (SMR=0.7, 95%CI 0.2-2.2), and ischemic heart disease was slightly greater than expected (SMR=1.1, 95%CI 0.9-1.5).

There were 51 deaths among 465 unexposed workers. All causes of death (SMR=0.8, 95%CI 0.6-1.1) and all cancers combined (SMR=0.8, 95%CI 0.4-1.3) were less than expected. Lung cancers were at expected levels (SMR=1.0, 95%CI 0.1-2.5) and one death from non-Hodgkin's lymphoma occurred (SMR=1.6, 95%CI 0.0-8.7). There were no deaths from soft tissue sarcoma, Hodgkin's disease or multiple myeloma. Deaths from diabetes were slightly greater than expected (SMR=1.4, 95%CI 0.2-5.2) and deaths from ischemic heart disease were less than expected (SMR=0.9, 95%CI 0.5-1.5).

Table 2. Standardized mortality ratios (SMRs) and 95% confidence intervals (95% CI) for selected causes of death for TCDD exposed workers and workers with no known workplace exposure.

Death category (ICD-10 code)	**Exposed Workers**		**No Known Workplace Exposure**	
	Deaths	**SMR(95%CI)**	**Deaths**	**SMR(95%CI)**
All causes (A00-Y89)	196	1.0 (0.9-1.2)	51	0.8 (0.6-1.1)
All cancers (C00-C97)	61	1.1 (0.9-1.4)	15	0.8 (0.4-1.3)
Digestive organs and peritoneum (C15-C25)	22	1.3 (0.8-2.0)	5	0.9 (0.3-2.5)
Bronchus, trachea, lung (C33-C34)	11	0.8 (0.4-1.5)	4	1.0 (0.3-2.5)
Soft tissue sarcoma (C49)	1	3.4 (0.1-19.5)	0	0.0 (0.0-34.9)
Non-Hodgkin's lymphoma[1] (C82, C83.0-83.8, C84, C85.1-C85-9)	3	1.6 (0.3-4.7)	1	1.6 (0.0-8.7)
Diabetes mellitus (E10-E14)	3	0.7 (0.2-2.2)	2	1.4 (0.2-5.2)
Ischemic heart disease (I20-I25)	61	1.1 (0.9-1.5)	14	0.9 (0.5-1.5)
Persons	1,134		465	
Person-years	26,377		10,749	

[1] Comparison rates only available since 1960.

Table 3 presents SMRs by cumulative exposure levels to TCDD for 1,134 exposed workers for 9 selected causes of death. We observed no trend of increasing SMR with increasing exposure for any cause of death. We observed the highest SMRs in the highest exposure category for lung cancer (SMR=1.3, 95%CI 0.4-3.0) but the remaining categories of exposure all have SMRs less than one. There was one soft tissue sarcoma among exposed workers occurring in the 3rd highest exposure category. We also employed a proportional hazards model and found no increasing disease risk with TCDD exposure.

This study examined a large group of workers potentially exposed to dioxins from TCP and 2,4,5-T operations between 1969 and 1988. The exposures to TCDD have been verified by use of work history information to determine where and how long an employee worked in the job and a serum dioxin evaluation of a large sample of these employees to estimate past TCDD levels. Exposed workers in this study have TCDD levels that are well above New Zealand background levels. While there have been many studies which have examined cancer and disease risk from exposure to TCDD, several studies have used serum dioxin levels to estimate past exposures and examine cancer disease risk.[8,11-16] Studies which assess dioxin exposures based on serum evaluations are important for assessing causality because they confirm high dioxin exposure, determine which workers had the highest exposures, and allow exposure-response evaluations based on measured serum dioxin levels. The current study is of this type.

Table 3. Standardized mortality ratios (SMRs), number of observed deaths (obs), and 95% confidence intervals (95% CI) by cumulative area under the curve for 2,3,7,8-TCDD for selected causes of death with the New Zealand population as referent.

Death category	0-68.3 ppt-months* SMR(95%CI)[obs]	68.4-475.0 ppt-months* SMR(95%CI)[obs]	475.1-,085.7 ppt-months* SMR(95%CI)[obs]	2,085.8+ ppt-months* SMR(95% CI)[obs]
All causes	1.2(0.9-1.6)[49]	0.9(0.7-1.2) [49]	1.0(0.8-1.4) [48]	1.0(0.7-1.3) [50]
All cancers	1.3(0.7-2.1)[15]	0.9 (0.5-1.6) [14]	1.1 (0.6-1.8) [14]	1.2 (0.7-1.9) [18]
Digestive Organs	2.3(1.0-4.4)[8]	0.9 (0.2-2.2) [4]	0.7(0.3-2.1)[3]	1.5 (0.6-3.1) [7]
Bronchus, trachea, lung	0.8(0.1-2.8) [2]	0.9 (0.2-2.6)[3]	0.3 (0.1-1.7)[1]	1.3 (0.4-3.0)[5]
Soft tissue sarcoma	0.0(0.0-44.8)[0]	0.0(0.0-43.2)[0]	15.5(0.4-86.5)[1]	0.0(0.0-61.0)[0]
Non-Hodgkin's Lymphoma	2.3 (0.1-12.8) [1]	0.0 (0.0-7.1) [0]	2.4(0.1-13.2)[1]	2.1(0.1-11.5) [1]
Diabetes mellitus	2.4 (0.3-8.7) [2]	0.0(0.0-3.3)[0]	0.0(0.0-4.0)[0]	0.9(0.0-4.8)[1]
Ischemic heart disease	1.4(0.8-2.3)[14]	1.3(0.7-2.0)[18]	1.1 (0.6-1.8) [15]	0.9(0.5-1.6)[14]
Persons	1,061	668	363	162
Person-years	10,114	8,498	4,874	2,890

*The cumulative exposure cutpoints were chosen to place the same number deaths for all causes of deaths combined in each category.

Recent causal evaluations of dioxins and disease risk have focused on total cancers, lung cancer, ischemic heart disease, and diabetes. Of these diseases, increased total cancers and lung cancers are the most consistent finding in studies with high exposure.[1,8,12,13] The four previous worker studies which have used serum dioxin levels for exposure estimation each report a small increase in all cancers combined related to TCDD exposure levels but no particular cancer site has been consistently prominent across studies.[8,11-13] In our study, all cancers combined are at expected levels among exposed workers and we see no linear trend with increasing cumulative exposure. In fact, the relative risk estimates for all cancers combined are close to expected levels in each cumulative exposure category. It may be that TCDD exposures are lower in this study than in the NIOSH Dioxin Registry and this could explain why we observe no increasing cancer risk with exposure. However, another explanation for the differences between this study and the four previous studies could be other exposures adding to cancer risk at these other sites. Each of the four previous studies occurred at plants with many other exposures. For example, there was evidence of asbestos exposure and aromatic amines exposure in the NIOSH Dioxin Registry which could explain the increased risk of lung and bladder cancer observed in these studies.[5] The New Plymouth site, however, was a relatively new TCP operation with no known exposure to other potential carcinogens. Further, a relationship of all cancers combined with dioxin exposure across four studies with no particular cancer site consistently elevated across studies would be very unusual in occupational studies since all know human carcinogens cause one or more specific cancer types.[5] It could be the excess in all cancers combined seen in some studies is the result of exposures other than TCDD. Our findings provide some support for this view.

Lung cancer rates for all exposed workers were below expected levels and we found no trend of increasing risk with cumulative exposure. However, we did observe the highest relative risk for lung cancer in the highest cumulative exposure category. Based on the cross-sectional survey of tobacco use, this cumulative exposure category had the highest percentage of ever smokers (61%) compared to the other cumulative exposure categories groups with percentages ranging from 51 to 56%. These smoking data should be interpreted cautiously since we have smoking history on only a sample of workers, none of whom have developed lung cancer. Further, estimating smoking rates for the entire study population is difficult because smokers would be underreported in a cross-sectional survey since non-smokers would be overrepresented among surviving workers. Nevertheless, there is an indication that workers in the highest cumulative exposure category are more likely to be smokers than workers in the other categories. Thus smoking cannot be ruled out as a potential confounding exposure contributing to the higher lung cancer rates in this category. Given the low rates of lung cancer among exposed workers in general and the lack of an increasing trend with risk, we find little evidence in this study for TCDD increasing lung cancer risk.

This study of workers at a New Zealand site which made TCP and 2,4,5-T with exposure to TCDD found cancer rates and disease rates at expected levels. While the study is relatively large, and exposure well defined, we cannot rule out a small risk from TCDD exposure. However, we find no coherent evidence of increased cancer or disease risk related to TCDD exposures.

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