BMJ Open Cohort study of workers at a New Zealand agrochemical plant to assess the effect of dioxin exposure on mortality

David I McBride,¹ James J Collins,² Thomas John Bender,³ Kenneth M Bodner,³ Lesa L Aylward⁴

To cite: McBride DI, Collins JJ, Bender TJ, *et al.* Cohort study of workers at a New Zealand agrochemical plant to assess the effect of dioxin exposure on mortality. *BMJ Open* 2018;**8**:e019243. doi:10.1136/bmjopen-2017-019243

► Prepublication history and additional material for this paper are available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2017-019243>).

Received 19 August 2017
Revised 25 May 2018
Accepted 22 August 2018

© Author(s) (or their employer(s)) 2018. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

¹Department of Preventive and Social Medicine, University of Otago, Dunedin, New Zealand
²Saginaw Valley State University Center, Midland, Michigan, USA
³The Dow Chemical Company, Midland, Michigan, USA
⁴Summit Toxicology, Falls Church, Midland, Michigan, USA

Correspondence to

Dr David I McBride;
david.mcbride@otago.ac.nz

ABSTRACT

Objectives To describe how the exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) influenced mortality in a cohort of workers who were exposed more recently, and at lower levels, than other cohorts of trichlorophenol process workers.

Design A cohort study.

Setting An agrochemical plant in New Zealand

Participants 1,599 men and women working between 1 January 1969 and 1 November 1988 at a plant producing the herbicide 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) with TCDD as a contaminant. Cumulative TCDD exposure was estimated for each individual in the study by a toxicokinetic model.

Primary outcome measures Calculation of cause-specific standardised mortality ratios (SMRs) and 95% confidence intervals (95% CI's) compared those never and ever exposed to TCDD. Dose-response trends were assessed firstly through SMRs stratified in quartiles of cumulative TCDD exposure, and secondly with a proportional hazards model.

Results The model intercept of 5.1 ppt of TCDD was consistent with background TCDD concentrations in New Zealand among older members of the population. Exposed workers had non-significant increases in all-cancer deaths (SMR=1.08, 95% CI 0.86 to 1.34), non-Hodgkin lymphoma (SMR=1.57, 95% CI: 0.32 to 4.59), soft tissue sarcoma (one death) (SMR=2.38, 95% CI: 0.06 to 13.26), diabetes (SMR=1.27, 95% CI: 0.55 to 2.50) and ischaemic heart disease (SMR=1.21, 95% CI: 0.96 to 1.50). Lung cancer deaths (SMR=0.95, 95% CI: 0.56 to 1.53) were fewer than expected. Neither the stratified SMR nor the proportional hazard analysis showed a dose-response relationship.

Conclusion There was no evidence of an increase in risk for 'all cancers', any specific cancer and no systematic trend in cancer risk with TCDD exposure. This argues against the carcinogenicity of TCDD at lower levels of exposure.

INTRODUCTION

The International Agency for Research on Cancer (IARC) classifies 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) as a human carcinogen. The mechanistic evidence for this classification was multi-site action in animal studies, the strongest human evidence being an increase in risk for all cancers combined,

Strengths and limitations of this study

- A high proportion of workers were sampled and provided serum data.
- Cumulative dioxin exposure estimates allowed more valid comparisons than studies based on job titles, duration of or potential for exposure.
- The relatively small cohort reduced our ability to evaluate rare causes of death.
- Exposures were relatively recent, limiting assessment of causes of death with a long latent period.

although rates of lung cancer, soft tissue sarcoma and non-Hodgkin lymphoma were greater than expected in some studies.¹ The effects were found in early cohorts with high levels of exposure. However, there is still an ongoing debate about the consistency of the cancer findings across studies.²⁻⁴ Most of the effects were seen in workers producing or using 2,4,5-trichlorophenol (TCP) where TCDD is an unwanted contaminant. Since TCDD has a relatively long half-life in the human body, it is possible to estimate past exposure to TCDD from serum samples. This is a follow-up of workers with more recent exposure from the production or use of TCP at a New Zealand plant.⁵ TCDD exposure indices were based on serum dioxin measurements, thus adding biological monitoring data to assist the investigation of TCDD toxicity. We report on an additional 7 years of cohort mortality experience, in which an additional 102 deaths were observed.

METHODS

As described previously, work history records were assembled for current and past workers from the New Plymouth, New Zealand, plant and a nearby field station where 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), a herbicide made from TCP, was manufactured and occasionally field tested. The study group

included 1,599 men and women who worked at any time between 1 January 1969, the first date of complete work records for the site, and 1 November 1988, the last day 2,4,5-T was used at the plant or at the field station. For each worker, vital status follow-up began on the first day of employment at the New Plymouth site or 1 January 1969, whichever came later. Each subject's vital status was then followed until his or her known date of death, the date of last verifiable vital status, the date the subject emigrated from New Zealand or the end of the study period (31 December 2011), whichever was earliest.

The New Zealand Ministry of Health Mortality Collection, through notification from the Registrar of Births, Deaths and Marriages, was the ultimate source for assigning the underlying cause of death. The validity of the data is verified from a number of sources that included electronic hospital discharge data from the National Minimum Dataset Hospital Events, private hospital discharge notifications, the New Zealand Cancer Registry, the Ministry of Justice and Coronial Services, the Police, the NZ Transport Agency, Water Safety NZ, through media searches and from writing letters to certifying doctors, coroners and medical records officers in public hospitals. Vital status follow-up began with searches through personnel and pension records, and then from habitation and business indices, telephone records, electoral rolls, the internet, notices of deaths, name changes and marriages from births, deaths and marriages and other public databases, also involving personal contacts with subjects and relatives. Deaths recorded between 1969 and 1987 were identified by matching names and dates of birth to the Mortality Collection. Additional deaths up to 1990 were sought from the Registrar-General's Index to Deaths. After 1988, computerised and manual searches were performed by the MoH team using the National Health Index (NHI) number, unique to each individual and linked to the Mortality Collection.

Besides 2,4,5-T, other phenoxy herbicides had been manufactured at the site. These included 2,4-dichlorophenoxyacetic acid (2,4-D) from 1960 onwards; 4-chloro-2-methylphenoxyacetic acid (MCPA) from 1962 to the late 1990's and 4-(2-methyl-4-chlorophenoxy) butyric acid (MCPB) from 1971 to the late 1990s; and 2,2-dichloropropionic acid was imported as an active ingredient for the formulation of herbicide products. The only other feedstock with possible dioxin contamination was 2,4,6-trichlorophenol, imported, converted to the sodium salt on site and incorporated into a fungicide for use on pelts and hides.⁶ Other herbicides formulated or packaged at the site included picloram, atrazine, simazine, dicamba, phenmedipham and amitrole. Apart from these, products with other applications, such as surfactants, were manufactured at the site.

Workplace exposures were validated through discussion with long-term employees, taking into account job titles, tasks and activities, process changes and the results of past biological monitoring for TCP. Jobs from the same department, with the same exposure potential,

were classified into job exposure groups. Within these groups, exposure was classified as being continuous or intermittent. Jobs with continuous exposure were sub-classified into very low, low, medium or high groups. Intermittently exposed groups were classified as being exposed very infrequently, infrequently, once a month, once a week or once a day. Work histories indicated that 1,134 workers (71% of the total workforce of 1,599) had potential workplace exposure to TCDD. The remaining 465 workers, classified as 'never exposed', were either in administrative and support roles or in production jobs assessed as having negligible potential for TCDD exposure.

Through 2005 and 2006, a serum dioxin evaluation validated this assessment and estimated past exposures.⁷ In short, all current and former workers employed at the site during the study period and, for logistic and quality control purposes still living within 75 kilometres of the site, were asked to participate. Sixty-eight per cent of the eligible workers volunteered, 22% (346/1,599) of the total study population, yielding 346 serum samples. Seventy per cent (241/346) of the serum sample participants were exposed workers. Approximately 80 ml of blood was collected from each volunteer, allowed to clot, centrifuged and stored at -20°C awaiting laboratory analysis. The laboratory used high-resolution gas chromatography/mass spectrometry to determine the levels for 2,3,7,8-substituted dioxins and furans following the procedures described in EPA Method 8290, and Method 1668 for PCB measurement. When levels were below the limit of detection (LOD), the values were estimated by assuming a value of LOD/ $\sqrt{2}$.⁸ All results were lipid adjusted.

At the clinic visit, body mass index (BMI) was measured and a self-report exposure survey⁹ included questions about smoking: 'in your lifetime have you smoked 100 or more cigarettes,'; recent weight loss or gain of 10 kg or more; previous occupational history to assess other potential exposure to TCDD; and consumption of locally produced seafood, eggs and vegetables. Consuming local eggs showed some correlation with TCDD levels; however, consumption of local vegetables and fish did not. The main determinants were age, BMI and employment history.

The 2005 lipid-adjusted serum TCDD levels for workers with exposure to TCP or 2,4,5-T averaged 9.9 ppt.ⁱ The highest levels were found in the TCP operation workers (23.4 ppt), particularly those involved in a release in 1986 (37.9 ppt), a level which is well outside the maximum level (7 ppt) found in the serum of non-occupationally exposed New Zealanders.¹⁰ Unexposed workers averaged 4.9 ppt, which is similar to New Zealand background level of 3.9 ppt for persons of similar age. There were no cases of chloracne, a hallmark of very high TCDD exposure, in this study population.

ⁱ Equivalent to ng.kg⁻¹

Full details of the exposure modelling were the subject of an earlier report.¹¹ The work history records and serum data were used to estimate TCDD dose rates for each job exposure group, and because of the 7-year half-life of TCDD, this informed earlier exposure levels. There were two basic assumptions in the exposure reconstruction model: firstly that exposure for an individual job within a job exposure group could be modelled as a constant, consistent and average exposure rate in nanograms per year. Secondly, that the toxicokinetics of TCDD can be modelled as a first-order process with distribution in the body solely to adipose or lipid tissue. Age was a parameter in the model, the estimation of which involved the average TCDD dose rate for each job, the volume of distribution in adipose or lipid tissues and the elimination rate. The volume of distribution was estimated, at the time of serum sampling, using a formula for percent body fat accounting for age, sex and BMI and the elimination rate by age-specific and smoking-specific factors. Multiple linear regression estimated the dose rate associated with employment in specific job groups, the final model yielding a serum lipid versus time profile for each individual and contributing to an 'area under the curve' analysis. In effect, the latter allows the estimation of TCDD levels at discrete points in time, and the calculation of cumulative workplace TCDD exposure above background at any point in the worker's life after the time of first exposure at the site.

The model performance when compared with the actual serum data was relatively modest, producing an adjusted R^2 of 0.30. The model intercept of 5.1 ppt TCDD was consistent with background TCDD concentrations in New Zealand among older members of the population.¹⁰ The mean cumulative modelled TCDD at the end of follow-up was 1,218 ppt-months and the maximum was 46,988 ppt-months.

Cause-specific SMRs and 95% CIs were calculated using the Occupational Cohort Mortality Analysis Programme (OCMAP)¹² for workers ever exposed to TCDD at New Plymouth and workers never exposed, the expected number of cases being calculated from New Zealand national death rates. For ever exposed workers, we also stratified the SMR analyses by four cumulative exposure levels, chosen to place an approximately equal number of decedents per level, also examining risk for latencies of 0, 15, and 20 years. Exposure categories (0–75, 75–450, 450–2000, and >2000 ppt-months) were approximately log-normally distributed.

Using these categories, internal trends in mortality for exposed workers were examined using the SAS program PROC PHREG, the algorithm being based on the Cox proportional hazards model.¹³ To be consistent with the approximately log-normal categories applied to the SMR analyses, the dioxin exposures were log transformed. This log transformation provided the benefit of reducing the influence of outlying exposure estimates that could result from exposure misclassification.¹⁴

The same exposure categories were used in the proportional hazards model, allowing the examination of

dose-response relationships. We first examined risks in the individual exposure categories versus the lowest exposure category using unweighted indicator variables for each of the four categories in the model, calculating maximum likelihood estimate coefficients and 95% CIs for each. A P value for linear trend was provided by constructing orthogonal polynomial contrasts, computing one-degree of freedom Wald chi-square statistics and their associated P values. We then applied a continuous proportional hazards model, testing for trend using the natural log of cumulative exposure, P values being obtained by a chi-square test on the maximum likelihood estimate of the coefficient. This model was more powerful, not subject to the exposure misclassification inherent in stratification, but less sensitive to non-linear response patterns.

The models were applied to the disease categories of all deaths, all cancers combined, lung cancer, non-Hodgkin lymphoma, diabetes mellitus and ischaemic heart disease. Age was included as the time variable for the modelling, and exposure treated as a time-dependent variable.

Ethical oversight was sought, and approval received from, the Northern B Health and Disability Ethics Committee. The Ngai Tahu Research Consultation Committee advised us on the value of, and implications for, the project to New Zealand Māori.

Patient and public involvement

The study involved neither patients nor the public.

RESULTS

Of 1599 workers in the study, 163 migrated from New Zealand while 100 (6.3%) were lost to follow-up. There were 102 additional deaths observed, a total of 349. Table 1 presents the SMRs and 95% CIs for the 1,134 workers exposed to TCDD and 465 workers with no known workplace exposure.

There were 273 deaths observed in exposed workers (SMR=1.06, 95% CI 0.94 to 1.20). For the cancers that have been related to high dioxin exposures in some studies, cancer of the lung (SMR=0.95, 95% CI 0.56 to 1.53, observed 17) and prostate (SMR=0.60, 95% CI 0.16 to 1.53, observed 4) were below the expected levels, while all cancers combined (SMR=1.08, 95% CI 0.86 to 1.34, observed 84), soft tissue sarcoma (SMR=2.38, 95% CI 0.06 to 13.26, one observed case), Hodgkin's disease (SMR=6.80, 95% CI 0.82 to 24.55, observed 2), non-Hodgkin lymphoma (SMR=1.57, 95% CI 0.32 to 4.59, observed 3) and multiple myeloma (SMR=1.48, 95% CI 0.18 to 5.34, observed 2) were greater than expected. For the other cancer sites, the SMRs were close to those expected. For non-cancers that have also been related to high dioxin exposures in some studies,^{15 16} diabetes (SMR=1.27, 95% CI 0.55 to 2.50, observed 8) and ischaemic heart disease (IHD) (SMR=1.21, 95% CI 0.96 to 1.50, observed 81) were slightly greater than expected.

There were 76 deaths among 465 never exposed workers. The number of deaths from all causes (SMR=0.86,

Table 1 Standardised mortality ratios (SMRs) and 95% CIs for selected causes of death, TCDD ever exposed and never-exposed workers compared with the New Zealand population

Death category (International Classification of Disease Code)	Ever exposed		Never exposed	
	Deaths	SMR (95% CI)	Deaths	SMR (95% CI)
All causes (A00-Y89)	273	1.06 (0.94 to 1.20)	76	0.86 (0.68 to 1.07)
All cancers (C00-C97)	84	1.08 (0.86 to 1.34)	25	0.87 (0.56 to 1.28)
Buccal Cavity and Pharynx (C00-C14)	4	2.52 (0.69 to 6.44)	0	0.0 (0.0 to 8.22)
Nasopharyngeal (C11)	0	0.0 (0.0 to 19.51)	0	0.0 (0.0 to 72.01)
Digestive organs and peritoneum (C15-C25)	27	1.11 (0.73 to 1.62)	8	0.96 (0.42 to 1.89)
Oesophagus (C15)	4	1.69 (0.46 to 4.32)	1	1.45 (0.04 to 8.09)
Stomach (C16)	4	1.09 (0.30 to 2.80)	3	2.62 (0.54 to 7.67)
Large intestine (C18)	4	0.56 (0.15 to 1.44)	1	0.37 (0.01 to 2.06)
Rectum (C20-C21)	8	2.03 (0.88 to 3.99)	2	1.57 (0.19 to 5.68)
Biliary passages and liver primary (C22, C24)	3	1.33 (0.27 to 3.88)	0	0.0 (0.0 to 5.23)
Pancreas (C25)	4	1.20 (0.33 to 3.06)	0	0.0 (0.0 to 3.11)
Respiratory system (C30-39)	19	1.01 (0.61 to 1.57)	6	0.97 (0.36 to 2.11)
Larynx (C32)	1	1.89 (0.05 to 10.55)	1	7.45 (0.19 to 41.51)
Bronchus, trachea, lung (C33-C34)	17	0.95 (0.56 to 1.53)	5	0.85 (0.27 to 1.97)
Bone (C40-41)	0	0.0 (0.0 to 18.24)	0	0.0 (0.0 to 56.85)
Malignant melanoma of the skin (C43)	2	0.68 (0.08 to 2.44)	0	0.0 (0.0 to 3.76)
Soft tissue sarcoma (C49)	1	2.38 (0.06 to 13.26)	0	0.0 (0.0 to 23.66)
Breast (C50) (female only)	2	1.00 (0.12 to 3.61)	1	0.35 (0.01 to 1.94)
Cervix uteri (C53) (female only)	0	0.0 (0.0 to 12.06)	1	2.19 (0.06 to 12.20)
Corpus uteri (C54-C55) (female only)	0	0.0 (0.0 to 17.78)	0	0.0 (0.0 to 13.18)
Ovary (C56) (female only)	0	0.0 (0.0 to 6.56)	0	0.0 (0.0 to 4.82)
Prostate (C61) (male only)	4	0.60 (0.16 to 1.53)	3	1.93 (0.40 to 5.64)
Testes (C62) (male only)	0	0.0 (0.0 to 14.44)	0	0.0 (0.0 to 70.33)
Kidney (C64-C65)	3	1.56 (0.32 to 4.56)	0	0.0 (0.0 to 6.17)
Bladder and other urinary (C66-C68)	3	1.62 (0.33 to 4.73)	2	3.66 (0.44 to 13.22)
Central nervous system (C70-C72)	4	1.49 (0.41 to 3.82)	0	0.0 (0.0 to 3.99)
Thyroid gland and other endocrine glands and related structures (C73-C75)	0	0.0 (0.0 to 14.20)	0	0.0 (0.0 to 32.57)
All lymphatic and haematopoietic tissue (C81-C96)	9	1.29 (0.59 to 2.44)	4	1.64 (0.45 to 4.21)
Hodgkin's disease (C81)	2	6.80 (0.82 to 24.55)	0	0.0 (0.0 to 38.33)
Non-Hodgkin lymphoma (C82, C83.0-83.8, C84, C85.1-C85.9)	3	1.57 (0.32 to 4.59)	3	4.56 (0.94 to 13.34)
Leukaemia and aleukaemia (C91-C95)	2	0.80 (0.10 to 2.88)	0	0.0 (0.0 to 4.25)
Multiple myeloma (C90)	2	1.48 (0.18 to 5.34)	1	2.14 (0.05 to 11.90)
Benign neoplasms (D10-D36)	0	0.0 (0.0 to 6.91)	0	0.0 (0.0 to 17.58)
Diabetes mellitus (E10-E14)	8	1.27 (0.55 to 2.50)	3	1.34 (0.28 to 3.93)
Cerebrovascular disease (I60-I69)	17	0.96 (0.56 to 1.54)	5	0.73 (0.24 to 1.70)
All heart disease (I00-I02, I05-I09, I11, I13-I14, I20-I28, I30-I52)	88	1.12 (0.90 to 1.37)	19	0.76 (0.46 to 1.19)
Ischaemic heart disease (I20-I25)	81	1.21 (0.96 to 1.50)	17	0.83 (0.48 to 1.32)
Non-malignant respiratory disease (J00-J99)	13	0.63 (0.34 to 1.08)	5	0.70 (0.23 to 1.63)
Ulcer of stomach and duodenum (K25-K27)	0	0.0 (0.0 to 3.42)	0	0.0 (0.0 to 10.97)
Cirrhosis of liver (K70, K74)	5	2.38 (0.77 to 5.55)	0	0.0 (0.0 to 5.73)
Nephritis and nephrosis (N00-N29)	1	0.51 (0.01 to 2.85)	2	2.77 (0.34 to 10.00)

Continued

Table 1 Continued

Death category (International Classification of Disease Code)	Ever exposed		Never exposed	
	Deaths	SMR (95% CI)	Deaths	SMR (95% CI)
All external causes of death (V01-Y89)	25	1.09 (0.70 to 1.60)	7	1.08 (0.44 to 2.23)
Accidents (V01-X59)	20	1.30 (0.79 to 2.01)	6	1.39 (0.51 to 3.02)
Persons	1134		465	
Person-years	32 495		13 469	

95% CI 0.68 to 1.07, observed 76), all cancers combined (SMR=0.87, 95% CI 0.56 to 1.28, observed 25) and lung cancer (SMR=0.85, 95% CI 0.27 to 1.97, observed 5) was less than expected.

There were three deaths from non-Hodgkin lymphoma (SMR=4.56, 95% CI 0.94 to 13.34) but no deaths from soft tissue sarcoma, Hodgkin's disease or multiple myeloma. Deaths from diabetes were slightly greater than expected (SMR=1.34, 95% CI 0.28 to 3.93, observed 3) and deaths from ischaemic heart disease slightly less than expected (SMR=0.83, 95% CI 0.48 to 1.32, observed 17). The SMR analysis by stratified cumulative exposure levels (data not shown) did not reveal any trends with exposure, with or without an adjustment for latency.

The results of the proportional hazard modelling for exposure categories on selected causes of death, using the lowest exposure category as an internal referent, are presented in table 2.

Apart from the increase in the 'all deaths' rate ratio (RR) of 1.46, 95% CI 1.02 to 2.07 in the penultimate cumulative exposure category, which was marginally statistically significant, none of the relative risks were significantly greater than unity. Furthermore, none of the models for any cause of death had a statistically significant linear trend with discrete cumulative exposure levels. However, the RR for lung cancer was higher in the highest exposure group (RR of 3.03, 95% CI 0.72 to 11.73) based on a small number of cases. With regard to smoking, the percentage of smokers in the respective cumulative exposure categories of 0–75 ppt.months, 75.1–450 ppt.months, 450.1–2000 ppt.months and greater than 2000.1 ppt.months were 56% (95% CI: 41 to 71), 51% (95% CI: 40 to 63), 51% (95% CI: 38 to 63), and 61% (95% CI: 48 to 72), respectively, the highest percentage being in the high exposure group.

There were positive dioxin exposure coefficients for each cause of death examined in the proportional hazards model with the exception of diabetes and ischaemic heart disease, with a lesser trend. None of the trends reached statistical significance.

Discussion

This additional 7 years of follow-up added 109 decedents. For all cancers combined, considered by IARC to be the strongest evidence for classifying TCDD as a carcinogen, the SMR of 1.08, 95% CI 0.86 to 1.34, was essentially unchanged from our previous report. As regards

specific causes, the number of lung cancers observed among exposed workers was slightly less than expected at 17; however, the highest exposure group did reveal a higher risk, although non-significantly so and lacking a systematic trend with exposure. There were more deaths than expected for non-Hodgkin lymphoma, with an additional three deaths in the non-exposed group, also with diabetes, ischaemic heart disease and all causes of death combined. There was, however, no evidence of an exposure trend in either the SMR analyses or the proportional hazards model.

Strengths and weaknesses

The major strength was the biological monitoring data from the serum TCDD evaluation of 346 workers, 22% of the workforce, selected to represent the spectrum of activities at the site rather than the likelihood of exposure. Allied to work history information that was accurate and complete, this allowed us to estimate cumulative dioxin exposure estimates for all of the workers in the study, and facilitated the calculation of dose–response relationships. Relatively few dioxin cohort studies have based exposure estimates on serum dioxin evaluations but with a much smaller sample of the study population.^{17–23}

The limitations were the relatively small size of the cohort, making it difficult to evaluate rare causes of death such as soft tissue sarcoma, for which we observed one death with 0.4 deaths expected. The exposures to dioxins were also relatively recent, making it difficult to evaluate cancers with a latent period in excess of 20 years.

There is some evidence that workers in the highest cumulative exposure category were more likely to be smokers than those in the other categories. Confounding by smoking is therefore a possible explanation for the slightly higher lung cancer rates in this category. This should, however, be interpreted conservatively, because we only have smoking history on a cross-sectional sample of workers. Smokers would be under-represented, non-smokers being more likely to survive, and the definition of smoking, that is to say smoking more than 100 cigarettes, would classify some non-smokers and infrequent smokers with heavy smokers.

The performance of the exposure reconstruction model was also modest, explaining some 30% of the variance of the observed TCDD concentrations. Apart from inaccuracies in the work records, five other factors contributed. Firstly, the low serum TCDD concentration: many of the

Table 2 Proportional hazards model results for exposed workers including rate ratios and 95% CI by cumulative exposure levels versus an internal comparison group and evaluation of linear trends

Cause	Cumulative Exposure Categories					Continuous Model		
	Rate Ratio (95% CI)*					Exposure		
	0-75 ppt/month (referent)	75.1-450.0 ppt-month	450.1-2000 ppt-month	2,000.1 +ppt-month	P values Linear Trend†	Coefficient‡ (SE)	P values§	
All deaths	1.00	1.17 (0.83 to 1.66)	1.46 (1.02 to 2.07)	1.20 (0.81 to 1.76)	0.90	0.01462 (0.02643)	0.58	
All cancers	1.00	1.53 (0.82 to 2.84)	1.46 (0.75 to 2.82)	1.54 (0.78 to 3.05)	0.98	0.03912 (0.04737)	0.41	
Lung cancer	1.00	1.26 (0.30 to 5.24)	0.39 (0.04 to 3.60)	3.03 (0.72 to 11.73)	0.17	0.12696 (0.11372)	0.26	
Non-Hodgkin lymphoma	1.00	0.00 (0.00-∞)	2.00 (0.12 to 33.36)	1.95 (0.10 to 37.03)	1.00	0.24766 (0.27255)	0.36	
Diabetes mellitus	1.00	0.63 (0.10 to 3.77)	0.00 (0.00-∞)	0.39 (0.50 to 3.06)	0.67	-0.09991 (0.14776)	0.50	
Ischaemic heart disease	1.00	0.89 (0.47 to 1.67)	1.11 (0.59 to 2.08)	0.70 (0.33 to 1.47)	0.51	-0.04482 (0.04831)	0.35	

*The time variable was age and both models included sex, year first employed, and year of birth. Since there were no diabetes deaths among women, the model for diabetes was restricted to men.

†Tested by constructing orthogonal polynomial contrasts and computing one-degree of freedom Wald chi-square statistics and associated p values.

‡The natural log of estimated cumulative exposure.

§P value calculated by chi-square of the maximum likelihood estimator of the coefficient.

exposures showed concentrations close to background (supplementary data table 1). Secondly, the assumption of average and consistent exposure across time ignores individual variability in work practices such as poor work hygiene and failure to use personal protective equipment. Thirdly, several 'outlying' individuals reported possible TCDD exposure to 2,4,5-T in other jobs in agriculture and timber processing. Fourthly, even though the exposure estimates are based on serum dioxin evaluation for a large sample of workers, estimating past exposures from a single recent blood survey almost certainly introduces some exposure misclassification. The serum sample was, however, drawn regardless of exposure, showing dioxin exposure above background in the departments expected such as TCP production, but also in 'across site' jobs such as maintenance. The risk of misclassification is substantially less than would be the case with crude assignment to exposure groups based on job titles, with less likelihood of bias towards the null. Finally, if exposures are time-dependent, workers who survived to the date of the blood test may not accurately represent exposure levels of those who died before that time. This could have resulted in a potential bias in identifying an association between dioxin and mortality.

The loss to follow-up of 16% was the result of high emigration rates, also because NHI numbers had not been issued to older cohort members. This attrition might result in an underestimation of disease risks; however, we were reassured by the earlier estimate that those lost to follow-up, based on jobs held and estimated from the toxicokinetic model, had an average TCDD level of 3.2 ppt while employed than those workers not lost to follow-up, who had an average TCDD during employment of 5.7 ppt. In any case there would have been less impact on the proportional hazards model.

Comparisons with other studies

As regards comparisons, the New Plymouth cohort was included in the earliest investigation of TCDD toxicity, an international cohort of 18,910 phenoxy herbicide sprayers and production workers. The results, published in 1991, indicated that deaths from soft-tissue sarcomas and non-Hodgkin lymphoma were greater than expected among workers with exposure to 2,4,5-T; however, there was no increase in all-cancer risk.²⁴ In a later follow-up, all-cancer risks were slightly increased, with an SMR of 1.12, 95% CI 1.04 to 1.21.²⁵

tMannetje *et al* carried out a follow-up of the New Zealand component of this study in 2005.²⁶ The cohort was employed between 1969 and 1984 and included storemen involved in product re-packing elsewhere in New Zealand, 1,025 employees in total, with a loss to follow-up of 22%. The 'all-cancer' SMR was 1.24, 95% CI 0.90 to 1.67, with a significant excess, based on three cases with 0.5 expected, of multiple myeloma (SMR 5.51, 95% CI 1.14 to 16.1). We failed to reproduce this in the present update or the earlier report.

In the other cohort studies examining cancer and mortality in relation to TCDD exposure, only a few used serum dioxin levels in the exposure categorisation: five production worker studies^{18 20 22 23 27}; an 'end user' study of Air Force veterans exposed to Agent Orange²⁸; and a population-based cohort exposed after the 1976 industrial disaster in Seveso.¹⁹

The four worker studies finding an excess risk of all cancers were reported by Flesch-Janys *et al.* in 1995,²⁰ Ott and Zober in 1996,²² Hooiveld *et al.* in 1998²⁷ and Steenland *et al.* in 1999.²³

Flesch-Janys *et al.*²⁰ followed up 1,184 employees working at a Hamburg plant between 1952 and 1984, with serum or adipose TCDD estimates for 190 male workers. Total mortality, all cancers, cardiovascular disease (CVD) and ischaemic heart disease were all increased, with an all-cancer RR of 3.30, 95% CI 2.05 to 5.31 in the top decile, 344.7–3890.2 ppt, measured at the end of exposure. Ischaemic heart disease was also elevated in the high exposure group.

Ott and Zober²² followed up 243 males involved in a TCP reactor accident in Germany, with serum TCDD levels in 29 men. The greatest all-cancer risk lay in a high exposure group lagged by 20 years (SMR of 1.97, 95% CI 1.05 to 3.36). Respiratory cancers were also higher than expected. At the time of the survey TCDD levels lay in the range 29–553 ppt.

Hooiveld *et al.*²⁷ reported on a Dutch cohort of 1,129 workers (562 exposed, 567 non-exposed) in 'factory A'. For all cancers the RR was 4.1, 95% CI 1.8 to 9.0. From a total of 144 individuals selected for serum sampling, results were available for 47: 14 exposed as the result of an accident, 17 'other' exposed and 16 'non-exposed' workers. Measured TCDD levels (1993) had an arithmetic mean of 96.3 ppt for those involved in the accident, 16.6 for those exposed but not in the accident and 7.6 for non-exposed workers. The exposure categories were based on an extrapolation to the time of maximum exposure, TCDD_{max}, the referent category being 7.1 ppt, 'medium' exposure between 7.7 and 124.1 ppt, and 'high' between 124.1 and 7307.5 ppt TCDD_{max}. The medium and high exposure groups had adjusted RRs of 4.8 and 4.4 for 'all-cancer' deaths, both being significant. There were more cases than expected of respiratory cancer, non-Hodgkin lymphoma and ischaemic heart disease.

Boers *et al.*¹⁷ reported on a follow-up of this cohort, those employed at the original factory A employed between 1955 and 1985, but including 'factory B' employed between 1965 and 1986, the latter previously having too few deaths to analyse. The predictive model was not used, since the data was available only for factory A and the sample size was small. For those in the accident (compared with non-exposed), the HR was, for all cancers, 1.56 95% CI 0.86 to 2.8; for exposure in main production an HR of 0.85, 95% CI 0.44 to 1.66; and for occasionally exposed workers an HR of 1.46, 95% CI 0.9 to 2.35. There were more cases of urinary cancers than expected.

Collins *et al.* carried out a follow-up study of 773 pentachlorophenol process workers in 2009.¹⁸ A serum survey of 128 workers was used in a time-dependent AUC model, weighting six dioxins by the WHO toxic equivalency factors (WHOTEQ) scheme. The cumulative serum exposures on the WHOTEQ basis ranged from 0.007 to 113.4 ppt-years, with a mean of 5.2 ppt-years. The SMR for all cancers in the highest exposure category, 4.0–113.4 ppt-years, was 1.2, 95% CI 0.8 to 1.7.

Ketchum and Michalek²⁸ carried out the largest 'end user' occupational serum dioxin study, including 1016 Air Force Vietnam veterans involved in spraying Agent Orange and 1436 controls. Those with a serum dioxin less than 10 ppt were assigned to the background category, those exceeding background had their initial dioxin levels estimated using a first order kinetic model with a half-life of 7.6 years. Those with an initial level of less than or equal to 117.6, a median level in this subgroup, were assigned to a low category, the remainder to the high category. There was a non-significantly increased of cancer deaths in the background category, an RR of 1.3, 95% CI 0.7 to 2.3, giving a decreased trend of risk with increasing exposure. A subsequent analysis²⁹ used restriction in terms of days spraying, calendar period and time in the operational theatre, stratifying by these variables. The restricted cohort of 530 individuals and a comparison group of 268 did show an increase in all-cancer risk over controls (RR 1.4, 95% CI 1.1 to 1.7) and a trend with exposure, those in the highest risk group having an RR of 2.2, 95% CI 1.1 to 4.4.

The largest population-based serum survey¹⁹ was carried out in the Seveso cohort, in which residents exposed after the 1976 industrial accident were stratified into three zones, A, B and R, with 296, 94 and 48 serum samples in each, revealing median TCDD levels of 447, 94 and 48 ppt respectively. All-cancer risk was not significantly increased overall, but in zone A, more than 20 years post-accident, the RR was 1.65, 95% CI 1.04 to 2.62. There were also some increased risks for lymphohaematopoietic cancers in both zones A and B.

It is difficult to compare the serum levels in the New Plymouth cohort with those described in other studies. This is due to a number of factors, including the lag in serum sampling, the serum modelling technique and the different exposure metrics used. The New Plymouth exposures are, however, at the low end of the range internationally. Importantly, we found no evidence of chloracne, a hallmark of high TCDD exposure, which is not normally seen at a level below 1,000 ppt. The estimated exposure for those involved in the 1986 release was equivalent to a single dose in the order of 0.04 µg/kg bodyweight, consistent with an increase in serum lipid of approximately 100 to 150 ppt at the time of the release. This dose estimate is consistent with, but less than, that reported by Ott and Zober, in which more than half the workers were reported to experience a dose less than 0.1 µg/kg, with a few experiencing more than 2.0 µg/kg.

In summary, the increase in all-cancer risk in these studies resides in the high exposure sub-groups, with long latency, in the more heavily exposed cohorts. Compared with the other industrial cohort studies, the New Plymouth exposures were relatively recent, meaning that we were restricted in the ability to look at latency of greater than 20 years, and on average were also much lower. We cannot therefore rule out a risk from TCDD exposure, however, within the range found in this population, our findings do not support it.

Contributors KMB analysed the data. LLA developed and applied the toxicokinetic model. DIM, JJC and TJB supervised the study and wrote the initial drafts. All co-authors were involved in critical appraisal and re-drafting of the manuscript.

Funding The study was funded by The Dow Chemical Company through an unrestricted grant.

Competing interests JJC, TJB and KMB are either current or former members of the staff at Dow Epidemiology.

Patient consent Not required.

Ethics approval New Zealand Health and Disability Central Regional Ethics Committee.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

REFERENCES

1. Baan R, Grosse Y, Straif K, *et al*. A review of human carcinogens—Part F: chemical agents and related occupations. *Lancet Oncol* 2009;10:1143–4.
2. Boffetta P, Mundt KA, Adami HO, *et al*. TCDD and cancer: a critical review of epidemiologic studies. *Crit Rev Toxicol* 2011;41:622–36.
3. Cole P, Trichopoulos D, Pastides H, *et al*. Dioxin and cancer: a critical review. *Regul Toxicol Pharmacol* 2003;38:378–88.
4. Steenland K, Bertazzi P, Baccarelli A, *et al*. Dioxin revisited: developments since the 1997 IARC classification of dioxin as a human carcinogen. *Environ Health Perspect* 2004;112:1265–8.
5. McBride DI, Collins JJ, Humphry NF, *et al*. Mortality in workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin at a trichlorophenol plant in New Zealand. *J Occup Environ Med* 2009;51:1049–56.
6. International Agency for Research on Cancer. *IARC Monographs on the evaluation of carcinogenic risks to humans. Vol 62: Wood dust and formaldehyde*. IARC: Lyon, 1995.
7. Collins JJ, Wilken M, McBride D, *et al*. Serum concentrations of chlorinated dibenzo-p-dioxins and dibenzofurans among former New Zealand trichlorophenol workers. *Chemosphere* 2009;76:1550–6.
8. Hornung RW, Reed LD. Estimation of average concentration in the presence of nondetectable values. *Appl Occup Environ Hyg* 1990;5:46–51.
9. Burns CJ, Collins JJ, Humphry N, *et al*. Correlates of serum dioxin to self-reported exposure factors. *Environ Res* 2010;110:131–6.
10. Bates MN, Buckland SJ, Garrett N, *et al*. Persistent organochlorines in the serum of the non-occupationally exposed New Zealand population. *Chemosphere* 2004;54:1431–43.
11. Aylward LL, Bodner KM, Collins JJ, *et al*. TCDD exposure estimation for workers at a new zealand 2,4,5-t manufacturing facility based on serum sampling data. *J Expo Sci Environ Epidemiol* 2010;20:417–26.
12. Marsh GM, Youk AO, Stone RA, *et al*. OCMAP-PLUS: a program for the comprehensive analysis of occupational cohort data. *J Occup Environ Med* 1998;40:351–62.
13. SAS. *Overview: PHREG Procedure*. Cary, North Carolina: SAS Institute Inc Carolina Carolina. https://support.sas.com/documentation/cdl/en/statug/63347/HTML/default/viewer.htm#statug_phreg_sect001.htm (cited to 2nd Jan 2018).
14. Cheng H, Aylward L, Beall C, *et al*. TCDD exposure-response analysis and risk assessment. *Risk Anal* 2006;26:1059–71.
15. Goodman M, Narayan KM, Flanders D, *et al*. Dose-response relationship between serum 2,3,7,8-tetrachlorodibenzo-p-dioxin and diabetes mellitus: a meta-analysis. *Am J Epidemiol* 2015;181:374–84.
16. Humblet O, Birnbaum L, Rimm E, *et al*. Dioxins and cardiovascular disease mortality. *Environ Health Perspect* 2008;116:1443–8.
17. Boers D, Portengen L, Bueno-de-Mesquita HB, *et al*. Cause-specific mortality of dutch chlorophenoxy herbicide manufacturing workers. *Occup Environ Med* 2010;67:24–31.
18. Collins JJ, Bodner K, Aylward LL, *et al*. Mortality rates among workers exposed to dioxins in the manufacture of pentachlorophenol. *J Occup Environ Med* 2009;51:1212–9.
19. Consonni D, Pesatori AC, Zocchetti C, *et al*. Mortality in a population exposed to dioxin after the Seveso, Italy, accident in 1976: 25 years of follow-up. *Am J Epidemiol* 2008;167:847–58.
20. Flesch-Janys D, Berger J, Gurn P, *et al*. Exposure to polychlorinated dioxins and furans (PCDD/F) and mortality in a cohort of workers from a herbicide-producing plant in Hamburg, Federal Republic of Germany. *Am J Epidemiol* 1995;142:1165–75.
21. Michalek JE, Ketchum NS, Tripathi RC. Diabetes mellitus and 2,3,7,8-tetrachlorodibenzo-p-dioxin elimination in veterans of operation ranch hand. *J Toxicol Environ Health A* 2003;66:211–21.
22. Ott MG, Zober A. Cause specific mortality and cancer incidence among employees exposed to 2,3,7,8-TCDD after a 1953 reactor accident. *Occup Environ Med* 1996;53:606–12.
23. Steenland K, Piacitelli L, Deddens J, *et al*. Cancer, heart disease, and diabetes in workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin. *J Natl Cancer Inst* 1999;91:779–86.
24. Saracci R, Kogevinas M, Bertazzi PA, *et al*. Cancer mortality in workers exposed to chlorophenoxy herbicides and chlorophenols. *Lancet* 1991;338:1027–32.
25. Kogevinas M, Becher H, Benn T, *et al*. Cancer mortality in workers exposed to phenoxy herbicides, chlorophenols, and dioxins. An expanded and updated international cohort study. *Am J Epidemiol* 1997;145:1061–75.
26. 't Mannetje A, McLean D, Cheng S, *et al*. Mortality in New Zealand workers exposed to phenoxy herbicides and dioxins. *Occup Environ Med* 2005;62:34–40.
27. Hooiveld M, Heederik DJ, Kogevinas M, *et al*. Second follow-up of a dutch cohort occupationally exposed to phenoxy herbicides, chlorophenols, and contaminants. *Am J Epidemiol* 1998;147:891–9.
28. Ketchum NS, Michalek JE. Postservice mortality of Air Force veterans occupationally exposed to herbicides during the Vietnam War: 20-year follow-up results. *Mil Med* 2005;170:406–13.
29. Michalek JE, Pavuk M. Diabetes and cancer in veterans of operation ranch hand after adjustment for calendar period, days of spraying, and time spent in southeast asia. *J Occup Environ Med* 2008;50:330–40.