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Serum concentrations of chlorinated dibenzo-*p*-dioxins, furans and PCBs, among former phenoxy herbicide production workers and firefighters in New Zealand

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Abstract

Purpose To quantify serum concentrations of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) and dioxin-like compounds in former phenoxy herbicide production plant workers and firefighters, 20 years after 2,4,5-T production ceased.

Methods Of 1025 workers employed any time during 1969–1984, 430 were randomly selected and invited to take part in a morbidity survey and provide a blood sample; 244 (57 %) participated. Firefighters stationed in close proximity of the plant and/or engaged in call-outs to the plant between 1962 and 1987 also participated (39 of 70 invited). Reported here are the serum concentrations of TCDD and other chlorinated dibenzo-dioxins, dibenzofurans, and

polychlorinated biphenyls (PCBs). Determinants of the serum concentrations were assessed using linear regression. **Results** The 60 men who had worked in the phenoxy/TCP production area had a mean TCDD serum concentration of 19.1 pg/g lipid, three times the mean concentration of the 141 men and 43 women employed in other parts of the plant (6.3 and 6.0 pg/g respectively), and more than 10 times the mean for the firefighters (1.6 pg/g). Duration of employment in phenoxy herbicide synthesis, maintenance work, and work as a boilerman, chemist, and packer were associated with increased serum concentrations of TCDD and 1,2,3,4,7-pentachlorodibenzo-*p*-dioxin (PeCDD). Employment as a boilerman was also associated with elevated serum concentrations of PCBs.

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Conclusions Occupations in the plant associated with phenoxy herbicide synthesis had elevated levels of TCDD and PeCDD. Most other people working within the plant, and the local firefighters, had serum concentrations of dioxin-like compounds comparable to those of the general population.

Keywords Occupational exposure · 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin · Biological monitoring · Polychlorinated biphenyls · 1,2,3,4,7-Pentachlorodibenzo-*p*-dioxin

Introduction

The production of the phenoxy herbicide 2,4,5-T and its intermediates (e.g., chlorophenols) generates the contaminant 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). TCDD has been associated with a range of health outcomes including chloracne, neurological symptoms, diabetes mellitus, and reproductive effects (EPA 1994), and is classified as a human carcinogen by the International Agency for Research on Cancer (IARC) (WHO 1997).

In 1980 IARC established an international cohort of producers and sprayers of phenoxy herbicides (Kogevinas et al. 1997; Saracci et al. 1991). The collaboration involved 36 cohorts from 12 countries, including a New Zealand cohort of 1025 phenoxy herbicide producers which constituted the source population for this study. The IARC study found a 29 % overall increased risk of cancer in workers exposed to dioxin compared with unexposed workers (Relative Risk = 1.29, 95 % Confidence Interval (CI) 0.94–1.76). A later update of the New Zealand component of the international cohort (‘t Mannetje et al. 2005) found a similar elevation in cancer mortality in production workers with potential exposure to TCDD (standardized mortality ratio (SMR) = 1.24, 95 % CI 0.90–1.67); for synthesis workers (SMR = 1.69, 95 % CI 0.85–3.03), and there was an increase in cancer mortality by duration of employment ($p = 0.04$).

At the time, the above-mentioned study did not involve determination of TCDD serum levels of the New Zealand phenoxy herbicide producers, but a study conducted in 2004 reported a mean TCDD serum concentration of 6.5 pg/g lipid for 52 residents who lived near the New Plymouth production plant for 3 years or more during the plant’s production period of 2,4,5-T(1962–1987) (Fowles et al. 2009). Because this was above expected background levels, this report generated concern that the producers, as well as firefighters who were stationed in close proximity and had regular safety drills and occasional emergency call-outs to the plant, could have similar or higher levels of TCDD in their blood, and could experience related health effects. We therefore conducted a morbidity survey

in these two occupationally exposed populations, aiming to (1) quantify individual serum concentrations of TCDD and related compounds and (2) evaluate the association between TCDD exposure and a range of health outcomes. A series of manuscripts will be published from this work.

In this paper we address the first aim by reporting on the serum concentrations of chlorinated dioxins, furans, and PCBs in 244 members of the original New Zealand phenoxy herbicide producers cohort, and in 39 firefighters who were stationed in close proximity to the plant, as measured in serum collected during 2007–2008.

Materials and methods

Study population

The pesticide producers included in this study were part of the New Zealand component of the IARC international cohort of producers and sprayers of phenoxy herbicides (‘t Mannetje et al. 2005), and had worked for at least 1 month between 1969 and 1984 in the pesticide production plant in New Plymouth, New Zealand. In February 2005, the surviving cohort (164/1025 had died by the end of 2000) was linked to the 2005 Electoral Roll and the New Zealand Health Information System (NZHIS) databases. This link identified cohort members who at 01/01/2006 were known to be alive, had a current address available from these databases, and were aged less than 80 years. Due to limitations of the study budget, of the 631 subjects who met these criteria, 430 were randomly selected and invited to participate in the study. This study was funded by the Health Research Council of New Zealand (HRC). During the same period, the pesticide production company funded a study focussing on (ex) employees still living in the New Plymouth area (Burns et al. 2010; Collins et al. 2009). To avoid multiple requests for blood from participants, it was decided, under advisement of the ethics committee, that the 133 individuals who had participated in the industry-funded study would be asked to give consent for access to a copy of their individual blood test results for the HRC-funded study. Information about avoidance of fatty foods prior to blood donation, questionnaires, and laboratory used for the determinations of chlorinated compounds was the same for all individuals, independent of the study they participated first.

For the selection of firefighters, the New Zealand Fire Service provided a database listing 131 firefighters who were stationed in New Plymouth. Potential participants were then selected based on the following criteria: (1) employed by the fire service for at least 1 year between 1962 and 1987 (the relevant exposure period); (2) participated in call-outs to the production plant and/or were based at the fire station near the plant; (3) alive; and (4) living

in New Zealand with a known address. According to these criteria, 59 firefighters were classified as ineligible leaving 72 firefighters who were sent a screening questionnaire by mail. The screening questionnaire was then used to make the final selection of 40 exposed firefighters, using the following criteria: (1) willing to participate in the study; (2) had not had other non-production-related significant occupational exposure to dioxins (e.g., 2,4,5-T applicator, pentachlorophenol-exposed timber worker).

Of the 72 invitation letters sent, two were returned to sender and 20 firefighters declined to take part. Forty-one firefighters provided consent, of whom 39 took part in the study.

This study received ethical approval from the Central Regional Ethics Committee (ref: CEN/06/02/002) on the 19 May 2006. The firefighters study received ethical approval from the Central Regional Ethics Committee (ref: CEN/06/08/077) on the 22 December 2006. All participants gave their informed consent prior to their inclusion in the study.

Data collection

Research nurses travelled to the individuals' homes or offices rented for the study (e.g., local medical rooms), administered the questionnaire, and collected approximately 90 ml of blood in glass serum tubes and 4.5 ml in EDTA vacutainer tubes. Participants were asked to avoid 'fatty' foods on the morning of the appointment, due to their possible effects upon lipids in the blood samples. The questionnaire collected information on demographic factors, lifetime work history, employment at the pesticide production plant/fire service, as well as health and lifestyle factors (e.g., tobacco smoking).

Laboratory analyses

Glass tubes with whole blood were transported back to the Centre for Public Health Research, Massey University, Wellington, where they were centrifuged to separate the serum, aliquoted, and stored in a -80°C freezer. One aliquot of serum was analyzed for glucose and blood lipids (cholesterol, triglyceride, HDL cholesterol, LDL cholesterol, cholesterol/HDL ratio) at Aotea Pathology Medical Laboratory. The remaining serum samples were sent toASUREQuality, Lower Hutt, New Zealand, and analyzed for seven polychlorinated dibenzo-dioxins (PCDDs: 2,3,7,8-TCDD; 1,2,3,7,8-PeCDD; 1,2,3,4,7,8-HxCDD; 1,2,3,6,7,8-HxCDD; 1,2,3,7,8,9-HxCDD; 1,2,3,4,6,7,8-HpCDD; OCDD) and 10 polychlorinated dibenzofurans (PCDFs: 2,3,7,8-TCDF; 1,2,3,7,8-PeCDF; 2,3,4,7,8-PeCDF; 1,2,3,4,7,8-HxCDF; 1,2,3,6,7,8-HxCDF; 1,2,3,7,8,9-HxCDF; 2,3,4,6,7,8-HxCDF; 1,2,3,4,6,7,8-HpCDF; 1,2,3,4,7,8,9-HpCDF; OCDF). All but one of the samples (due to insufficient sample volume) were analyzed for 15 polychlorinated

biphenyls (PCBs: PCB#77; PCB#81; PCB#126; PCB#169; PCB#105; PCB#114; PCB#118; PCB#123; PCB#156; PCB#157; PCB#167; PCB#189; PCB#138; PCB#153; PCB#180).

The USEPA Method 1613b (Isotope Dilution) was used for dioxins/furans analyses, and the USEPA Method 1668a (Isotope Dilution) was used for the PCBs. Serum lipid content was calculated from the average total cholesterol and triglyceride levels using the following calculation: $\text{Total Lipid} = 2.27 \times \text{Total Cholesterol} + \text{Triglycerides} + 0.632$. Levels are expressed in picograms of compound found in one gram of lipids measured in blood (pg/g). The total toxic equivalence of the dioxin-like compounds was calculated using the 2005 World Health Organization toxic equivalency factors (WHO TEFs) (Van den Berg et al. 2006).

Data analyses

All statistical analyses were performed using SAS 9.3 software (2011). For serum concentrations below the limit of detection (LOD), half of the detection limit was used in all calculations. Mean serum concentrations were estimated for different demographic and exposure groups, which were compared through analyses of variance (one-way ANOVA). Individual serum concentrations of TCDD at time of phlebotomy were back-calculated to time of last exposure defined as the last time of plant employment prior to 1987 for some analyses by using a first-order elimination model.

$$C_0 = \frac{C_t - C_{\text{background}}}{e^{-kt}} + C_{\text{background}}$$

C_0 —Concentration at last time of exposure; C_t —Concentration at time of phlebotomy (>20 years after last exposure); k —elimination rate constant [$\ln 2/\text{half-life}$, with half-life 7.6 years (Michalek and Tripathi 1999)]; t —number of years between $t = 0$ and $t = 1$; $C_{\text{background}}$ —assumed background concentration of TCDD in this population (2 pg/g; if $C_t < 2$ pg/g then $C_0 = C_t$).

A half-life of 7.6 years was used as determined based on a 15-year follow-up of US Vietnam war veteran of operation Ranch hand (Michalek and Tripathi 1999), and a background concentration of 2 pg/g was assumed. Determinants of the measured serum concentrations of all analytes were assessed using linear regression, with the natural logarithm of the serum concentrations as the dependent variable.

Results

A total of 244 production cohort employees participated in the study, of which 133 had already provided blood as part of the company funded study. Thirty-nine firefighters also participated.

Table 1 Demographic characteristics of the study population

	Pesticide producers (<i>n</i> = 244)						Firefighters (<i>n</i> = 39)		<i>p</i> value (ANOVA)
	Group 1: production workers phenoxy/TCP		Group 2: production workers Other (male)		Group 3: production workers Other (female)		Group 4: firefighters stationed near plant		
<i>n</i>	60	min–max	141	min–max	43	min–max	39	min–max	
Sex	Male		Male		Female		Male		–
Age (mean)	61.6	(44–79)	60.0	(44–80)	59.7	(45–78)	60.7	(47–73)	0.666
Year of birth (mean)	1945	(‘27–‘62)	1947	(‘27–‘63)	1947	(‘29–‘62)	1947	(‘34–‘60)	0.632
Ethnicity									
European New Zealander	93.3 %		95.0 %		90.7 %		97.4 %		0.574
Maori	5.0 %		3.5 %		7.0 %		2.6 %		0.729
Other	1.7 %		1.4 %		2.3 %		0.0 %		0.841
Tobacco smoking (3 missing)									
Current	26.7 %		12.1 %		9.5 %		10.8 %		0.029
Ex	45.0 %		49.6 %		23.8 %		43.2 %		0.032
Never	28.3 %		38.3 %		66.7 %		45.9 %		0.001
<i>n</i> smoked per day	15.9	(3–60)	15.5	(0.2–80)	12.9	(1.5–20)	19.9	(2–50)	0.360
Years smoked	29.0	(0.8–52)	24.3	(0.8–61)	26.3	(4–55)	21.1	(4–53)	0.222
Current BMI ^a (32 missing)	29.2	(20–42)	28.1	(19–50)	26.6	(20–56)	27.9	(21–39)	0.100
Employment production plant									
Year start	1973	(‘63–‘83)	1972	(‘52–‘84)	1974	(‘60–‘84)	–		0.362
Duration (years)	6.9	(0.5–30)	6.9	(0.5–42)	5.7	(0.5–35)	–		0.659
Stationed near plant									
Year start	–		–		–		1976	(‘71–‘86)	–
Duration (years) in shifts	–		–		–		11.5	(0–19)	–

^a BMI body mass index at time of blood collection, calculated as weight (in kg) divided by height² (in m)

The study population was categorized into four groups, based on gender and potential for exposure. Group 1 consisted of production cohort workers who had indicated in the questionnaire to have worked in the phenoxy herbicide or trichlorophenol (TCP) plant (*n* = 60), which was considered a priori to have potentially the highest TCDD exposure. This group was exclusively male, and the most common occupations within this group were phenoxy herbicide synthesis worker (75 %) and maintenance worker (10 %). Groups 2 and 3 included all other production cohort workers not directly involved in the phenoxy or TCP process, who worked in other departments but were considered a priori to have potential exposure to TCDD due to workplace contamination or product handling. This group was divided into males (*n* = 141, group 2) and females (*n* = 43, group 3). The most common occupations in the men in group 2 were: maintenance worker (23 %), storeman (15 %), laboratory worker (11 %), and engineer (10 %). The most common occupations for the women in group 3 were: laboratory worker (47 %) and packer (35 %). Group 4 consisted of the 39 firefighters (exclusively male), who were considered a priori to have had potential exposure to dioxin through site visits and being stationed in close proximity to the plant.

There were no major differences between the four groups in terms of age, ethnicity, or duration of employment (Table 1). The average age at the time of interview was approximately 60 years (range 44–80 years) for all four groups. Smoking habits differed between groups, with the highest smoking rates in the phenoxy/TCP workers (group 1) and the lowest in the female production cohort workers (group 3). The mean body mass index (BMI) was highest for the phenoxy/TCP group and lowest for the female production cohort workers, but this was not statistically significant.

Table 2 lists the serum concentrations of PCDD/Fs and PCBs measured for each of the four exposure groups. The largest differences in serum concentrations among the exposure groups were evident for TCDD. The mean TCDD concentration in exposure group 1 was 19 pg/g lipid, three times higher than the other production cohort workers and 12 times higher than the firefighters.

The highest individual measured serum TCDD concentration was 335 pg/g lipid (Table 3). Table 3 also lists the mean TCDD serum concentrations back-calculated to the last year of employment at the plant (capped at 1987), indicating that mean serum concentration would have been more than 10 times higher at the time of last exposure.

Table 2 Serum concentrations of PCDD/Fs and PCBs for the four groups (pg/g lipid)

Congener (2005 WHO TEF)	% < LOD	Pesticide producers (<i>n</i> = 244 ^a)						Firefighters (<i>n</i> = 39)		Difference between groups	
		Group 1: produc- tion workers phenoxo/TCP		Group 2: produc- tion workers Other (male)		Group 3: produc- tion workers Other (female)		Group 4: firefight- ers stationed near plant			
		Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	<i>p</i> value (ANOVA)	
										All 4	1 versus 2
2,3,7,8-TCDD (1)	13.4	19.1	(46.4)	6.3	(10.5)	6.0	(6.0)	1.6	(1.3)	0.0004	0.002
1,2,3,7,8-PeCDD (1)	2.1	6.4	(8.3)	4.8	(3.5)	5.9	(6.6)	3.6	(2.0)	0.050	0.064
1,2,3,4,7,8-HxCDD (0.1)	34.3	2.0	(1.1)	2.0	(1.2)	3.6	(10.3)	1.6	(1.1)	0.118	0.991
1,2,3,6,7,8-HxCDD (0.1)	0.0	15.9	(9.0)	13.8	(7.8)	16.8	(12.5)	11.2	(7.2)	0.015	0.100
1,2,3,7,8,9-HxCDD (0.1)	20.5	3.0	(1.9)	2.7	(2.2)	3.6	(2.3)	2.2	(1.5)	0.014	0.365
1,2,3,4,6,7,8-HpCDD (0.01)	0.4	22.3	(16.4)	22.0	(17.7)	28.0	(18.6)	17.5	(9.0)	0.040	0.917
OCDD (0.0003)	0.0	225.4	(167.5)	192.7	(142.2)	264.2	(131.6)	168.9	(125.5)	0.009	0.160
2,3,7,8-TCDF (0.1)	25.1	0.9	(0.5)	0.8	(0.4)	0.9	(0.5)	0.9	(0.4)	0.394	0.247
1,2,3,7,8-PeCDF (0.03)	68.2	0.4	(0.3)	0.4	(0.3)	0.4	(0.3)	0.4	(0.3)	0.631	0.404
2,3,4,7,8-PeCDF (0.3)	0.0	4.5	(1.8)	4.1	(1.6)	4.6	(2.0)	4.0	(1.9)	0.127	0.084
1,2,3,4,7,8-HxCDF (0.1)	12.4	1.9	(1.1)	1.9	(1.0)	1.9	(0.9)	1.6	(0.7)	0.234	0.617
1,2,3,6,7,8-HxCDF (0.1)	12.4	2.5	(1.6)	2.2	(1.3)	2.2	(1.0)	1.7	(0.9)	0.026	0.185
1,2,3,7,8,9-HxCDF (0.1)	98.9	0.7	(0.6)	0.7	(0.5)	0.6	(0.5)	0.5	(0.3)	0.271	0.808
2,3,4,6,7,8-HxCDF (0.1)	41.3	0.9	(0.4)	0.9	(0.4)	0.9	(0.7)	0.8	(0.4)	0.643	0.777
1,2,3,4,6,7,8-HpCDF (0.01)	9.5	6.1	(9.9)	7.8	(15.4)	4.4	(4.8)	3.1	(2.1)	0.116	0.447
1,2,3,4,7,8,9-HpCDF (0.01)	98.9	1.1	(0.9)	1.0	(0.9)	1.1	(1.0)	0.8	(0.5)	0.584	0.668
OCDF (0.0003)	82.3	4.0	(8.5)	2.5	(3.4)	2.9	(4.3)	1.6	(0.9)	0.084	0.073
TEQ (PCDD/Fs 2005)	–	30.0	(54.9)	15.2	(15.0)	16.7	(14.7)	8.7	(4.8)	0.001	0.0034
PCB#77 (0.0001)	57.2	30	(30)	23	(21)	26	(27)	26	(51)	0.475	0.055
PCB#81 (0.0003)	83.4	14	(10)	13	(12)	14	(15)	21	(34)	0.106	0.659
PCB#105 (0.00003)	0.0	774	(499)	751	(644)	865	(499)	680	(648)	0.557	0.805
PCB#114 (0.00003)	1.8	255	(143)	235	(146)	296	(164)	204	(165)	0.036	0.365
PCB#118 (0.00003)	0.0	3822	(2681)	3474	(2885)	4393	(2480)	2991	(2178)	0.096	0.428
PCB#123 (0.00003)	41.7	40	(29)	43	(45)	43	(31)	36	(38)	0.777	0.688
PCB#126 (0.1)	65.4	25	(17)	26	(29)	27	(21)	22	(10)	0.726	0.747
PCB#138	0.0	22,104	(14,288)	18,679	(12,101)	21,277	(13,390)	19,152	(12,068)	0.301	0.086
PCB#153	0.0	30,806	(17,667)	26,458	(15,854)	29,645	(18,296)	28,128	(16,389)	0.353	0.089
PCB#156 (0.00003)	0.0	4685	(2481)	4060	(2342)	4118	(3343)	4193	(2246)	0.455	0.093
PCB#157 (0.00003)	0.0	823	(416)	732	(383)	785	(680)	747	(438)	0.607	0.136
PCB#167 (0.00003)	0.0	1061	(700)	960	(693)	1133	(577)	960	(675)	0.436	0.352
PCB#169 (0.03)	68.6	27	(14)	28	(20)	26	(17)	26	(14)	0.955	0.876
PCB#180	0.0	30,276	(14,802)	28,254	(14,901)	24,734	(13,129)	31,500	(14,122)	0.143	0.382
PCB#189 (0.00003)	0.0	645	(318)	588	(345)	487	(261)	604	(266)	0.098	0.277
TEQ (PCBs 2005)	–	3.7	(2.1)	3.8	(3.4)	3.8	(2.5)	3.3	(1.4)	0.754	0.824

^a PCDD/F serum concentrations were determined for 244 individuals, PCB serum concentrations were determined for 243 individuals due to insufficient serum volume for one individual

Most other PCDDs and some PCDFs also showed some differences in serum concentrations between groups (Table 2), but the magnitude of the differences were small and not statistically significant when groups 1 and 2 are compared. For PCBs there were no differences between the four groups.

Figure 1 shows the contributions to the total toxic equivalency, TEQ_(PCDD/F+PCB), of each of the dioxin-like compounds, for the four groups, and for the job title recorded on the employment records for each individual in the original cohort. When comparing the four groups, group 1 had

Table 3 Serum TCDD concentrations (pg/g lipid) of the study population, back-calculated to time of last exposure (half-life 7.6 (Michalek and Tripathi 1999); excluding a background level of 2 pg/g from back calculation)

	All production plant workers (n = 244)	Group 1 (n = 60)	Group 2 (n = 141)	Group 3 (n = 43)	Fire- fighters group 4 (n = 39)
At time phlebotomy (2007/2008)					
Age (mean)	60.3	61.6	60.0	59.8	60.7
Serum TCDD (mean)	9.4	19.1	6.3	6.0	1.6
(Min)	0.4	0.5	0.4	0.6	0.3
(Max)	335.0	335.0	77.5	26.7	6.9
Back-calculated to last year of employment at plant (capped at 1987)					
Age (mean)	31.3	33.1	30.9	30.3	n.a.
Serum TCDD (mean)	102.4	197.8	71.7	69.9	n.a.
(Min)	0.4	0.5	0.4	0.6	n.a.
(Max)	2262.5	2262.5	2207.1	528.5	n.a.
Back-calculated to 1987 (last year of 2,4,5-T production)					
Age (mean)	40.3	41.6	40.0	39.8	40.7
Serum TCDD (mean)	49.2	109.0	30.4	27.6	3.3
(Min)	0.4	0.5	0.4	0.6	0.3
(Max)	2065.5	2065.5	169.8	155.1	32.7

n.a. not applicable

the highest total TEQ_(PCDD/F+PCB) (33.7 pg/g), followed by group 2 (20.5 pg/g), group 3 (19.0 pg/g), and the firefighters in group 4 (12.0 pg/g). For the production cohort groups (groups 1–3), TCDD was the largest single contributor to the total TEQ, particularly for group 1 for which 57 % of the total TEQ was from TCDD. For group 4 (firefighters), PeCDD was the largest single contributor to the TEQ and TCDD contributed only 13 % to the total TEQ. The highest mean total TEQ was observed for the production cohort job title ‘boiler-man’ (50.3 pg/g TEQ_(PCDD/F+PCB)), followed by phenoxy herbicide synthesis workers (35.1 pg/g TEQ_(PCDD/F+PCB)).

Determinants of exposure

Because TCDD levels were the main point of difference among the four exposure groups, we studied whether these differences remained when stratifying by demographic factors. TCDD levels were consistently lowest for the firefighters (group 4), in each stratum of age, smoking, BMI, and duration of employment (Table 4). To determine whether this was due to the relatively high number of <LOD observed in the firefighters, we conducted further analyses which excluded the individuals <LOD in all groups. The firefighters’ TCDD levels remained the lowest.

We observed the highest TCDD levels in group 1, followed by groups 2, 3 and the lowest levels for group 4 consistently over most strata, indicating that this pattern was independent of these demographic factors.

TCDD levels increased from the youngest to the oldest age group for all four exposure groups: approximately eightfold for group 1, sevenfold for group 2, fivefold for group 3, and twofold for group 4.

The contrast in TCDD serum concentrations between the four groups was present for all age groups, but was particularly high for the oldest age group (70–80 years). While the average concentration in the firefighters in this age group was below 2 pg/g, it was 20 times higher (41.1 pg/g) for the phenoxy/TCP group 1.

For the firefighters (group 4), there were no notable differences in TCDD concentrations between current/ex/never smokers, between BMI strata, or for duration of employment in proximity to the production plant.

Multivariate determinants of serum concentrations

Linear regression was used to assess whether demographic and/or work-related variables were determinants of the measured serum congener concentrations. Demographic variables included age at phlebotomy (in years), gender (male/female), ethnicity (Maori/non-Maori), obesity (BMI; 3 categories), and current smoking status.

Work-related determinants included 13 variables for duration (in years) of employment at the production plant in phenoxy herbicide synthesis, surfactants production, triazines production, formulations, maintenance, research, laboratory, and as an electrician, engineer, boilerman,

Fig. 1 Mean total toxic equivalency (TEQ) of PCDD/Fs and PCBs, $TEQ_{(PCDD/F+PCB)}$ for the four exposure groups and by job title group

packer, chemist, or sprayer (the main categories of job titles recorded on employment records of the original cohort). Variables for having worked in farming, pesticide spraying, timber work or as an electrician outside of the production plant were also included in the model.

Table 5 shows the linear regression results for those congeners for which the independent variables predicted 30 % or more of the variance in the congener concentrations (based on the adjusted R^2). For all these congeners, older age and Maori ethnicity were both positively associated with serum concentrations. Female sex and higher BMI were both associated with higher serum concentrations for all these congeners, with the exception of PCB#189 for which the opposite pattern was observed. Smoking was not consistently associated with serum concentrations. Of the variables related to possible occupational exposure to dioxin-like compounds outside of the production plant (employment in agriculture, pesticide spraying, timber, and in electrical occupations), having worked in an electrical occupation was generally associated with higher serum concentrations, but this was only statistically significant for PCB#189. Of the production-related variables, duration of employment in the following five occupations

was associated with higher serum concentrations of both TCDD and PeCDD: phenoxy synthesis worker, maintenance worker, boilerman, packer, and chemist. A particularly strong association between duration of employment as a phenoxy synthesis worker and serum TCDD concentration was observed, with the model predicting one year of employment in this job being associated with 16 % higher serum TCDD concentration ($\exp(0.149) = 1.16$). Variables related to production plant employment were only associated with TCDD, PeCDD, and $TEQ_{(PCDD/Fs)}$, with the exception of employment as a boilerman within the plant which was also associated with elevated serum concentrations of PCBs. Working in agriculture was not associated with elevated serum concentrations. Regression coefficients did not change substantially when the individual with the highest serum TCDD concentration was excluded from analyses.

Discussion

In this study, former herbicide production workers had an overall mean TCDD serum concentration of 9.4 pg/g

Table 4 Serum concentrations of 2,3,7,8-TCDD for the four exposure groups, by age, smoking, BMI, and employment duration (pg/g lipid)

	Pesticide producers (<i>n</i> = 244)									Firefighters (<i>n</i> = 39)			Difference between groups p-value (ANOVA)	
	Group 1: production workers phenoxy/TCP			Group 2: production workers Other (male)			Group 3: production workers Other (female)			Group 4: Firefighters stationed near plant				
	<i>n</i>	Mean	(SD)	<i>n</i>	Mean	SD	<i>n</i>	Mean	SD	<i>n</i>	Mean	SD	All 4	1 versus 2
All	60	19.1	(46.4)	141	6.3	(10.5)	43	6.0	(6.0)	39	1.6	(1.3)	0.0004	0.0021
<i>n</i> < LOD ^a	4			22			3			9				
Age														
40–50	4	5.0	(3.9)	20	2.1	(1.7)	6	1.9	(1.9)	3	0.8	(0.4)	0.0411	0.0198
50–60	18	4.5	(7.3)	51	3.7	(5.5)	18	3.8	(2.0)	14	1.1	(0.7)	0.2582	0.6314
60–70	26	21.2	(27.7)	40	5.3	(8.0)	10	7.4	(5.8)	18	2.1	(1.5)	0.0002	0.0010
70–80	12	41.1	(93.5)	30	14.6	(17.3)	9	11.4	(9.1)	4	1.6	(1.5)	0.2805	0.1384
Tobacco smoking														
Current	16	5.3	(5.5)	17	7.1	(10.7)	4	4.2	(3.6)	4	1.5	(1.1)	0.6266	0.5536
Ex	27	30.4	(65.6)	70	7.6	(12.4)	10	6.3	(4.4)	16	1.4	(0.9)	0.0085	0.0062
Never	17	14.1	(21.4)	54	4.2	(7.1)	28	5.7	(6.6)	17	1.5	(1.0)	0.0020	0.0044
BMI														
<25	13	5.4	(4.4)	27	3.9	(8.4)	19	4.8	(6.2)	10	1.8	(2.1)	0.5928	0.5573
25–30	20	27.4	(74.9)	64	5.5	(11.0)	10	7.6	(7.4)	16	1.5	(1.0)	0.0551	0.0245
≥30	22	20.7	(24.8)	31	8.6	(9.9)	6	7.0	(4.0)	13	1.6	(0.9)	0.0036	0.0171
Duration ^b														
1 year or less	12	5.6	(5.8)	34	2.3	(2.1)	12	5.4	(5.7)	13	1.6	(1.7)	0.0051	0.0057
1–5 years	24	9.4	(17.7)	59	6.1	(11.8)	22	5.6	(5.6)	8	1.5	(1.3)	0.4063	0.3262
>5 years	24	35.5	(68.6)	48	9.2	(11.6)	9	7.8	(7.8)	18	1.7	(1.0)	0.0078	0.0115

^a Number below limit of detection. For serum concentrations below LOD, half of the detection limit was used in all calculations

^b Duration of employment at production plant; for firefighters duration of stationed near production plant divided by 2 to account for rostering

lipid, with a highest individual concentration of 335 pg/g, based on serum collected in 2007/2008. New Zealanders of the same age would be expected to have a mean TCDD serum concentration of around 2 pg/g ('t Mannetje et al. 2013). Firefighters stationed in close proximity and servicing the plant had a mean serum concentration of 1.6 pg/g (maximum 6.9 pg/g), similar to the general population. Of the producers 54 % had TCDD concentrations below 4 and 33 % below 2 pg/g, indicating that a large proportion of the producers did not experience a substantial occupational exposure to TCDD. Duration of employment in specific occupations within the plant, in particular those directly involved in phenoxy herbicide synthesis, was strongly associated with elevated TCDD concentrations, in line with the a priori assumption that they would have potential for the highest TCDD exposure. The association with duration of employment suggests that the exposure was due to continued TCDD contamination during the phenoxy herbicide production process and not a single peak exposure. An earlier community-based study similarly found no clear period of peak TCDD exposure to be associated with nearby residential exposure to TCDD (Fowles et al. 2009).

Few other New Zealand populations are known to have been occupationally or accidentally exposed to TCDD and had their serum TCDD concentrations determined. In 1988, nine 2,4,5-T sprayers (aged 45–62 and selected for their greatest numbers of years and months per years of pesticide use) were tested and found to have a mean TCDD serum concentration of 53.3 pg/g (minimum 3.0; maximum 131 pg/g) (Smith et al. 1992). When compared with the serum concentrations of the producers back-calculated to 1987, the sprayers' mean concentration was comparable to the overall mean for the producers (which was 49 pg/g back-calculated to 1987), but lower than those directly involved in phenoxy herbicide production (which was 109 pg/g back-calculated to 1987). Also, the highest exposure measured among producers (335 pg/g in 2007/2008; 2066 pg/g back-calculated to 1987) was considerably higher than the maximum TCDD concentration measured for sprayers. In 2004 residents living near the plant (aged 15–65+), who were selected based on potential of high exposure, had a mean TCDD serum concentration of 6.5 pg/g (8.4 for males aged 50 + and 9.1 for females aged 50 +) (Fowles et al. 2009). This mean concentration is close to that of those working in plant operations other

Table 5 Linear regression for the 244 pesticide producers

Dependent variable log-transformed	2378-TCDD	12378-PeCDD	1234678-HpCDD	TEQ (PCDD/F 2005)	PCB#118	PCB#138	PCB#167	PCB#189
Adjusted R^2	52 %	36 %	32 %	51 %	31 %	32 %	36 %	32 %
Beta of the covariates								
Age (years)	0.034**	0.018**	0.011*	0.022**	0.019**	0.025**	0.024**	0.016**
Gender (male)	−0.335*	−0.247*	−0.206*	−0.211*	−0.292*	−0.141	−0.283*	0.175*
Maori ethnicity	1.098**	0.423*	0.476*	0.659**	0.728**	0.636**	0.693**	0.395*
BMI 25–30	0.216	0.259*	0.095	0.225*	0.155	0.181*	0.227*	−0.071
BMI > 30	0.737**	0.387**	0.334*	0.452**	0.361**	0.291*	0.391**	−0.219*
Tobacco smoker	−0.105	0.115	−0.686**	0.011	−0.158	0.210*	−0.110	0.076
Non-plant electrical occ.	0.279	0.178	0.009	0.213	0.072	0.239	0.126	0.276*
Plant: phenoxy (y)	0.149**	0.043*	−0.012	0.091**	−0.009	0.009	−0.003	0.010
Plant: maintenance (y)	0.083**	0.034*	0.001	0.048**	0.001	0.009	0.008	0.023*
Plant: boilerman (y)	0.092*	0.055*	0.001	0.062*	0.053*	0.049*	0.049*	0.055**
Plant: packer (y)	0.070*	0.035*	0.022	0.049**	−0.009	−0.002	−0.005	−0.002
Plant: chemist (y)	0.036*	0.025*	0.022*	0.025*	0.000	0.012	0.008	0.008

Coefficients are presented for those congeners with an adjusted R^2 of at least 30 %

Although included in the model, regression coefficients of the following variables are not listed because they were not statistically significant predictors for any of the congeners: duration of production plant employment as an electrician, engineer, sprayer, and in laboratory, research, surfactants, triazines, and formulations. Non-production plant employment in agriculture, pesticide spraying, and timber

* $p \leq 0.05$; ** $p \leq 0.001$

than phenoxy herbicide production (groups 2 and 3), but lower than those directly involved in phenoxy herbicide production.

Phenoxy herbicide producers from several countries have been serum tested for TCDD concentrations (reported in (Kogevinas et al. 1997). Direct comparison with these populations is difficult because the selection of tested workers was often not random (e.g., only those with chlo-racne), and because the studies differ greatly in the length of time between last exposure and year of serum sampling. TCDD serum concentrations reported for TCDD-exposed populations, ordered by year of serum sampling, are listed in Table 6. This indicates that the New Zealand serum concentrations back-calculated to 1987 are lower than those reported for the USA (Fingerhut et al. 1991) and Russian (Ryan and Schecter 2000) production workers, while comparable to levels reported for German (Flesch-Janys et al. 1995), Dutch (Heederik et al. 1998) and US Michigan (Collins et al. 2007) production workers. The New Zealand mean TCDD serum concentrations determined in 2007/2008 are also comparable with those reported for 777 US Air Force veterans of Operation Ranch Hand tested in 2002 (Pavuk et al. 2014).

Since 2005, PeCDD has been considered toxicologically equivalent to TCDD (Van den Berg et al. 2006). It is therefore noteworthy that, in this study, duration of employment in phenoxy herbicide synthesis, maintenance, and

as a boilerman, chemist, and packer was not only associated with elevated levels of TCDD, but also (although to a much lesser extent) PeCDD. This has also been reported for other phenoxy herbicide producer populations, notably from Russia (Ryan and Schecter 2000) and from the USA (Collins et al. 2007). Furans were not associated with duration of employment in phenoxy herbicide synthesis or other occupations within the plant. Serum concentrations of PCBs in this population were comparable to general population levels (t Mannetje et al. 2013), with the exception of the boilermen, who had significantly higher concentrations of PCBs (including PCB#118, PCB#138, PCB#167, PCB#189), adding significantly to their total TEQ (mean: 50 pg/g Fig. 1) and suggesting employment in this job involved PCB exposure.

Of the 244 production plant workers, 11 were of Maori ethnicity (4.5 %). The multivariate linear regression indicated that Maori ethnicity was associated with higher TCDD concentration. For the other congeners (Table 4), concentrations were also significantly higher for Maori compared to non-Maori. This ethnic difference has not been observed in population surveys in New Zealand, where serum concentrations of dioxin-like compounds were similar for Maori and non-Maori (t Mannetje et al. 2013; Buckland et al. 2001). Diet or other lifestyle factors determining background concentrations of dioxin-like compounds are therefore unlikely to explain the pattern

Table 6 TCDD serum concentrations reported for TCDD-exposed populations, ordered by year of serum sampling

TCDD-exposed population	Number of serum samples	Year of serum sampling	Mean TCDD (pg/g)	Max. TCDD (pg/g)	References
USA, workers from two plants	253	1987/1988	233	3400	Fingerhut et al. (1991)
Germany, workers from Hamburg plant	190	1985/1994	141	2252	Flesch-Janys et al. (1995)
Russia, workers from Ufa plant	34	1992	231	1680	Ryan and Schecter (2000)
Netherlands, workers from plant A	47	1993	37	194	Heederik et al. (1998)
Italy, Seveso zone A residents	7	1996	53	90	Landi et al. (1998)
Italy, Seveso zone B residents	52	1996	11	63	Landi et al. (1998)
USA, Ranch Hand veterans	777	2002	10	325	Pavuk et al. (2014)
USA, workers from Michigan TCP plant	237	2004/2005	16	nr	Collins et al. (2007)
New Zealand, workers from plant	244	2007/2008	9	335	This study
New Zealand, workers from plant (group 1)	60	2007/2008	19	335	This study
New Zealand, workers from plant	244	Back-calculated to 1987	49	2066	This study
New Zealand, workers from plant (group 1)	60	Back-calculated to 1987	109	2066	This study

nr not reported, max. maximum

observed in this study, and it is more likely to be due to work-related factors not measured by the variables included in the model.

BMI was positively associated with TCDD and other congeners. This is in agreement with previous data indicating that higher body fat percentage is associated with lower elimination rates of TCDD (Michalek and Tripathi 1999) and other persistent organic pollutants (POPs) (Wolff et al. 2007), so that in populations with peak exposure multiple half-lives before phlebotomy-positive associations between POPs serum concentrations and BMI are to be expected (Wolff et al. 2007). For PCB#189 a negative association with BMI was observed in our study, which could possibly be indicative of a more recent exposure, as in situations of recent uptake the greater lipid denominator in obese persons may result in serum concentrations lower than those of lean individuals (Wolff et al. 2007). Alternatively, this negative association between BMI and PCB#-189 may be directly related to its chemical properties. A negative association between fat mass and PCB#189 has been reported previously (Ronn et al. 2011), also reporting similar negative associations for other PCBs with more than five chlorine atoms, suggesting that the chemical properties associated with the degree of chlorination of the PCB, such as

lipophilicity, may influence its storage in fat tissue and therefore its association with BMI.

Our study included 43 women, none of whom were directly involved in phenoxy herbicide production at the plant. Their most common occupations were laboratory worker and packer. In linear regression adjusting for occupation, female sex was generally associated with higher serum concentrations for most compounds except for PCB#189, which was a pattern very similar to that observed for BMI. Although in New Zealand general population studies, serum concentrations of TCDD and other POPs have not been found to be different between men and women ('t Mannetje et al. 2013), in a study of highly exposed individuals men had faster elimination of TCDD compared to women (Aylward et al. 2005) which may explain our findings.

It has been previously suggested that exposure to tobacco smoke results in an up-regulated activity or induction of hepatic microsomal enzymes (cytochrome P-450) resulting in an enhanced elimination of PCB and PCDD/PCDF from the body (Jain and Wang 2011). Several population studies have found marginally lower serum concentrations of dioxin-like compounds in smokers compared with non-smokers (Jain and Wang 2011). In our study

linear regression indicated that smoking was not associated with TCDD, although a positive association was observed for PCB#-138 and a negative association for HpCDD.

In this study, TCDD exposure assessment was based on a single sampling point conducted decades after the last assumed exposure. Given that the relationship between current serum measurements and ‘actual’ historical exposure is subject to inter-individual variations in elimination efficiency (Aylward et al. 2005), and the elimination rate is also shown to be dose-dependent (Aylward et al. 2005), our back-calculated TCDD exposure based on a single half-life for all participants is only an approximate indication of historical serum concentrations. Nevertheless, this study has shown that 20 years after production of 2,4,5-T had ceased, levels of TCDD and PeCDD were elevated in former workers from specific locations and occupations within the production plant. These findings place this population as that with the highest known historical TCDD exposure in New Zealand, comparable to those reported for the US Ranch Hand cohort, and comparable to or lower than those reported for several 2,4,5-T production cohorts from other countries.

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Compliance with Ethical Standards

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Conflict of interest The authors declare that they have no conflicts of interest.

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