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Morbidity in New Zealand pesticide producers exposed to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD)

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ABSTRACT

Objectives: To conduct a cross-sectional morbidity survey among 245 former employees of a pesticide production plant exposed to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) in New Zealand.

Methods: Demographic factors and health information were collected in face-to-face interviews. TCDD, lipids, thyroid hormones, glucose and immunoglobulin G (IgG) were determined in non-fasting blood. For 111 participants, a neurological examination was conducted. Associations between health outcomes and working in a TCDD exposed job (prevalence 49%) and serum TCDD concentration ≥ 10 pg/g lipid (18%) were assessed using logistic regression whilst controlling for age, gender, smoking, body mass index and ethnicity.

Results: Diabetes was more common in those who had worked in TCDD exposed jobs (OR 4.0, 95%CI 1.0–15.4) and in those with serum TCDD ≥ 10 pg/g (OR 3.1, 95%CI 0.9–10.7). Non-fasting glucose levels > 6.6 mmol/l were more common in those with TCDD exposed jobs (OR 3.6, 95%CI 1.0–12.9), as were serum free thyroxine 4 < 12.8 pmol/l (OR 4.5, 95%CI 1.4–14.4), triglycerides > 1.7 mmol/l (OR 2.5, 95%CI 1.1–5.7) and high density lipoprotein cholesterol (HDL) < 1 mmol/l (OR 4.0, 95%CI 1.2–13.2). IgG was negatively associated with TCDD (linear regression $p = 0.05$). The neurological examination revealed a higher frequency of abnormal reflexes in those with serum TCDD ≥ 10 pg/g (OR 4.8, 95%CI 1.1–21.0).

Conclusions: In this occupationally exposed population, TCDD was associated with an increased risk of diabetes and a range of subclinical responses in multiple systems (peripheral nervous system, immune system, thyroid hormones and lipid metabolism), several decades after last exposure. These results need to be interpreted with caution due to the small study size and the cross-sectional nature of the study.

1. Introduction

TCDD (2,3,7,8-tetrachlorodibenzo-*p*-dioxin) is a persistent organic pollutant and the most potent congener among the dioxin-like compounds. TCDD has a long half-life in humans (Michalek and Tripathi, 1999), and has been associated with a range of health effects (EPA U, 1994). While epidemiological research into TCDD has focused largely on cancer, other outcomes have been investigated in a limited number of TCDD exposed populations for which individual serum TCDD concentrations were available. These include chemical workers in the US (Calvert et al., 1991; Calvert et al., 1992; Sweeney et al., 1993; Sweeney et al., 1997; Calvert et al., 1998; Calvert et al., 1999) (NIOSH study), Germany (Ott et al., 1994; Zober et al., 1994; Zober et al., 1997) (BASF study), and The Netherlands (Hosnijeh et al., 2011; Hosnijeh et al., 2012; Saberi Hosnijeh et al., 2012; Hosnijeh et al., 2013a; Hosnijeh et al., 2013b); the Ranch Hand Vietnam Veterans (Henriksen et al., 1997; Burton et al., 1998; Barrett et al., 2001; Michalek et al., 2001; Michalek et al., 2003; Kang et al., 2006; Fujiyoshi et al., 2006; Michalek and Pavuk, 2008; Pavuk et al., 2003) (Air Force Health Study); and the residents of Missouri USA (Stehrgreen et al., 1988; Webb et al., 1989) and Seveso Italy (Barbieri et al., 1988; Assennato et al., 1989; Bertazzi et al., 1998; Baccarelli et al., 2002; Pesatori et al., 2003; Baccarelli et al., 2005; Warner et al., 2013; Chevrier et al., 2014). These studies, when considered together with animal studies, show a complex (yet

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incomplete) picture of interconnected clinical and subclinical responses in multiple systems including dermatological, gastrointestinal, immunological, endocrine, cardiovascular and neurological effects (Sweeney and Mocarelli, 2000). While a causal link with TCDD exposure has been established for cancer and chloracne, for most other non-cancer outcomes the body of evidence is considered insufficient.

In 1987, the New Zealand phenoxy herbicide production plant in New Plymouth was the last in the world to stop the production of the herbicide 2,4,5-trichlorophenoxyacetic acid (2,4,5-T). Workers were potentially exposed to 2,4,5-T, its intermediates (e.g. chlorophenols), and TCDD, an inadvertent contaminant from the production of 2,4,5-T and its intermediate trichlorophenol (TCP). A morbidity survey was conducted in 2007/8 and serum concentrations of TCDD and other dioxin-like compounds of 245 New Zealand pesticide producers were measured ('t Mannetje et al., 2015). Mean TCDD concentrations were 19 pg/g lipid in 60 men directly involved in phenoxy/TCP production, and 6 pg/g lipid in 141 men and 43 women who worked in other parts of the plant. In comparison, serum TCDD levels in New Zealanders (in general) of comparable age are approximately 2 pg/g ('t Mannetje et al., 2015). Back-calculated to the last year of potential exposure (1987, or last year of employment) and assuming a TCDD half-life of 7.6 years, serum concentrations in the before mentioned groups of pesticide producers would have been 160, and 70 pg/g lipid, respectively. These concentrations are comparable to those of Vietnam veterans of Operation Ranch Hand (Michalek and Tripathi, 1999), and comparable to or lower than those reported for several 2,4,5-T production cohorts from other countries ('t Mannetje et al., 2015).

Here we present the findings of a morbidity survey conducted among 245 New Zealand pesticide producers approximately 30 years after last exposure, using the participants' occupational history at the plant as well as their individual TCDD serum concentrations determined in 2007/8, as indicators of exposure.

2. Methods

2.1. Study population

Participants were recruited from the New Zealand arm of a previously established international cohort of producers of phenoxy herbicides led by the International Agency for Research on Cancer, involving workers who were employed for at least 1 month between 1969 and 1984 by the pesticide production plant in New Plymouth, New Zealand (Kogevinas et al., 1997). Of the 1025 workers 631 were still alive, had a current address in New Zealand, and were aged below 80 on 01/01/2006. From these, 430 were randomly selected and invited to participate in the morbidity survey, of which 245 (57%) participated. The measured serum concentrations of chlorinated dibenzo-*p*-dioxins, furans and PCBs, among the 245 former phenoxy herbicide workers have been published previously ('t Mannetje et al., 2015).

2.2. The morbidity survey

The morbidity survey included: (i) a blood sample of approximately 120 ml collected in glass serum tubes for the measurement of TCDD and other dioxin-like compounds, and selected health related blood parameters; (ii) a blood sample of 4 ml in an EDTA vacutainer tube (BD, Auckland, New Zealand) for complete blood count; (iii) a face-to-face interview on demographic factors, lifetime work history, employment at the pesticide production plant, health, and lifestyle factors; and (iv) a neurological examination (Stephens, 1995). Of the 245 participants, 115 had already provided blood as part of a separate but parallel conducted study by the pesticide producing company aimed to assess serum concentrations in former employees still living in the New Plymouth area (Collins et al., 2009). Hence, on the advice of the Central Regional Ethics Committee, these participants were invited to participate in all aspects of the study except blood donation, and were asked for consent for us to access their previous serum test results for TCDD and other dioxin-like compounds. The serum samples were collected and processed using identical methods to our study and analysed by the same laboratory.

Appointments with participants were conducted during 2007–2008 around the country at local medical centres where bloods were taken, interviews conducted, and participants underwent a neurological examination by an occupational physician. The health related questionnaire included questions on a range of medical conditions (including asthma, eczema, acne, bronchitis, TB, diabetes, thyroid disorders, kidney disease, liver disease); for each disease, it was recorded whether these were diagnosed by a doctor and year of diagnosis. Also included was a list of non-specific medical complaints, and the Q16 (Lundberg et al., 1997) which covers questions about current neurological symptoms. Due to the geographical spread of participants the neurological examination was only completed for 111 of the 245 participants. The neurological examination (Stephens, 1995) included assessment of cranial nerves, a sensory examination with cotton wool and pin prick, vibration sense, joint position, two point discrimination, wasting, power (upper and lower limb), reflexes, and tests of coordination.

2.3. Laboratory analyses

The anonymised serum samples (n = 245, of which 115 had already been analysed as part of the parallel conducted company study and 130 as part of this study) were analysed at AsureQuality, Lower Hutt, New Zealand using the USEPA Method 1613b (Isotope Dilution) for chlorinated dioxins and furans, and the USEPA Method 1668a (Isotope Dilution) for PCBs, and lipids.

Serum aliquots (for the 130 participants who provided blood as part of this study) were analysed at Aotea Pathology medical laboratory in Wellington, New Zealand, for non-fasting Glucose and Blood lipids (Cholesterol; Triglyceride; HDL Cholesterol; LDL Cholesterol; Cholesterol/HDL Ratio) (Roche Modular P800); TSH (Roche Modular E170, Sandwich ECL Immunoassay); Free T4 (Roche Modular E170, Competitive ECL Immunoassay), and IgG (Roche Modular P800, Immunoturbidimetric assay).

2.4. Data analyses

Serum concentrations of TCDD were expressed in pg/g lipids. The lipid content was calculated as follows: total Lipid = 2.27 × Total Cholesterol + Triglycerides + 0.632 (Phillips et al., 1989). For samples below the detection limit, half the detection limit was used. For the analyses, we used two dichotomous indices of exposure: (Michalek and Tripathi, 1999) ever worked in a highly exposed job in the pesticide production plant ('t Mannetje et al., 2015); and (EPA U, 1994) serum TCDD concentration of ≥ 10 pg/g lipid. Highly exposed jobs were defined as those that had a mean serum concentration above 10 pg/g and for which duration of employment was associated with measured TCDD concentrations, as previously determined in a detailed analysis of the determinants of exposure of the study population ('t Mannetje et al., 2015). Jobs for which duration of employment was significantly associated with measured serum TCDD concentrations included phenoxy synthesis workers (n = 45; mean serum TCDD concentration 20.9 pg/g lipid), undefined process workers (n = 5; 13.4 pg/g), boilermen (n = 6; 24.0 pg/g), maintenance workers (n = 40; 10.2 pg/g) and packers (n = 25; 11.2 pg/g).

Weighted total duration in a highly exposed job was calculated: $\text{years}_{(\text{total})} = \text{years}_{(\text{phenoxy synthesis})} + \text{years}_{(\text{unidentified process worker})} + \text{years}_{(\text{boilerman})} * 0.62 + \text{years}_{(\text{maintenance})} * 0.56 + \text{years}_{(\text{packer})} * 0.47$. The weights were based on the ratios of the regression coefficients for the association between serum TCDD and a year of employment in each of the highly exposed occupations, relative to the highest exposure group (phenoxy workers), as previously defined as part of a