

# Dioxins: A Technical Guide

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**Te Whatu Ora**  
Health New Zealand

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# General information about dioxins

## What are dioxins?

The term 'dioxins' refers to a group of highly toxic chemical compounds largely produced as by-products of combustion and some industrial processes – the polychlorinated dibenzo-*p*-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs). Dioxins are persistent environmental pollutants. They share similar chemical structures and mechanism of toxicity.

Dioxins exist in the environment as complex mixtures. There are a few natural sources of dioxins, such as forest fires and volcanic activity, but generally these natural sources emit comparatively small amounts of dioxins into the environment compared with man-made sources, such as some industrial processes. Cigarette smoke also contains small amounts of dioxins.

Seventeen PCDD/Fs are thought to pose a health and environmental risk. Toxicity of the 17 varies; 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, abbreviated as 2,3,7,8-TCDD or TCDD and commonly referred to as dioxin, is the most toxic.

Polychlorinated biphenyls (PCBs) are structurally similar to dioxins and environmentally persistent. Twelve PCBs are referred to as being 'dioxin-like' because they have the same mechanism of toxicity as dioxins.

## Exposure to dioxins

Some exposure to dioxins is inevitable because of their persistence in the environment. For most New Zealanders, about 90 percent of exposure is through diet, mainly from foods that contain animal fats, such as meat, dairy products, eggs and fish. Dioxins enter the food chain after being deposited onto soil and plant surfaces and then being ingested by grazing animals. With the exception of *Cucurbitaceas* (eg, zucchini, pumpkin), plants take up only very small amounts of dioxins through their roots. Humans are also exposed from inhalation, skin absorption, and ingesting contaminated soil or dust.

Historic sources of dioxins include leaded petrol, pentachlorophenol (PCP) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T). Advances in chemical and environmental management practices since the late 1980s have reduced dioxins emissions in New Zealand. To identify priorities to achieve further reductions, the Ministry for the Environment

(MfE) prepared a dioxin inventory based on 1998 data (Buckland et al 2000). An update, using 2008 data, shows total dioxins emissions to air reduced by almost 50 percent over the preceding decade (MfE 2011).

## Dioxins in the body

Once in the body, dioxins accumulate in fat and persist for many years. The highest amounts are found in the liver and adipose tissue. In the blood, dioxins bind to lipids and lipoproteins and serum TCDD levels are highly correlated with adipose tissue TCDD levels when both are expressed on a lipid weight basis. Dioxins are eliminated mainly in faeces, with only small amounts eliminated in urine. Some is eliminated in breast milk.

An infant absorbs at least 95 percent of the dioxins in breast milk. Models indicate that the level of dioxins in a breastfed New Zealand infant balances the mother's level after about six months of breastfeeding and then exceeds it (Smith and Lopipero 2001). Modelling shows that, by about 10 years of age, the level of dioxins in breastfed children is similar to that found in formula-fed children (US EPA 2000). The estimated New Zealand infant daily intake of dioxin-like compounds by breast milk is low compared to other countries ('t Mannelje et al 2014). If potential adverse effects are balanced against positive health aspects for (breastfed) infants, the advantages of breastfeeding far outweigh the possible disadvantages (Van den Berg et al 2017).

The half-life of TCDD in humans is uncertain but an average of 7–11 years is generally accepted. Generally, TCDD has a shorter half-life in children, men and those with less body fat. Half-life also depends on concentration. High concentrations have an initial phase of rapid elimination with shorter than average half-lives (Aylward et al 2005a; Kerger et al 2006). The mechanism underlying the rapid elimination phase is unknown. Follow-up 20 years later of women exposed in Seveso in 1976 found half-life was 7.1 years for those aged over 10, 4.3 years for those under 5 and 5.2 years for those 6–10 years (Warner et al 2014).

The levels of dioxins in humans are declining. From 1988 to 1998, dioxins in breast milk of New Zealand women decreased by about 70 percent (Bates et al 2001) and from 1998 to 2008, by 40 percent ('t Mannelje et al 2010). From 1996 to 2012, the mean age-weighted concentration of serum PCDD/F TEQ<sup>1</sup> and PCB TEQ reduced by 49 and 68 percent respectively. The mean weighted concentration of PCDD/Fs in New Zealanders aged 19–64 years is 5.81 pg TEQ/g lipid. Mean concentrations increase with age, with concentrations in the 50–64 years age group being 2.6 times higher than concentrations in the 19–24 years age group ('t Mannelje et al 2013).

<sup>1</sup> Toxic Equivalent: the amount of TCDD it would take to equal the combined toxic effects of all the dioxins in the mixture.

New Zealand PCDD/Fs concentrations are generally comparable to or lower than those reported for other countries (Australia, United States) with recent population serum studies ('t Mannetje et al 2013).

# 2,4,5-T manufacture in New Zealand

The former Ivon Watkins-Dow (IWD), now Dow AgroSciences, chemical plant located in Paritutu, New Plymouth, manufactured the herbicide 2,4,5-T from 1962 to 1987. 2,4,5-T was used extensively in New Zealand to control the pest plant gorse.

Trichlorophenol (TCP), which is an intermediate in 2,4,5-T manufacture, was manufactured on site from 1969. During TCP manufacture, TCDD is formed and remains as a contaminant in 2,4,5-T. Processing and regulatory changes since 1973 significantly reduced the amount of TCDD produced. TCDD was not a contaminant in other chemicals known to have been manufactured at the plant.

Liquid waste was incinerated on site from 1975 until 1979, and in 1985 and 1986. In 1981, a solid waste incinerator was established. Since 1986, this incinerator has operated on a non-continuous basis. Under the Clean Air Act 1972 (replaced by the Resource Management Act 1991), air monitoring was undertaken by the Department of Health.

The Department of Scientific and Industrial Research, on behalf of the Department of Health, measured incinerator emissions for dioxins every six months from 1974 to 1979, and again periodically from 1983 to 1986. Available ambient air monitoring data for the peak years of liquid waste incineration (1975–79) are incomplete. What data are available on historical emissions from the waste incinerator do not account for the total mass of TCDD present in the soil environment.

The solid waste incinerator was upgraded in 1995.<sup>2</sup> Whilst historically the solid waste incinerator would have contributed to some of the residential exposure demonstrated in the Paritutu serum dioxins study, the study's report suggests it was very unlikely to have been the primary source (Fowles et al 2005).

Two chemical release incidents are known to have occurred at the site. In November 1972, there was an explosion in the plant that manufactured the herbicide 4-(4-chloro-2-

<sup>2</sup> The incinerator is used for the treatment and disposal of solid and liquid waste materials associated with Dow AgroSciences' operations. Dow AgroSciences' resource consent for discharge of contaminants to air was renewed in 2014 and is monitored by the Taranaki Regional Council. Consent conditions include an upper limit of 0.1 ng/m<sup>3</sup> dioxins in any discharge from the incinerator stack.

methylphenoxy) butanoic acid (MCPB). No TCDD was reported to have been released. In April 1986, a bursting disc failure in the TCP plant released an estimated 70–735 mg TCDD (Air and Environmental Sciences Ltd 2002).

In 1980, independent scientists, in association with a union representative, examined current work practices at the plant and found procedures to be satisfactory. However, it was recommended that existing procedures be extended to include the pilot plant facility, the functions of which included cleaning up plant wastes and recovering usable materials (Department of Health 1980a).

During the 1970s, there were a number of ‘clusters’ of birth defects in New Zealand which were alleged to have been caused by 2,4,5-T. These were investigated by the Department of Health and no evidence was found to implicate 2,4,5-T as a causal factor (Department of Health 1977).

Concerns relating to uncertainty over exposure to dioxin from the plant and health effects were the subject of a Ministerial inquiry in 1986. The inquiry found no substantiated evidence that the manufacture of 2,4,5-T had any adverse effect on residents’ health (Brinkman et al 1986).

In 2001, the Ministry of Health contracted the Institute of Environmental Science and Research (ESR) to investigate non-occupational exposure to dioxins among current and former Paritutu residents. The community were consulted and most agreed to instigation of a serum dioxins study (Baker et al 2003). This study found elevated mean TCDD levels (6.5 pg/g lipid; 1.7 pg/g lipid expected), particularly in those who had lived in the area for at least 15 years (14.7 pg/g lipid; 2.4 pg/g lipid expected) and in older people. The TCDD levels found have been largely attributed to historical fugitive emissions from the IWD plant throughout the production years (Fowles et al 2005).

Mortality, morbidity and serum dioxins studies of IWD workers have been undertaken by Massey University (‘t Mannetje et al 2005, 2016, 2019) and the University of Otago and Dow AgroSciences (Collins et al 2008b, McBride et al 2009).



# Dioxins and health

## General information

Many studies have looked at how dioxins, in particular TCDD, can affect health, and much is still not completely understood. Dioxins can affect the growth and development of cells in ways that have the potential to result in a broad range of adverse effects.

Dioxins bind to a cellular protein, the aryl hydrocarbon receptor (AhR), which regulates gene expression. Whether adverse effects result from this binding depends on what biological responses follow. These responses differ among and within species, and among tissues in individual species. Currently it is not possible to state how, or at what levels, exposed individuals will respond because of the potential diversity of biological responses to dioxins in the body. How much dioxins a person is exposed to and for how long are both important factors as well as individual susceptibility.

Dioxins differ in toxic potential. Each congener has a Toxic Equivalency Factor (TEF) assigned to it, which denotes its toxicity relative to TCDD. The product of the congener's concentration and its TEF is added to those of the other congeners to give the Toxic Equivalent (TEQ), which is the amount of TCDD it would take to equal the combined toxic effect of all the dioxins in the mixture.

Low doses of dioxins produce biochemical changes, such as enzyme induction (eg, CYP1A1) in animals and humans, the clinical significance of which is uncertain (DeVito et al 1995). At high doses, TCDD can cause a severe acne-like skin condition, known as chloracne, as well as cancer. The range of TCDD levels in the body that result in chloracne in humans is 436 to 13,600 pg/g lipid (DeVito et al 1995). DeVito et al (1995) estimated TCDD levels at the time of highest exposure associated with increased cancer incidence to be from 495 to 31,800 pg/g lipid, based on a study of workers (Fingerhut et al 1991) and a 10-year follow-up study of the Seveso general population cohort (Bertazzi et al 1993). The estimated range for increased cancer incidence needs updating to take account of more recent epidemiological and toxicokinetic evidence.

No case of chloracne was ever diagnosed among IWD workers, including those involved in the 1986 release (Aylward et al 2010).

Animal studies show immune, reproductive and developmental effects from dioxin exposure. Reproductive and developmental toxicity has been seen in all of the animal species tested and mostly at similar doses. These animal studies have been used internationally to establish health-based guidelines for exposure to dioxins in soil, air and food.

Differences have been observed among the epidemiological studies, particularly for non-cancer effects. Some of these could be explained by differences in exposure levels and length of observation periods since exposure, and, in the case of occupational cohorts, accompanying exposure to other chemicals. It is also reasonable to assume that Paritutu residents may have been exposed to other chemicals at the same time as TCDD.

The United States Environmental Protection Agency (US EPA) began reassessing the health risk of dioxin and related compounds in 1992. This eventually separated into assessments of the non-cancer and cancer risks. The reference dose<sup>3</sup> for non-cancer risk is 0.7 pg/kg/day based on epidemiological studies by Mocarelli et al (2008) and Baccarelli et al (2008) (US EPA 2012). The World Health Organization (WHO) set a tolerable daily intake range of 1–4 pg/kg in 1997 and a provisional tolerable monthly intake of 70 pg/kg in 2002 (WHO 1998; FAO/WHO 2002). In 2002 the New Zealand Ministry of Health adopted 30 pg/kg/month, as the lower end of this range, expressed as a monthly intake given the long half-lives in humans.

TCDD is not considered to be genotoxic. However, there is some evidence that it may have an indirect genotoxic effect through oxidative stress (National Research Council 2006). In animals, TCDD is a promoter and weak initiator of carcinogenesis. Therefore, it is plausible that a carcinogenic response to TCDD exposure in humans depends upon exposure to other initiators such as cigarette smoking.

## **National Academy of Sciences evaluation of studies on dioxin and health**

As a result of the (US) Agent Orange Act of 1991 and subsequent legislation, the Institute of Medicine (IOM) of the National Academy of Sciences in the United States has reviewed scientific evidence about health effects of exposure to herbicides used in Vietnam and any of their components or contaminants, such as dioxin.<sup>4</sup> This information is provided to the United States Department of Veterans Affairs and influences what diseases among Vietnam veterans are recognised for compensation. The reviews include toxicological studies (cellular and animal) and epidemiological studies of Vietnam veterans as well as occupationally exposed and environmentally exposed populations. Distinctions among categories are based on statistical association not causation. The most recent (and final) review was in 2018 (National Academies of Sciences, Engineering, and Medicine 2018).

The list of specific diseases and conditions has been developed from the literature, concerns raised by Vietnam veterans and requests from the United States Department of Veterans Affairs. The review committee takes a neutral stance in regard to any condition

<sup>3</sup> The US EPA defines a reference dose as an estimate, with uncertainty spanning perhaps an order of magnitude, of a daily oral exposure to the human population (including sensitive groups) that is likely to be without an appreciable risk of adverse effects during a lifetime.

<sup>4</sup> 2,4-D, 2,4,5-T, TCDD, cacodylic acid and picloram.

that has not yet been addressed in the literature as having an association or not with the chemicals of interest.

The most recent review resulted in two changes of category:

- addition of hypertension from the limited or suggestive evidence category into the sufficient evidence category
- addition of monoclonal gammopathy of undetermined significance into the sufficient evidence category

The committee did not achieve consensus on whether Type 2 diabetes which has previously been in the limited or suggestive category should remain there or move into the sufficient evidence category (National Academies of Sciences, Engineering, and Medicine 2018).

The conditions that have been accepted in the sufficient evidence of health effects category are:

- Hodgkin's disease<sup>5</sup>
- non-Hodgkin's lymphoma<sup>6</sup>
- soft tissue sarcoma (STS)
- chronic lymphocytic leukaemia (CLL)
- chloracne
- hypertension
- monoclonal gammopathy of undetermined significance<sup>7</sup>.

There is limited or suggestive evidence that exposure to dioxin may cause respiratory cancers (lung, bronchus, larynx and trachea), prostate cancer, multiple myeloma, early-onset peripheral neuropathy, porphyria cutanea tarda, AL amyloidosis, Parkinson's disease, ischaemic heart disease (IHD), stroke, bladder cancer and hypothyroidism. IHD and Parkinson's disease were added to the limited or suggestive evidence category as a result of the 2008 review and stroke as a result of the 2012 review. The 2008 review also clarified that CLL includes all chronic B-cell leukaemias, for example, hairy cell leukaemia. The 2014 review clarified the breadth of the 2008 findings for Parkinson's disease so that it includes Parkinsonism and Parkinson-like syndromes.

The 2010 review changed the terminology of early-onset transient peripheral neuropathy to early-onset peripheral neuropathy to reflect that the condition is not necessarily transient (Institute of Medicine 2012). The 2014 review resulted in addition of bladder cancer and

<sup>5</sup> Also known as Hodgkin disease and Hodgkin lymphoma.

<sup>6</sup> Also known as non-Hodgkin lymphoma.

<sup>7</sup> Asymptomatic condition characterised by the presence of an abnormal protein in blood and/or urine. It increases the risk of multiple myeloma and other plasma cell disorders.

hypothyroidism to the limited or suggestive evidence category and removal of spina bifida in offspring from the limited or suggestive evidence category into the inadequate or insufficient evidence category (National Academies of Sciences, Engineering, and Medicine 2016).

A number of other conditions have been suggested, but there is insufficient or inadequate evidence to confirm that these are associated with exposure to dioxin or herbicides used in Vietnam (Table 1) (National Academies of Sciences, Engineering, and Medicine 2018).

**Table 1: Evidence of association between exposure to herbicides and adverse health outcomes**

<b>Strength of association</b>	<b>Health outcome</b>
Sufficient evidence	Chloracne STS Non-Hodgkin’s lymphoma Hodgkin’s disease CLL Hypertension Monoclonal gammopathy of undetermined significance Type 2 diabetes?
Limited/suggestive evidence	Respiratory cancers (larynx, trachea, lung, bronchus) Prostate cancer Bladder cancer Multiple myeloma Early-onset peripheral neuropathy Porphyria cutanea tarda AL amyloidosis IHD Parkinson’s disease (including Parkinsonism & Parkinson-like syndromes) Stroke Hypothyroidism Type 2 diabetes?

<b>Strength of association</b>	<b>Health outcome</b>
Inadequate/insufficient evidence	<p>Cancers of oral cavity, pharynx or nasal cavity</p> <p>Cancers of pleura, mediastinum, and other unspecified sites within the respiratory system and intrathoracic organs</p> <p>Oesophageal cancer</p> <p>Stomach cancer</p> <p>Colorectal cancer</p> <p>Hepatobiliary cancers</p> <p>Pancreatic cancer</p> <p>Bone and joint cancer</p> <p>Cancers of the reproductive organs (cervix, uterus, ovary, testis, penis)</p> <p>Renal cancer</p> <p>Leukaemia (other than CLL)</p> <p>Other myeloid diseases, including myeloproliferative neoplasms</p> <p>Melanoma</p>
	<p>Non-melanoma skin cancers</p> <p>Breast cancer</p> <p>Cancers of the brain and nervous system, including eye</p> <p>Endocrine cancers</p> <p>Cancers at other and unspecified sites</p> <p>Infertility</p> <p>Spontaneous abortion (other than for paternal TCDD exposure)</p> <p>Birth defects (including spina bifida)</p> <p>Neonatal/infant death and stillbirth</p> <p>Low birth weight</p> <p>Childhood cancer in offspring, including acute myeloid leukaemia (AML)</p> <p>Neurobehavioural disorders</p> <p>Neurogenerative disorders, excluding Parkinson's disease</p> <p>Chronic peripheral nervous system disorders</p> <p>Gastrointestinal, metabolic and digestive disorders</p> <p>Immune system disorders</p> <p>Circulatory disorders (other than hypertension, IHD and stroke)</p> <p>Respiratory disorders</p> <p>Kidney disease</p> <p>Endometriosis</p> <p>Endocrine disruption (other than hypothyroidism)</p> <p>Hearing loss</p> <p>Eye problems</p>

Strength of association	Health outcome
	Bone conditions Chronic skin disorders
Limited/suggestive evidence of no association	Spontaneous abortion and paternal TCDD exposure

Source: National Academies of Sciences, Engineering, and Medicine 2018

The 2000 IOM review committee concluded that there was limited or suggestive evidence of an association between acute myeloid leukaemia (AML) in offspring and dioxin exposure. In 2002, this conclusion was rescinded, and AML was moved to the inadequate or insufficient evidence category. The earlier conclusion had largely been based on an Australian study, the data from which were later found to be faulty. After the data had been corrected, the study showed that children of Australian Vietnam veterans did not have an increased risk of AML. Evidence from German and Norwegian studies of AML in the children of parents who had occupational exposure to pesticides was also considered in the re-evaluation.

There is no evidence dioxins can mutate DNA sequences (ie, are genotoxic). However, toxicological studies indicate that TCDD could lead to multigenerational and transgenerational effects as a result of epigenetic changes.<sup>8</sup> Epigenetic changes in animals have been shown following paternal or maternal TCDD exposure of the embryo or fetus *in utero*. Effects include lowered male/female sex ratio, reduced fertility, adverse effects on reproduction and skeletal abnormalities. In humans, lowered male/female sex ratio has been found following paternal only, or paternal and maternal, but not maternal only, TCDD exposure (Viluksela and Pohjanvirta 2019).

The 2018 review committee concluded that there is inadequate or insufficient evidence to determine whether there is an association between exposure of men and women to TCDD before conception or during pregnancy and disease in their children or grandchildren. Findings from the Seveso second and third generation health studies initiated in 2014-2016 will contribute to addressing this knowledge gap.

## Cancer

The first evidence that dioxin caused cancer came from an animal study published in 1978. Dioxin was not classified as a human carcinogen until 1997 by the International Agency for Research on Cancer (IARC) and the United States National Toxicology Program in 1999.

<sup>8</sup> Influences on gene expression without a change in DNA sequence.

The first epidemiological studies suggesting a cancer risk were a case report of three STSs in phenoxy herbicide workers (Hardell 1977) followed by a case control study on STS that showed a six-fold excess risk among workers exposed to phenoxy herbicides or chlorophenols (Hardell and Sandstrom 1979). In the 1980s, three large cohort studies were set up – two (United States National Institute for Occupational Safety and Health (NIOSH) and IARC) involve chemical workers and workers producing or spraying phenoxy herbicides and chlorophenols from many sites, and one involves people who were exposed to TCDD in Seveso, Italy, following an explosion at a TCP plant in 1976 (the Seveso studies).

At the time of IARC's 1997 evaluation, there was debate about whether classification as a human carcinogen based on limited human, sufficient animal and AhR-mediated mechanistic evidence was appropriate. In 2009, IARC reaffirmed carcinogenicity of TCDD based on sufficient human evidence for all cancers combined and limited human evidence for lung cancer, STS and non-Hodgkin's lymphoma. In 2009, 2,3,4,7,8-pentachlorodibenzofuran (PeCDF) and PCB 126 were also classified as human carcinogens based on sufficient animal and AhR-mediated mechanistic evidence (Baan et al 2009).

## Birth defects

Cleft palate has been observed in several animal species, in particular the mouse, following perinatal TCDD exposure. In mice, TCDD exposure that is not toxic to the mother, results in hydronephrosis and cleft palate (Smith and Lopipero 2001). Studies in several rodent species also show malformations of female offspring external genitalia as a result of a single dose of TCDD being administered to the mother. Animal studies of potential male-mediated birth defects following TCDD exposure are too limited for conclusions to be reached.

There are problems with extrapolating results from animals to humans because the factors that determine susceptibility to effects vary among species. There is also a lack of strong evidence of organ-specific effects among species and differences in route, dose, duration and timing of TCDD exposure.

From 1996 until 2014, the IOM concluded that there was suggestive evidence that paternal exposure to TCDD and herbicides used in Vietnam was associated with spina bifida in veterans' children but that there was insufficient or inadequate evidence of any other birth defect association. As a result of the 2014 review, spina bifida was moved into the inadequate or insufficient evidence of association category consistent with all other birth defects. This occurred because the further evidence that in 1996 was anticipated would support the association between spina bifida and paternal exposure did not eventuate.

Most epidemiological studies have investigated paternal rather than maternal TCDD exposure and its effects on offspring. These studies are frequently limited by small numbers of birth defects and poorly characterised exposure.

During the 1970s, there were a number of 'clusters' of birth defects that were alleged to have been caused by 2,4,5-T. In 1972, a letter to the editor of the *New Zealand Medical Journal* raised concerns about aerial 2,4,5-T spraying after two babies from adjacent Waikato farms were born with neural tube defects within a month of one another (Sare and Forbes 1972). The Department of Health reviewed the toxicology and epidemiology of 2,4,5-T and investigated three alleged clusters of neural tube defects in Waikato, Northland and Taranaki. No evidence was found to implicate 2,4,5-T as a causal factor in any of the cases investigated (Department of Health 1977). The Department also carried out an investigation in response to a medical practitioner linking the birth of two babies with fatal congenital abnormalities to 2,4,5-T exposure. One baby had biliary atresia, and the other had cardiac defects. It was not established that either mother was significantly exposed to 2,4,5-T at any time during her pregnancy (Department of Health 1980b).

All birth defects in Northland maternity hospital catchment areas from 1960 to 1977 were compared with densities of aerial 2,4,5-T spraying in the same areas and over the same time period. No association was found between spraying and spina bifida, anencephaly, cleft lip with or without cleft palate, isolated cleft palate, cardiac defects or hypospadias/epispadias. Aerial spraying was significantly associated with talipes, independent of ethnicity (Hanify et al 1981a, 1981b).

A study of New Zealand male pesticide applicators using 2,4,5-T found the rate of birth defects among their children did not differ from the rate among male agricultural contractors. The rate for each group was similar to that reported in other New Zealand studies (Smith et al 1981, 1982).

A meta-analysis of 22 studies of Agent Orange (50 percent 2,4-D and 50 percent 2,4,5-T) exposure in Vietnam shows an increased risk of birth defects (RR<sup>9</sup> 1.95; 95% CI<sup>10</sup> 1.59–2.39) (Ngo et al 2006). However, the conclusions that can be drawn from this study are limited as more than 50 percent of the studies (13 of 22) included have not been published in a peer-reviewed journal and 11 of the 13 Vietnamese studies included are unpublished. Schecter and Constable (2006) who have also studied dioxin exposure in Vietnam, have considered the Ngo et al study and state:

“... we are not convinced that Vietnamese investigations linking congenital malformations to dioxin are, as yet, more than suggestive. We know of no non-Vietnamese studies linking herbicide or dioxin exposure to congenital malformations other than spina bifida and anencephaly .... This article and its novel approach confirm the need for continued rigorously controlled research to definitively answer

<sup>9</sup> RR = relative risk.

<sup>10</sup> 95% CI = lower and upper 95% confidence interval around the mean.



the question [has exposure to Agent Orange or its dioxin contaminant resulted in an increased incidence of birth defects in Vietnam?] To date the answer is, at best, scientifically equivocal and, at worst, without valid positive scientific evidence.” (p1231)

## Cardiovascular disease

Twelve cohort studies (10 occupational, two environmentally exposed) have examined the relationship between dioxins and cardiovascular mortality.

Of the six occupational cohort studies that included internal comparisons and detailed exposure assessments,<sup>11</sup> dose-related increases in IHD mortality were found in four studies that reported this outcome and weaker associations with all cardiovascular disease (CVD) mortality. Only two of these studies adjusted for potential confounding by major CVD risk factors (Humblet et al 2008).

In contrast, the Seveso cohort reported no dose-related increase in IHD or all CVD mortality. This may relate to the younger population age and acute (not chronic) exposure. Excess circulatory disease mortality was seen in men in zone A of the Seveso area, the most heavily exposed zone, within 10 years of exposure which Bertazzi et al (2001) hypothesised resulted from psychosocial stress.

In its 2008 review the IOM concluded that there is suggestive evidence of an association between exposure to TCDD and herbicides used in Vietnam and IHD (Institute of Medicine 2009).

## Occupational studies

### Mortality

Four highly exposed occupational cohort studies show small increases in mortality from all cancers combined (SMR<sup>12</sup> for the combined cohorts is 1.4; 95% CI 1.2–1.6) and lung cancer (SMR 1.4; 95% CI 1.1–1.7). All-cancer mortality has been shown to increase with higher TCDD exposure and latency period of at least 20 years since exposure (Smith and Lopipero 2001).

All-cancer mortality for 2,187 United States Dow Chemical Company workers exposed to dioxins from 1940 to 1983 and followed up to 1994 was the same as the background level (SMR 1.0; 95% CI 0.8–1.1). This Dow cohort was the largest in the IARC cohort and has

<sup>11</sup> These studies are of higher quality than the others because they minimise exposure misclassification and confounding due to workers being healthier than the general population ie, the healthy worker effect.

<sup>12</sup> SMR = standardised mortality ratio.

the longest follow-up. Eleven percent of this cohort had developed chloracne, but this subgroup had lower than expected all-cancer mortality (SMR 0.5; 95% CI 0.3–1.0) (Bodner et al 2003).

Further follow-up to the date of death or 2012 found no trends of increased mortality with increased TCDD levels except for STS (SMR = 3.08, 95% CI 0.84–7.87). However, the number of deaths was small. There were nine deaths in TCP workers from acute non-lymphatic leukaemia (SMR = 2.88, 95% CI 1.32–5.47), four mesothelioma deaths (SMR = 5.12, 95% CI 1.39–13.10) and four STS deaths (SMR = 3.08, 95% CI 0.84–7.87) (Collins et al 2016).

In New Zealand, production workers along with sprayers<sup>13</sup> were included in the IARC cohort study of about 22,000 workers in 12 countries exposed to phenoxy herbicides, chlorophenols and dioxins. This study found an association between exposure to phenoxy herbicides contaminated with TCDD or higher chlorinated dioxins with increased mortality from circulatory disease, particularly IHD, and possibly diabetes (Vena et al 1998) and from STS and slight elevations from all cancers (SMR 1.2; 95% CI 1.1–1.3), non-Hodgkin's lymphoma and lung cancer. A 29 percent non-significant excess all-cancer mortality was found when workers exposed to TCDD or higher chlorinated dioxins were compared with workers in the IARC cohort with no such exposure (rate ratio 1.29; 95% CI 0.94–1.76) (Kogevinas et al 1997). New Zealand findings were not published separately because the short follow-up time to 1990 meant relatively few deaths had occurred.

The two New Zealand cohorts that were part of the IARC cohort have been subsequently followed up. Follow-up covered 1969–2000 for 813 IWD production workers<sup>14</sup> and 1973–2000 for 699 sprayers classified as exposed to TCDD, higher chlorinated dioxins and phenoxy herbicides. Non-significant excess all-cancer mortality was found among the production workers (SMR 1.24; 95% CI 0.90–1.67). All-cancer mortality was highest for synthesis workers (SMR 1.69; 95% CI 0.85–3.03) for whom it was significantly associated with duration of exposure. Lymphohaematopoietic cancer mortality was non-significantly increased (SMR 1.65; 95% CI 0.53–3.85) particularly for multiple myeloma (SMR 5.51; 95% CI 1.14–16.1). All-cancer mortality was reduced for workers who handled the final products (SMR 0.83; 95% CI 0.40–1.53) and sprayers (SMR 0.82; 95% CI 0.57–1.14) (t Mannetje et al 2005).

In another study with different inclusion criteria, follow-up to the end of 2004 of all IWD workers (n=1599)<sup>15</sup> found 196 deaths among the 1,134 workers potentially exposed to TCDD. Non-significant excess mortality was found for all cancers (SMR 1.1; 95% CI 0.9–1.4), STS (SMR 3.4; 95% CI 0.1–19.5) and non-Hodgkin's lymphoma (SMR 1.6; 95% CI 0.3–4.7) and lower than expected mortality from lung cancer. Diabetes mortality was less

<sup>13</sup>The sprayers cohort comprised 703 sprayers on the chemical applicators register from 1973–1984 which was previously studied by Smith et al (1982) in a study of birth defects.

<sup>14</sup>Employed for at least one month from January 1969 to December 1984.

<sup>15</sup>Employed for at least one day from January 1969 to November 1988. 1 November 1988 was the last day of 2,4,5-T use.

than expected, and there was a small increase in IHD mortality (SMR 1.1; 95% CI 0.9–1.5). No trend of increasing mortality with increasing cumulative TCDD exposure was seen for selected causes of death, including all cancers (McBride et al 2009).

Follow-up to 2004 found an increase in all cancers (RR 1.4; 95% CI 1.1–1.7) in veterans of Operation Ranch Hand, the United States Air Force unit that aeri ally sprayed herbicides in Vietnam from 1962 to 1971, after stratification by calendar period of service (during or before 1968), days of spraying (at least 30) and time spent in South-East Asia (up to two years).<sup>16</sup> Without stratification, there was no significant increase in cancer in the Ranch Hand cohort or any of the three TCDD exposure categories (Michalek and Pavuk 2008).

Almost 30 years after Vietnam service, United States Army veterans who had sprayed herbicides showed significantly higher risks of diabetes (OR<sup>17</sup> 1.5; 95% CI 1.15–1.95), heart disease (OR 1.52; 95% CI 1.18–1.94), hypertension (OR 1.32; 95% CI 1.08–1.61) and chronic respiratory diseases (OR 1.62; 95% CI 1.28–2.05) compared with non-sprayers. Odds ratios for these outcomes were also elevated for Vietnam veterans compared with veterans who did not serve in Vietnam but, apart for chronic respiratory diseases, were not statistically significant. All cancers (excluding non-melanoma skin cancers) were significantly elevated among Vietnam compared with non-Vietnam veterans (OR 1.46; 95% CI 1.02–2.10), but not among Vietnam sprayers compared with Vietnam non-sprayers of herbicides. Odds ratios were adjusted for factors that included age and current smoking status (Kang et al 2006). An association between diabetes and spraying herbicides has also been found among Ranch Hand veterans (Henriksen et al 1997, Michalek and Pavuk 2008).

A study of New Zealand Vietnam veterans who served between 1964 and 1975, with follow-up to the end of 2008, found significantly lower all-cause mortality; significantly increased mortality for head and neck cancers, and cancers of the oral cavity, pharynx and larynx; a non-significant excess cancer incidence; significantly increased CLL; and non-significant excess incidence and mortality for HD and multiple myeloma (McBride et al 2013).

## Morbidity

A small morbidity survey during 2007-8 of 245 former IWD employees found that TCDD exposure was associated with self-reported diabetes and non-fasting glucose levels > 6.6 mmol/l and a range of subclinical effects, including decreased immunoglobulin G (IgG), increased triglycerides, decreased high density lipoprotein (HDL) cholesterol, decreased free thyroxine (T4), and a higher frequency of abnormal reflexes among those with serum TCDD ≥10 pg/g. Blood results, other than for TCDD, were available for only 53% of participants ('t Mannelje et al 2018).

<sup>16</sup>All-cancers risk increased with years of service in South-East Asia among the veterans who were compared, hence the stratum of interest was no more than two years of service.

<sup>17</sup>OR = odds ratio.

A record linkage study of New Zealand Vietnam veterans' first hospital admissions for major causes between 1988 and 2009 found a small but significant increase in hospital admissions (standardised hospitalisation ratio for all causes was 1.18; 99% CI 1.15–o 1.21). Small increases were seen for cardiovascular and cerebrovascular disease. There was an increasing trend with age for chronic obstructive respiratory disease and chronic renal failure (Cox et al 2015).

## Seveso studies

An explosion at a TCP plant in Seveso, Italy, in 1976 released up to 30 kilograms of TCDD into the environment. This is the highest TCDD exposure known in a human residential population. However, the exposure (as measured by blood TCDD levels) was in the order of 10 to 25 times less than that reported in occupational cohort studies. It is also unique in that the exposure was to TCDD alone, and both genders and all ages are included in the exposed population. The Seveso Women's Health Study, initiated in 1996 with follow-up in 2008 and 2014, is the only comprehensive study to date of the health of a female population exposed to TCDD.

Following the incident, three exposure zones were classified based on decreasing soil TCDD levels, which were subsequently validated by blood TCDD results. Populations of the zones at the time of the incident were about 730 (zone A: highest exposure), about 5,900 (zone B: mid-range zone of exposure) and about 38,000 (zone R: low exposure). About 232,000 people from the surrounding non-exposed area have also been followed up to serve as the reference population.

For a summary of the health studies of Seveso residents, see Eskenazi et al (2018).

The findings for various health outcomes are described in more detail below.

## Chloracne

Chloracne (193 cases) was the only health effect established with certainty at the time of the incident. Most cases occurred in children, and the highest prevalence was seen in the highest exposed zone, in particular close to the plant.

## Cancer incidence

There was a non-significant excess (RR 1.2; 95% CI 0.7–2.1) in cancer incidence in the first 10 years (1977–1986) after the explosion among all young people (aged 0–19 years) who had been living in any of the three exposure zones at the time of the incident. The three zones were grouped because of the small size of the population aged 0–19 years in the two most exposed zones and the rarity of the outcomes being studied in this age group (Pesatori et al 1993).

Twenty years after the explosion, cancer incidence among all residents who had been aged 0–74 years in 1976 did not differ from expected in any of the three zones. Excess lymphohaematopoietic cancer was found in the two most contaminated zones (zone A, RR 1.39; 95% CI 0.52–3.71 and zone B, RR 1.56; 95% CI 1.07–2.27). After 15 years, excess breast cancer was found among women in zone A (RR 2.57; 95% CI 1.07–6.20). A non-significant excess for lung cancer was also noted after 15 years in zone A (RR 2.04; 95% CI 0.76–5.47). No cases of STS were found in the two most exposed zones (Pesatori et al 2009).

When follow-up was extended to 30 years, a slight increase in lymphohaematopoietic cancer incidence in zone A (RR 1.2; 95% CI 0.5–2.7) and a significant excess in zone B (RR 1.5; 95% CI 1.1–2.0) were found. A two-fold increase in all leukaemias (lymphatic and myeloid) was found in both zone A (RR 2.3; 95% CI 0.7–7.2) and B (RR 2.0; 95% CI 1.2–3.4) (Pesatori et al 2011).

Follow-up of the Seveso Women's Health Study (SWHS) cohort in 2008 found a significant positive association of individual serum TCDD with cancer incidence. The study cohort comprises women who were 1 month to 40 years of age in 1976, lived in one of the most highly exposed zones and had blood taken and stored soon after the incident. Sixty-six (6.7 percent) of the women had been diagnosed with cancer. Mean age at diagnosis was 48.8 years and geometric mean serum TCDD level was 95.3 pg/g. The adjusted hazard ratio for cancer associated with a 10-fold increase in serum TCDD level was 1.80 (95% CI 1.29–2.52) (Warner et al 2011).

## Mortality

After 20 years of follow-up, the Seveso cohort study found increased all-cancer (SMR 1.1; 95% CI 1.0–1.3), lung and rectal cancer mortality for men. Diabetes mortality was increased for women after 10 years since exposure. For men and women there was a moderate increase in lymphohaematopoietic (includes Hodgkin's disease, non-Hodgkin's lymphoma and leukaemia) cancer mortality. These results are for the two most exposed zones combined. Increased chronic cardiovascular and respiratory disease mortality occurred in the 5 to 10 years immediately after the incident among the most exposed zone residents which might be related in part to psychosocial stress (Bertazzi et al 2001).

After 25 years of follow-up, the researchers noted the finding of excess lymphohaematopoietic cancer mortality in both of the most highly exposed zones and for both men and women. All-cancer mortality was not increased but was in the 20 or more-years latency category in the most exposed zone (RR 1.65; 95% CI 1.04–2.62) because of increased male mortality (RR 1.93; 95% CI 1.12–3.33). There was suggestive evidence of excess mortality for rectal cancer, lung cancer, circulatory diseases, chronic obstructive respiratory disease and diabetes (Consonni et al 2008).

Most of the elevated mortality excesses found previously have been confirmed in the most recent update including deaths to 2013. The observed increased mortality from lympho-

haematopoietic cancers in zones A and B persisted, in particular among women. Diabetes-related deaths increased, mainly among women, with an exposure zone related gradient (zone A (n=5, RR 2.1; 95% CI 0.9–5.0); zone B (n=24, RR 1.7; 95% CI 1.1–2.5); zone R (n=161, RR 1.4; 95% CI 1.2–1.6)) (Consonni et al 2016).

Women in the two most exposed zones had elevated mortality from lymphohaematopoietic cancers (zone A (n=4, RR 1.8; 95% CI 0.7-4.9); zone B (n=20, RR 1.5; 95% CI 1.0-2.4)), diabetes (zone A (n=5, RR 2.1; 95% CI 0.9-5.1); zone B (n=24, RR 1.7; 95% CI 1.1-2.5)), chronic obstructive respiratory disease (zone B (n=17, RR 1.8; 95% CI 1.1-3.0)), and hypertension (zone A (n=9, RR 3.2; 95% CI 1.7-6.2)). Mortality was elevated 30+ years after the explosion for stomach cancer (zone A (n=3, RR 6.7; 95% CI 2.1-21.2)); melanoma (zone B (n=3, RR 5.3; 95% CI 1.6-17.8)), and hypertension (zone A (n=4, RR 5.4; 95% CI 2.0-14.4)). Men in zone A showed increased mortality from chronic ischaemic heart disease (n=9, RR 1.9; 95% CI 1.0-3.7) and other heart diseases (n=9, RR 2.0; 95% CI 1.0-3.8). In zone B, all-cancer mortality was elevated in males 20-29 years after the explosion (n=21, RR 1.7; 95% CI 1.1-2.6) (Consonni et al 2016).

## Reproductive health

A cytogenetic study in 1977 found no consistent evidence of chromosomal effects associated with TCDD exposure (Pesatori et al 2003).

There was no evidence of birth defects attributable to TCDD in 34 cases of abortion that occurred in 1976 after the incident (Pesatori et al 2003).

There was no increase in birth defects among live births and stillbirths to women who were living in the area at the time of the incident in any of the three exposure zones during the five-year period 1977–1982. The small number of exposed pregnancies in the two most exposed zones might have meant non-detection of a low risk and/or rare defects (Pesatori et al 2003).

Children born to potentially exposed parents in the 20 years (1977–1996) after the incident showed a significantly lower sex ratio (ie, increased females) with increasing paternal serum TCDD levels. This effect occurred from about 100 pg/g. Males who had been younger than 19 years old when they were exposed, fathered significantly more girls than boys (sex ratio 0.38; 95% CI 0.30–0.47) (Mocarelli et al 2000).

The Seveso Women's Health Study (n=981) was initiated in 1996 to mainly study the effects of TCDD on reproductive health. Results have been published about menstrual cycle characteristics, age at menarche and menopause, cancer incidence, endometriosis, ovarian function, uterine leiomyoma (fibroids), time to pregnancy, and birth outcomes. Differing exclusion criteria, such as age and oral contraceptive use, were applied to various components of the SWHS.

About 300 women participated in the survey on menstrual function (some women were excluded for reasons such as, older than 44 and use of hormonal contraceptives). A 10-fold increase in TCDD was associated with reduced odds of having an irregular menstrual cycle. The same increase in TCDD in women who were pre-menarcheal at the time of the explosion was associated with slightly longer (less than a day) reported menstrual cycle and reduced odds of scanty menstrual flow. There was no change in other menstrual cycle characteristics (Eskenazi et al 2002b) or age at menarche (Warner et al 2004). There was no change in age at menopause with a 10-fold increase in TCDD but a dose-related increasing risk of earlier menopause up to about 100 pg/g (Eskenazi et al 2005).

By 1998, 15 women in the SWHS cohort had been diagnosed with breast cancer. Serum TCDD close to the time of the explosion ranged from 13.1–1,960 pg/g (median 71.8 pg/g). Modelling of these results predicted a statistically significant two-fold increase (HR 2.1; 95% CI 1.0–4.6) in the hazard ratio for breast cancer associated with a 10-fold increase (eg, from 10 to 100 pg/g) in serum TCDD (Warner et al 2002). By the 2008 follow-up, the increase was not statistically significant. There were 33 cases, the majority of which were premenopausal. The adjusted hazard ratio associated with a 10-fold TCDD increase was 1.44 (95% CI 0.89–2.33) (Warner et al 2011). Serum TCDD and breast cancer incidence will be re-examined using the 2014–2016 follow-up data as the majority of the SWHS cohort will then have reached menopause and breast cancer incidence will likely have peaked (Eskenazi et al 2018).

A two-fold non-significant excess (RR 2.1; 90% CI 0.5–8.0) for endometriosis was found among women with serum TCDD levels greater than 100 pg/g close to the time of the incident, but there was no clear dose-response relationship. Nineteen women in the SWHS cohort were diagnosed with endometriosis (surgically confirmed or ovarian endometriosis diagnosed by ultrasound). Serum TCDD ranged from 9.6–686 pg/g (median 77.3 pg/g). Study limitations include a small number of cases and the possibility of misclassification of disease status as it was not possible to confirm this surgically or by ultrasound for all the participants. Disease status was uncertain for 305 women (Eskenazi et al 2002a).

No adverse effects on ovarian function were found (Warner et al 2007). There was a reduced age-adjusted risk of fibroids associated with serum TCDD above 20 pg/g collected soon after the incident (Eskenazi et al 2007).

Dose-related increases in time to pregnancy and infertility have been found. A 10-fold increase in TCDD measured at the time of the incident or extrapolated to the time of the first post-incident pregnancy was associated with about a 25 percent reduction in the monthly probability of conception (adjusted OR 0.75; 95% CI 0.60–0.95) and about a doubling of odds that pregnancy took at least 12 months to conceive (adjusted OR 1.9; 95% CI 1.1–3.2). Results were similar for different subgroups in sensitivity analyses. Median time to pregnancy was two months. Seventeen percent reported taking at least 12 months to conceive (Eskenazi et al 2010). Follow-up 40 years after the explosion, when most women will have completed their families, also found a 10-fold increase in serum

TCDD was associated with longer time to pregnancy (adjusted OR 0.80; 95% CI 0.66–0.98). Preliminary analyses suggest gene-environment interaction (between AhR pathway gene variants and TCDD levels) may play a role (Eskenazi et al 2019).

A retrospective study of pregnancy outcomes in women from the two most exposed zones found no significant findings in terms of birth outcomes such as birth weight, birth defects, spontaneous abortion and gestational age. Median serum TCDD level was 46.6 pg/g at the time of the incident.<sup>18</sup> Associations for TCDD and lowered birth weight and gestational age were stronger though non-significant for pregnancies that occurred within the first half-life (ie, eight years) after the explosion. Within the first year after the explosion, about one-third of all pregnancies ended in voluntary abortion, but the rate did not vary by exposure. Some of these pregnancies could have resulted in an adverse outcome. The authors noted the possibility that the effects are yet to be observed since the most heavily exposed women were the youngest and the least likely to have had a pregnancy at the time of the study (Eskenazi et al 2003). The 2008 SWHS follow-up found no association between estimated TCDD at pregnancy (ie, *in utero* TCDD) and spontaneous abortion, fetal growth or gestational age and a non-significant inverse association between 1976 TCDD and birth weight (Wesselink et al 2014).

In the most recent SWHS follow-up (2014–2016), no associations were found between maternal initial serum TCDD or maternal TCDD estimated at pregnancy and spontaneous abortion. Results were also similar when the analysis was limited to first post-explosion pregnancies only.

As of the most recent follow-up (2014–2016), 52 children were born with any birth defect and 13 children were born with a major birth defect (hypospadias/epispadias (n=2), anencephaly (n=1), anomalies of the heart (n=5), anomalies of the vascular system (n=3), cleft palate/lip (n=2)). In unadjusted analyses, a 10-fold increase in maternal initial serum TCDD was not associated with having a child with a birth defect (RR 1.18; 95% CI 0.72–1.91). Results were similar for maternal TCDD estimated at pregnancy (RR 1.30; 95% CI 0.84–2.02). The small number of cases limits statistical power and there was no medical record confirmation of cases (Eskenazi et al 2018).

Decreases in sperm quality (count and motility) were reported in 1998 in men who were under 10 years of age at the time of the explosion. The opposite effect was seen in men exposed during puberty. No effect was seen for those exposed as young adults (18–26 years). In both the 1–9 and 10–17 years age groups, there was a significant reduction 22 years later in the reproductive hormone estradiol and a corresponding increase in follicle stimulating hormone (FSH). These effects were seen at TCDD concentrations less than 68 pg/g. TCDD concentrations in 1976 were comparable among the three age groups (Mocarelli et al 2008).

<sup>18</sup>TCDD results are for blood taken shortly after the explosion and before conception.



About 50 percent lowered sperm concentration and total sperm count and 20 percent lowered sperm motility has been found in young adult men born to women who were living in zone A in 1976, who were exposed both *in utero* and through breastfeeding. In addition, the concentration of FSH was increased and inhibin B decreased. These findings were seen starting from 19 to 40 pg/g above the background level. They were not seen in males who had been exposed *in utero* but had not been breastfed (Mocarelli et al 2011).

## Other

Childhood TCDD level was associated with developmental enamel defects, particularly in those aged less than five years at the time of the explosion, and hypodontia (Alaluusua et al 2004).

## Other SWHS findings

The 2008 SWHS follow-up found no adverse effect on bone mineral density in those exposed aged 20 or less years. Median serum TCDD soon after the explosion was 73 pg/g (Eskenazi et al 2014). TCDD and dioxin-like PCBs have been shown to impair bone metabolism in some animal studies.

A 10-fold increase in TCDD was associated with metabolic syndrome in 2008 but only among women aged 12 years or younger at the time of the explosion (adjusted OR 2.03; 95% CI 1.25–3.30). There was no association between a 10-fold increase in TCDD and obesity, irrespective of age at exposure, or diabetes (Warner et al 2013).

Serum TCDD concentration in 1976 was inversely associated with total thyroxine concentration in 1996, but not in 2008, in women who were pre-menarche at the time of the explosion. No association was seen between TCDD concentration in 1996 and total thyroxine in 1996 or 2008. There was no association between TCDD and any other thyroid hormone (Chevrier et al 2014).

No associations were found between serum TCDD in 1976 and cognitive function (verbal or spatial working memory) measured 30 years later. No associations were also found between serum TCDD and physical function (walking speed, lower body flexibility, or manual dexterity) measured 20 years after, with the exception of a U-shaped relationship with grip strength with poorer strength at lowest and highest levels of TCDD exposure. The authors commented that further follow-up is warranted given the women were relatively young (average age 52 for memory and 57 for physical function) at the time of assessment and limited neuropsychological tests were undertaken (Ames et al 2018a).

## Effects on the second generation

Evidence suggests that maternal TCDD exposure affects neonatal thyroid function. A study of singleton live births from 1994 to the end of 2009 found that the level of

neonatal thyroid-stimulating hormone (TSH) was significantly associated with maternal TCDD levels in 1996 and at pregnancy but not in 1976 among SWHS women who were aged less than five years at the time of the 1976 explosion. There was no relationship between neonatal TSH and maternal TCDD levels among women aged five years or older at the time of the explosion (Mocarelli et al 2013). Baccarelli et al (2008) found significantly higher mean neonatal TSH levels in children born between 1994 and 2005 to women from Seveso zones A and B (resident at the time of the explosion or who had moved into the area some time up to the end of 1979) compared with the level in children born to women from the surrounding non-contaminated area. Neonatal TSH levels were also highest in the children whose mothers had the highest TCDD levels at delivery. The association between maternal serum TCDD and neonatal TSH is being re-evaluated in a larger sample through data collected in the Seveso Second Generation Health Study (Eskanazi et al 2018).

In 2014–2016, 611 children of SWHS participants who were born after the explosion were enrolled in the Seveso Second Generation Health Study (66.4% of 920 alive and eligible children born to 402 mothers). This study's goal is to describe the health impacts of *in utero* TCDD exposure in the children of SWHS participants (Eskanazi et al 2018).

Sixty-five percent (n=161) of children who were 7–17 years old at enrolment had a neuropsychological assessment. A 10-fold increase in 1976 maternal serum TCDD and maternal serum TCDD estimated to pregnancy were not significantly associated with their children's neuropsychological performance. There were suggestive findings of differences by sex and breastfeeding history to learning (more errors in boys than girls) and attention (0-1 month breastfeeding) measures (Ames et al 2019). The authors commented that further research that includes the adult children in the second generation, many of whom received the highest prenatal exposures, may better reveal the long-term neuropsychological effects of prenatal TCDD exposure.

Aryl hydrocarbon receptor genetics may explain variation in human susceptibility to dioxin. Wesselink et al (2014) found a 10-fold increase in 1976 maternal serum TCDD was associated with a non-significant reduction in birthweight. A stronger adverse association between maternal TCDD and child birthweight was found for some variations in maternal AhR genotypes suggesting gene-environment interaction (Ames et al 2018b).

In experimental studies, prenatal and perinatal exposure to TCDD suppresses immune function.

Maternal TCDD in 1976 or estimated at pregnancy was not significantly associated with asthma or hay fever. Maternal TCDD in 1976 was significantly inversely associated with eczema (adjusted RR 0.63; 95% CI 0.40–0.99). Maternal TCDD estimated at pregnancy was not significantly associated with eczema. There was no strong evidence of effect modification by child sex (Ye et al 2018).

The ratio of the length of the second finger to the fourth finger (2D:4D) is a biomarker of androgen levels and the androgen/estrogen balance *in utero*. Although TCDD is an endocrine disruptor, *in utero* TCDD exposure, either maternal TCDD in 1976 or TCDD estimated at pregnancy, was not significantly associated with 2D:4D ratio in the Seveso children (Slama et al 2019).

Warner et al (2019) found prenatal TCDD exposure alters cardiometabolic endpoints in a sex-specific manner. Maternal TCDD soon after the explosion was inversely associated with body mass index (BMI) for daughters only and associated with increased risk for metabolic syndrome (hyperglycaemia, hypertension, and dyslipidaemia) for sons only (adjusted RR 2.09, 95% CI 1.09– 4.02). Results for TCDD estimated at pregnancy were comparable.

Study of the Seveso third generation (ie, the SWHS grandchildren) has also begun. Of the 431 SWHS children who were 18 years or older, 76 daughters have reported 134 pregnancies and 45 sons have reported 76 pregnancies at interview (Eskenazi et al 2018).

## Dioxins in breast milk

The mean TCDD level in the 1988 New Zealand breast milk study which sampled 38 women who were breastfeeding their first child was 5.1 pg/g (range 0.9–13) (Bates et al 1990). Ten years later, a repeat study of 53 breastfeeding women found the mean TCDD level was 1.22 pg/g (range 0.35–2.9) (Bates et al 2001). In 2008, this had further declined to 0.75 pg/g (range 0.29–1.72) (‘t Mannetje et al 2010).

The third national breast milk study of 39 women used the same methodology. Total TEQ was 4.8 pg/g compared with 8.7 pg/g in 1998, and higher in rural than in urban areas. About 75 percent of the total TEQ was attributable to dioxins; the rest to dioxin-like PCBs. There was a 40 percent decrease in total TEQ for dioxins and a 54 percent decrease for dioxin-like PCBs. There was also a decline in levels of selected organochlorines, for example, dieldrin, over the 10 years, ranging between 34 and 90 percent (‘t Mannetje et al 2010).

New Zealand submitted the first two samples collected for its 1988 national breast milk study to the 1988 WHO breast milk survey of dioxins. Participating countries followed the same study protocol as far as possible. The purpose was to compare the total toxic burden in breast milk in different countries and in some instances, different areas within a country. Outside the European region, the lowest TEQ levels were reported from New Zealand, Thailand, India and north Vietnam (Hanoi). The highest TEQ values were reported in some areas of south Vietnam, although large differences were reported between areas in Vietnam. Large differences for TCDD levels were also reported between areas in Vietnam, including within south Vietnam. Table 2 compares the TCDD results for New Zealand with those of some other countries, including specific areas in Vietnam (Yrjanheikki 1989).

Comparison of breast milk dioxins results from different studies is not valid unless the study protocols for collecting and analysing the samples are consistent. For example, breast milk dioxins decrease over the period of lactation and generally are lower as the parity (or number of children) of the woman increases.

**Table 2: TCDD levels (pg/g lipid) in breast milk in certain countries (1988 WHO breast milk survey)**

	TCDD (pg/g)
Vietnam (Song Be)	17
Belgium	9.7
Vietnam (Ho Chi Minh)	7.1
Netherlands	5.3
United Kingdom	5.5
Poland	3.6
USA	3.3
Vietnam (Hanoi)	2.2
<b>New Zealand</b>	<b>1.4</b>
India	<1
Thailand	<1

The most recent national breast milk study ('t Mannelje et al 2010) submitted a pooled sample taken from 37 first-time mothers aged 20–30 years to the fourth WHO breast milk survey. The TCDD concentration was 0.55 pg/g lipid. The PCDD/F TEQ was 3.51 pg/g and the PCB TEQ 1.95 pg/g ('t Mannelje 2012).

# Blood TCDD levels

## Occupational studies

### New Zealand

A study of nine New Zealand 2,4,5-T applicators, with an average of 193 months spraying, found that the mean TCDD serum level (53.3 pg/g) in 1988 was almost 10 times that of the matched control subjects (mean 5.6 pg/g). In general, the serum TCDD level increased with duration of 2,4,5-T exposure. These applicators had sprayed 2,4,5-T from 83 to 372 months. Given the half-life of TCDD, the findings suggest that the increase in TCDD would be about 3 pg/g among workers who only sprayed for one year (Smith et al 1992).

Over the period 2005–2007, serum samples were collected from 241 of 1134 IWD workers who had been employed between 1962 and 1988 for at least one day and were estimated to have potential TCDD exposure based on one or more of their jobs and/or were involved in the 1986 Paritutu accidental release. These workers had spent an average of 32.5 months in a job with potential TCDD exposure. Current mean serum TCDD was 9.9 pg/g.

**Table 3: Mean TCDD levels of IWD workers by department and exposure level (pg/g lipid)**

Department	Estimated exposure level	Serum TCDD level
<b>Continuous exposure</b>		
Trichlorophenol	Low	23.4
	High	21.9
Phenoxy	Low	12.4
	Medium	13.9
	High	17.9
Formulations	Very low	8.6
	Low	5.9
Herbicides	Low	6.6
Pilot plant	High	7.5
<b>Intermittent exposure</b>		
Construction and maintenance	Very infrequent	8.4
	Infrequent	13.1
	Monthly	13.9

<b>Department</b>	<b>Estimated exposure level</b>	<b>Serum TCDD level</b>
Mechanics and transport	Very infrequent	6.6
	Infrequent	19.1
	Monthly	22.1
Phenoxy laboratory	Daily	3.6
TCDD laboratory	Daily	5.9
Other laboratories, R&D	Very infrequent	3.7
	Infrequent	3.5
	Monthly	3.9
Professional personnel (including engineering and manufacturing)	Very infrequent	15.8
	Infrequent	6.2
	Monthly	10.0
	Daily	17.5
<b>Accident</b>		
1986 release	NA	37.9
<b>Unexposed workers</b>		
Never exposed	NA	4.9

NA = not applicable

Source: Collins et al 2008b

Mean serum TCDD was 4.9 pg/g for 105 of 465 workers whose work histories indicated they were never exposed to TCDD. These workers spent an average of 53.9 months in these jobs.

There were no significant differences between the exposed and non-exposed groups for dioxins other than TCDD, furans or PCBs.

The highest current mean serum TCDD of 37.9 pg/g was found among those involved in the 1986 release. Among workers with routine continuous exposures, levels of 21.9 or 23.4 pg/g, depending on job type, were found in the TCP department. Phenoxy plant workers ranged from 12.4 to 17.9 pg/g, and workers with jobs in formulations, herbicides and the pilot plant ranged from 5.9 to 8.6 pg/g. Those with intermittent exposure, such as construction and maintenance workers, mechanics and transport and professional personnel, had levels generally consistent with many continuous exposure jobs (see Table 3 above). The lowest TCDD levels were found in laboratory workers, with the exception of the TCDD laboratory (5.9 pg/g) (Collins et al 2008b).

Measured current serum TCDD levels of former IWD workers are relatively low compared with other occupational cohorts with a similar time period between blood collection and last

occupational exposure. Estimated serum TCDD levels<sup>19</sup> for all workers in the cohort (n=1599) were less than 300 pg/g over the study period (Aylward et al 2010).

Another serum study of former IWD workers<sup>20</sup> who provided blood around the same time as the company funded study found 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 workers in other parts of the plant. Duration of employment in certain occupations, in particular phenoxy herbicide synthesis, was associated with increased serum TCDD.

Most other workers, and 39 firefighters stationed near the plant and/or who attended call-outs to the plant during the period of 2,4,5-T manufacture had serum concentrations of dioxin-like compounds comparable to those of the general population. Mean TCDD serum concentration for the firefighters was 1.6 pg/g ('t Mannetje et al 2016).

The historical TCDD exposure of the former IWD workers is comparable to that reported for the US Ranch Hand cohort by Pavuk et al (2014), and comparable to or lower than that reported for several 2,4,5-T production cohorts from other countries ('t Mannetje et al 2016).

The serum dioxin congener profile from former sawmill workers randomly selected from a morbidity study cohort 20 years after PCP use had ceased showed a predominance of 1,2,3,6,7,8-HxCDD, 1,2,3,4,6,7,8-HpCDD and OCDD (see Table 4 below). Age-adjusted levels increased with duration of exposure, particularly those with more than 10 years exposure. Levels of specific higher chlorinated dioxin congeners were significantly higher in those whose work involved high exposure (mixing PCP, cleaning sludge from dip tanks and handling treated timber on a sorting table) (McLean et al 2009b).

Exposed sawmill workers' jobs were PCP concentrate mixer, dip bath operator, timber grader, green table hand or green chain puller, yard hand, order man or boron diffusion plant operator.

<sup>19</sup> Measured TCDD levels for 346 workers, work histories and a pharmacokinetic model were used to estimate the levels for all workers.

<sup>20</sup> This study of 244 production cohort workers included the serum PCDD/Fs results of 133 workers who had already provided blood as part of the company funded study.

**Table 4: Mean levels of selected dioxin congeners in former sawmill workers (pg/g lipid)**

	Exposed (n=71)	Non-exposed (n=23)
2,3,7,8-TCDD	1.88	1.48
1,2,3,7,8-PeCDD	5.64	4.62
1,2,3,4,7,8-HxCDD	2.98	2.46
1,2,3,6,7,8-HxCDD	29.39	13.54
1,2,3,7,8,9-HxCDD	3.78	2.53
1,2,3,4,6,7,8-HpCDD	28.51	13.58
OCDD	309.25	157.83
WHO-TEQ	13.67	9.56

Source: McLean et al 2009b

Serum results from 23 members of Sawmill Workers Against Poisons (SWAP) tested by the Accident Compensation Corporation (ACC) in 2006 (at the same laboratory, using the same analytical method) showed considerably higher levels than the exposed sawmill workers but also elevated non-PCP specific congeners (see Table 5 below). The SWAP members worked at the Whakatane sawmill.

**Table 5: Levels of selected dioxin congeners in SWAP members (pg/g lipid)**

	Mean	Range
2,3,7,8-TCDD	3.58	0.62–9.25
1,2,3,7,8-PeCDD	14.84	5.97–28.4
1,2,3,4,7,8-HxCDD	9.82	2.37–18.3
1,2,3,6,7,8-HxCDD	95.26	21.5–285
1,2,3,7,8,9-HxCDD	9.95	2.71–27.4
1,2,3,4,6,7,8-HpCDD	83.96	9.27–200
OCDD	917.60	184–2200
WHO-TEQ	37.74	13.7–77.7

Source: McLean et al 2009b

## International

The blood TCDD levels estimated at the last time of exposure from three occupational cohorts that have shown increased all-cancer mortality are 2,000 pg/g (mean) up to 32,000 pg/g, 1000 to 2400 pg/g, and 345 to 3890 pg/g (Smith and Lopipero 2001).



The mean serum TCDD level of 30 United States Dow Chemical Company workers exposed to chlorophenols was estimated to be 582 pg/g, assuming a seven-year half-life, and 1928 pg/g, using a toxicokinetic model at the time workplace exposure ended (Collins et al 2006).

## Non-occupational studies

### New Zealand population

In the 2012 national population (aged 19–64 years) serum persistent organic pollutants study the mean weighted TCDD concentration was 0.88 pg/g lipid. TCDD was only detected in 37 percent of the sample (t Marnette et al 2013).

Arithmetic mean TCDD was 62 percent lower than in the 1997 survey. The weighted geometric mean of PCDDs/Fs was 5.3 pg/g which increased by age (3.2, 4.4, 4.8 and 8.1 pg/g for the 19-24, 25-34, 35-49 and 50-64 years age groups). The toxic equivalency for the overall weighted arithmetic mean PCDD/F (using WHO 1998 toxic equivalence factors) was 50 percent lower than in the 1997 survey (Coakley et al 2018).

### Paritutu, New Plymouth

Modelling was used in the Paritutu serum dioxins study to identify a potentially highly exposed group of current and former residents from a self-selected sample of the population who had lived within a 2-kilometre radius east and 1-kilometre radius south of the former IWD plant for at least one year during the period of 2,4,5-T manufacture.

The mean serum TCDD concentration was 6.5 pg/g, while the expected national mean for a similar group in 2004 was 1.7 pg/g (ie, there was a 3.8-fold increase). Expected background TCDD levels in 2004 were extrapolated from the MfE's national serum organochlorines study carried out from 1996 to 1997 (Buckland et al 2001). Individual TCDD levels ranged from 0.85 to 33.3 pg/g. Mean elevations in the age-gender subgroups were up to seven times higher than those expected, with greater elevations for older than younger people. The serum TCDD levels for each subgroup are given in Tables 6 and 7 below.

There was a non-significant mean elevation in serum TEQ of 1.2-fold, which was predominantly due to the elevation in TCDD.

Duration of residence throughout the period 1962–1987 was important in terms of whether participants had an elevated TCDD level or not. The mean TCDD level for those who had lived in Paritutu for at least 15 years was 14.7 pg/g (n=14) compared with an expected mean of 2.4 pg/g, whereas for those who had lived in Paritutu for less than 15 years, it was 3.6 pg/g (n=38) compared with an expected mean of 1.5 pg/g.

There was a statistically significant two-fold elevation in mean TEQ for those who had lived in Paritutu for at least 15 years, but there was no difference from the background TEQ level when TCDD was subtracted from the total TEQ.

**Table 6: 2004 Paritutu serum TCDD concentrations (pg/g lipid)**

Age group (in 1997)	N	Range	Mean	Median
<b>Female</b>				
19–24 years	4	0.9–2.1	1.4	1.3
25–34 years	4	0.9–1.7	1.3	1.2
35–49 years	7	1.2–13.5	5.3	5.1
50–64 years	11	1.8–17.9	6.0	4.5
65+ years	4	8.3–25.4	17.8	18.8
<b>Total</b>	<b>30</b>	<b>0.9–25.4</b>	<b>6.2</b>	<b>3.4</b>
<b>Male</b>				
25–34 years	2	1.1–2.2	1.7	1.7
35–49 years	3	1.3–2.4	1.8	1.9
50–64 years	12	1.6–24.3	6.0	3.7
65+ years	5	4.3–33.3	14.0	11.8
<b>Total</b>	<b>22</b>	<b>1.1–33.3</b>	<b>6.9</b>	<b>3.7</b>
<b>All ages</b>	<b>52</b>	<b>0.9–33.3</b>	<b>6.5</b>	<b>3.7</b>

Source: Fowles et al 2009

After the Fowles et al study had been published, the study’s principal investigator re-examined the data, using toxicokinetic information about half-lives that had not been published when they originally completed their study. This unpublished re-analysis suggests that exposure was most significant in the years 1965–1968. The volume of 2,4,5-T produced and the concentration of dioxin in 2,4,5-T was also greatest for the period 1962–1973, in particular 1964 and 1967–1973 (Fowles et al 2004).

## Mapua

A morbidity study of nearby Mapua residents concerned about onsite mechano-chemical dehalogenation remediation of a site extensively contaminated by previous pesticides manufacture, included some serum dioxins testing. Dioxin levels and measures of health did not differ significantly between the exposed community and a control community of similar socioeconomic status. TCDD was below the limit of detection in most serum samples, with some congeners being higher in controls (McBride et al 2016).

## International

With the exception of Australia, the TCDD levels in Table 8 below may not be representative of the general population of these geographical areas.

The United States mean TCDD level of 1.9 pg/g is based on four studies, totalling 588 blood samples collected from 1996 to 2001 from non-exposed people and, with the exception of one study, is not based on a population sample.

In some geographical areas other dioxins are a much greater contributor to total toxicity than TCDD, for example, despite having lower TCDD levels, the TEQ for all dioxins for Germany is similar to that for United States and two areas (Binh Hoa, Dong Nai) in south Vietnam (Schechter et al 1994).

**Table 7: Blood TCDD levels in selected countries**

	TCDD (pg/g lipid)	Reference
Germany	3.6 (n=102; whole blood)	Schechter et al 1994
Vietnam:		Schechter et al 1994
• Binh Hoa (south)	28 (pooled n=50; whole blood)	
• Dong Nai (south)	12 (pooled n=33; whole blood)	
• Ho Chi Minh City (south)	3.4 (pooled n=50; whole blood)	
• Hanoi (north)	<2.4 (pooled n=32; whole blood)	
Australia	0.9	Harden et al 2004
United States	1.9	Patterson et al 2004

Aerial spraying of Agent Orange occurred in parts of south Vietnam between 1962 and 1971, with the heaviest spraying occurring between 1967 and 1969. Blood samples were taken in 1999 from people living in three communes in central Vietnam where aerial spraying had occurred from 1965 to 1970. The amount of aerial spraying was least in Hong Van. Results of pooled whole blood samples from men and women at least 25 years old are given in Table 9 below.

**Table 8: Blood TCDD levels in Central Vietnam, 1999**

	Male	Female
Huong Lam	17 (n=31)	5.3 (n=29)
Hong Thuong	21 (n=43)	12 (n=37)
Hong Van	ND <sup>21</sup> (n=37)	ND (n=27)

Source: Dwernychuk et al 2002

At the time of the Seveso explosion in 1976, no methods were available to measure low TCDD concentrations in small blood samples. Therefore, blood taken soon after the incident was stored and analysed from the late 1980s.

TCDD concentrations for zone A ranged from 828–56,000 pg/g for 10 children with chloracne and from 1770–10,400 pg/g for nine adults with no chloracne (Bertazzi et al 1998).

Median serum TCDD levels from blood collected from the supposedly most exposed residents in 1976 were 447.0 and 94.0 pg/g for zones A and B respectively (Pesatori et al 2009).

Between 1992 and 1993 blood was also taken from randomly selected people over 20 years of age, and TCDD levels were back-calculated to 1976, assuming a half-life of 7.1 years (see Table 10 below).

**Table 9: Back-calculated Seveso TCDD results by zone**

Exposure zone	Mean	Median	N
A	333.8	388.7	6
B	111.4	76.6	52
Reference	5.3	5.5	52

Source: Bertazzi et al 1998

TCDD results close to the time of the Seveso explosion for the SWHS cohort give a range of 3.2–56,000 pg/g (median 272.0 pg/g) for zone A and 2.5–3,140 pg/g (median 47.1 pg/g) for zone B. The youngest children at the time of the incident had the highest levels, and levels decreased with age until about 13 years when they became constant. Zone of residence and age were the strongest predictors of serum TCDD. Other factors related to serum TCDD were:

<sup>21</sup>ND = not detected.

- chloracne
- nearby animal mortality
- being outdoors at the time of the incident
- consumption of home-grown produce (Eskenazi et al 2004).

In 1996 (ie, 20 years later) the mean TCDD results among randomly sampled exposed residents were 53.2 pg/g for those in zone A and 11 pg/g for those in zone B. This compares with 4.9 pg/g for those in the non-exposed zone. This study excluded people with severe medical illness and previous chloracne (Landi et al 1998). Levels ranged from 1.0 to 62.6 pg/g in zone B (Landi et al 1997).

A blood serum dioxin study in 1999 of 28 adult residents from a community in Louisiana, United States, who were concerned about exposure from nearby chemical industries found a mean TCDD level of 7.6 pg/g. Study participants had a mean age of 53 years and had lived in the area at least five years. Most reported eating locally caught fish and shellfish, although a public health advisory had been issued that limited consumption because of chemical contamination (Orloff et al 2001).

The United States Dow Chemical Company funded the University of Michigan to undertake a dioxin exposure study (University of Michigan Dioxin Exposure Study) in response to public concern that soil dioxins contamination from its plant in Midland, Michigan may have resulted in elevated serum dioxins levels. In 2005, serum testing of randomly selected adults who had lived for at least five years in one of five areas including a flood plain area and a control area found significantly elevated median TEQ in the flood plain area compared with the control area. Three of the five congeners contributing most to the serum TEQ were the main contributors to elevated soil TEQ in the flood plain (2,3,4,7,8-PeCDF) and plume area downwind of the Dow plant (2,3,7,8-TCDD and 1,2,3,7,8-PeCDD) (Hedgeman et al 2009). Modelling of the serum results showed that demographic factors, including age, gender and body fat, were the most important contributors to population variation in both serum TEQ and TCDD. Living on contaminated soil and contaminated household dust were very small contributors (Garabrant et al 2009).

## Paritutu TCDD levels in comparison to other non-occupational studies

The mean Paritutu serum TCDD result of 6.5 pg/g in 2004 (ie, 17 years after 2,4,5-T manufacture ceased in the area) is lower than that in the mid-range exposed zone of Seveso 20 years after the explosion there, and is lower than most reported results found in areas of central and south Vietnam where aerial spraying of Agent Orange is known to have occurred about 20 to 28 years previously. It is similar to that found in 1999 in a

United States community that is situated close to chemical plants but is higher than that found near the United States Dow plant.

The mean serum TCDD result of 14.7 pg/g in 2004 for those who had lived in Paritutu for at least 15 years from 1962 to 1987 is slightly higher than that of the mid-range exposed zone of Seveso 20 years after the explosion there and similar to some, but not as high as the highest, reported results found in areas of central and south Vietnam where aerial spraying of Agent Orange is known to have occurred about 20 to 28 years previously.

## Paritutu soil study

A residential Paritutu soil study undertaken in 2002 for the MfE found TCDD at all Paritutu sites investigated, but all but one result was below the most conservative international residential guidelines set to protect people's health (Pattle Delamore Partners Ltd 2002). The results are also below the New Zealand soil contaminant standard for TCDD to protect human health in regard to residential land that includes 10 percent home-grown produce consumption (Resource Management (National Environmental Standard for Assessing and Managing Contaminants in Soil to Protect Human Health) Regulations 2011).<sup>22</sup>

These soil findings are consistent with historical emissions from the IWD plant as the source of TCDD in the area, with the level of TCDD normally low in relation to other dioxins when the primary source of dioxin is combustion. A previous MfE study did not find TCDD in urban soils in any parts of New Zealand other than New Plymouth (Buckland et al 1998).

Concentrations tend to be highest close to the former IWD plant and drop off rapidly within 800 to 1000 metres of the plant. Concentrations to the east of the plant, towards Mount Moturoa Domain, are higher than to the south of the plant. This is consistent with the prevailing winds in the area.

Dioxin is very stable under most environmental conditions, undergoing only very slow change in undisturbed soil over many decades.

<sup>22</sup> Available from [www.legislation.govt.nz](http://www.legislation.govt.nz)

# Other New Plymouth studies

In 1980, an independent clinical assessment of 45 current IWD workers (90 percent response rate) involved with 2,4,5-T manufacture found no evidence that their health had been adversely affected by their work. The assessment included a comprehensive medical examination and routine laboratory tests. Three pregnancies among the partners of workers during their time employed by IWD had resulted in miscarriages; in two cases, there was a history of miscarriage, stillbirth or birth defects before the worker had been employed at IWD (Department of Health 1980a).

A cancer mortality atlas, using 1974–1978 mortality data, found a higher rate of non-Hodgkin's lymphoma and Hodgkin's disease in New Plymouth compared with the national mean (Borman 1982). At that time, there was no scientific evidence of an association between lymphatic cancer and dioxin.

From 1965 to 1971, 3.1 percent of babies born at Westown Maternity Hospital, in New Plymouth were reported by a former midwife to have had birth defects. Her study recorded 48 of 167 birth defects as neural tube defects, defined as including anencephaly, hydrocephaly, microcephaly and spina bifida (Carnachan 2002). Neural tube defects are usually defined as including anencephaly and spina bifida but not hydrocephaly, which may be caused by spina bifida or microcephaly.

A former medical officer of health carried out two studies in response to public concerns about health effects associated with living near the former IWD plant (O'Connor 2001, 2002). The first study compared health effects for the local Paritutu community with those for the New Zealand population and found no difference in cancer registrations (1990–1997), a lower rate of birth defects notifications (1988–1999) and 6 percent (within the range of variation expected by chance) higher cancer mortality (1988–1997). The results do not exclude a small increased cancer risk. Data for multiple sclerosis<sup>23</sup> were insufficient to draw conclusions about comparative incidence rates of the disease (O'Connor 2001).

The same former medical officer of health also investigated the incidence of neural tube defects, since the historically available labour ward records mention only major defects and at that time there was suggestive evidence of an association between spina bifida and exposure to TCDD.<sup>24</sup> The New Plymouth rate of neural tube defects (1965–1972) was slightly higher than the estimated national rate but the difference was not statistically significant. Three cases were identified from an area near IWD, which was two cases more than what was expected based on the New Plymouth rate. Although not a statistically

<sup>23</sup> Multiple sclerosis had been raised as a concern by the community.

<sup>24</sup> As a result of the 2014 IOM review, spina bifida in offspring was moved from the limited or suggestive evidence category into the inadequate or insufficient evidence category (National Academies of Sciences, Engineering, and Medicine 2016).

significant difference, this result is uncertain given uncertainties with the data and the definition of the study area (O'Connor 2002).

The prevalence of birth defects, and specifically talipes and congenital dislocation of the hips, in New Plymouth from Westown Maternity Hospital unpublished data for 1965–1971 was found to be significantly higher than that reported in published New Zealand hospital and population-based national and local studies from that period. There was no difference between the rates of spina bifida (which has been associated with TCDD in some studies), Down syndrome, congenital heart defects and facial clefts (Borman and Read 2010).

The New Zealand Birth Defects Monitoring Programme (NZBDMP) was established in 1977. Analysis of the earliest available data (1980–1989) from the NZBDMP showed that the rate of birth defects was consistently higher in New Plymouth than the national average and many other areas. The difference was likely due to an ascertainment bias with very high rates of congenital dislocation of the hips and talipes in New Plymouth (Borman and Read 2010).

In late 2005, the Ministry of Health released the findings of a study of all-cancer and Hodgkin's disease, non-Hodgkin's lymphoma, STS and CLL incidence and mortality in New Plymouth from 1970–2001. This study found excess all-cancer (SIR<sup>25</sup> 111; 95% CI 104–119), non-Hodgkin's lymphoma (SIR 175; 95% CI 121–246) and CLL (SIR 251; 95% CI 144–408) incidence for 1970–1974 compared with the rest of New Zealand. This is the only time period that shows an elevated cancer risk for all cancers and at least one of the four specific cancers associated with dioxin exposure. Assuming a 10-year minimum latency period and that the cause was TCDD, the period of exposure would have been 1960–1964, which is partially outside the 2,4,5-T manufacturing period and before TCP was manufactured on site. Moreover, annual 2,4,5-T production was lower over the period 1962–1964 compared with other years when the level of TCDD in 2,4,5-T was the same. Whilst TCDD exposure in the first few years of 2,4,5-T manufacture may have had a role, unknown exposure(s) before the start of 2,4,5-T manufacture and chance are also possible explanations. The study's limitations mean the possibility of an undetectable small elevation in cancer risk cannot be excluded (Read et al 2007).

<sup>25</sup> SIR = standardised incidence ratio.



# The health of the Paritutu population

To date, there has been no scientific evidence of increased disease rates in the New Plymouth population attributable to dioxin. However, current data limitations mean the possibility of a small increased risk cannot be excluded.

It is possible that the TCDD levels found may have health consequences for individuals or may cause increased rates of disease, in particular cancer, on a population basis. The extent of the cancer risk is highly uncertain, but based on the evidence from the more highly exposed IARC occupational cohort and the Seveso cohort, in 2005 the Ministry of Health estimated that it may be up to 10 percent above the national cancer mortality rate as a worst-case scenario for the population who lived for at least 15 years in the most exposed areas (ie, 1 kilometre to the east and about 400 metres to the south) during the 2,4,5-T manufacturing period or possibly in the period 1965–1968.

This risk estimation was based on the scientific evidence at the time the findings of the Paritutu serum dioxins study were released. Since then, further published studies from Seveso (Consonni et al 2008, Pesatori et al 2009) and on toxicokinetics (Aylward et al 2005a, 2005b) support the conclusion that any increase in total cancer mortality in Paritutu is likely to be very small, most likely in the order of a few percent at most.

## Serum dioxins testing

Individual blood dioxins testing is not recommended. The results only indicate if a person has been exposed to dioxins and cannot be used to predict either whether that person will develop health effects or not because of the exposure or the outcome of health effects that the person currently has. Back-calculation from a current serum TCDD level to estimate peak historic exposure is also limited due to varying half-life with age, body mass index and exposure dose.

Toxicokinetic models that take account of evidence that TCDD elimination is dose-dependent, using a first-order elimination model based on an average half-life (eg, 7–11 years) to back-calculate peak exposure could significantly underestimate peak exposure (Aylward et al 2005a; Aylward et al 2005b; Emond et al 2005).

Tests for measuring dioxins levels in people are not routinely available. A blood dioxins test costs about \$2,200 per person tested and, depending on the detection limit, a large volume of blood is required, for example, 90 millilitres.

If the detection limit is too high and various dioxins are not detected, the scientific convention when calculating the TEQ is to assume that those dioxins are actually present at a level of half the detection limit value. Depending on the number of non-detectable dioxins, this may result in an over-estimated and uninformative result.

# Pentachlorophenol

Pentachlorophenol is another chemical that was used widely in New Zealand and was contaminated with dioxins. Use in New Zealand differed from overseas where it was used mainly as a PCP in oil timber preservative. Its predominant use in New Zealand was as an antisapstain fungicide in the treatment of *Pinus radiata* either by spraying or more commonly dipping the timber in baths containing PCP solution. At four sawmills (Waipa, Hanmer Springs, Christchurch, Waikoau) a PCP-in-oil mixture, which is associated with much greater PCP absorption through the skin, was used as a timber preservative though Waikoau was a comparatively small user.

No PCP was manufactured in New Zealand. Use in the timber industry voluntarily ceased in 1988 and it was deregistered by the Pesticides Board in 1991. PCP is not approved for import or manufacture under the Hazardous Substances and New Organisms (HSNO) Act 1996.

Dioxins in PCP are mostly hexa-, hepta- and octa-chlorodibenzo-*p*-dioxins and some higher chlorinated furans. Most of the evidence on the health effects of dioxins relates to TCDD rather than these congeners. The PCP manufacturing process in the United States did not result in TCDD contamination, but elsewhere this could occur (Ruder and Yiin 2011). Results of a serum dioxins study of former New Zealand sawmill workers are given in Table 5 above. Although the dioxins in PCP are considered much less toxic than TCDD they were present in PCP at much higher concentrations than that of TCDD in 2,4,5-T. TEFs for the congeners typically found in PCP solutions are 0.1 for 1,2,3,6,7,8-HxCDD, 0.01 for 1,2,3,4,6,7,8-HpCDD and 0.0003 for OCDD.

Pentachlorophenol is readily absorbed through the lungs, skin and gastrointestinal tract. The most significant exposure route is typically skin. Elimination is predominantly in urine. Half-life is about 30 hours from plasma and 33 hours from urine following oral exposure and 19–20 days following inhalation exposure among workers. There are no human data following dermal exposure (Agency for Toxic Substances and Disease Registry 2001). Given these half-lives and the time since use ceased in New Zealand, there is no measure of PCP exposure possible now other than its dioxins contaminants.

Although PCP has acute health effects, these are not discussed here as PCP is no longer used in New Zealand.

Information on chronic health effects is limited. Epidemiological studies of chronic effects have reported impaired immune function, inflammation of the upper respiratory tract and bronchitis, reduced glomerular filtration rate and tubular function, and hepatic effects (increased biliary acid concentrations, urinary porphyrin, and serum alanine and aspartate transaminases) (Agency for Toxic Substances and Disease Registry 2001).

A study of male British Columbia sawmill workers employed for at least one year found that high exposure to chlorophenols was associated with excess risk of several birth defects. Estimated cumulative exposure during preconception and pregnancy was associated with congenital cataracts and, during pregnancy, with congenital abnormalities of genital organs. The maximal index of exposure (hours per year) for any sawmill job during preconception was associated with neural tube defects. No associations were found for low birth weight, small for gestational age, prematurity, stillbirths or neonatal deaths (Dimich-Ward et al 1996).

Pentachlorophenol is classified by the IARC as a Group 2B or possible human carcinogen based on sufficient evidence of carcinogenicity in animals but inadequate evidence of carcinogenicity in humans. No consistent association between PCP exposure and cancer has been found.

Up to 64 years of follow-up of 773 PCP<sup>26</sup> manufacturing workers from the Dow Chemical Company's Midland, Michigan plant found no excess all-cancer mortality (SMR 1.0; 95% CI 0.8–1.2) and a higher than expected non-Hodgkin's lymphoma mortality rate. Mortality results were similar when 196 workers who also had TCP exposure were excluded – for non-Hodgkin's lymphoma (SMR 2.8; 95% CI 1.1–5.7 Collins et al 2008a). Further follow-up to the date of death or 2012, found there were eight deaths from non-Hodgkin's lymphoma (SMR 1.92, 95% CI 0.83–3.79), 150 from ischaemic heart disease (SMR 1.20, 95% CI 1.01–7.89) and five from stomach ulcers (SMR 3.38, 95% CI 1.10–7.89) (Collins et al 2016).

A larger study with follow-up through to 2005 of 1,402 workers from the NIOSH cohort, including the Dow workers, who manufactured PCP but not TCP found excess all-cancer mortality (SMR 1.25; 95% CI 1.09–1.42). Excess lung cancer (SMR 1.56; 95% CI 1.27–1.90) and chronic obstructive respiratory disease (SMR 1.71; 95% CI 1.28–2.24) mortality were also found, but information on smoking was not available. These workers did not have significantly elevated non-Hodgkin's lymphoma mortality in contrast to workers who had produced both PCP and TCP (SMR 2.50; 95% CI 1.08–4.93) (Ruder and Yiin 2011).

## New Zealand studies of health effects

Walls et al (1998) carried out a questionnaire-based study of 127 self-selected PCP workers who attributed their health problems to PCP exposure. Exposure was estimated

<sup>26</sup>PCP manufactured in the United States was contaminated with dioxins but not TCDD.

from the participants' work and task history. A dose-response relationship was observed between PCP exposure and reported fever/sweating, weight loss, fatigue, nausea, and a screening test for neuropsychological dysfunction (previously used in studies of solvent-exposed workers).

A cohort mortality study of 3,895 workers who had worked at least six months in the timber industry from 1970 to 1990 and were followed up to the end of December 2003 found slightly lower than national average mortality. This is likely to be due to the healthy worker effect. Non-transport accident mortality, which mainly comprises non-transport workplace accidents, was significantly elevated.

Among exposed workers there was excess non-malignant respiratory disease mortality (SMR 1.91; 95% CI 0.98–3.33). Excess all-cause mortality (RR 1.21; 95% CI 0.94–1.55), all-cancer mortality (RR 1.41; 95% CI 0.80–2.47) and non-malignant respiratory disease mortality (RR 2.98; 95% CI 1.18–7.55) was found among exposed workers compared with non-exposed workers (McLean et al 2007).

A morbidity study by McLean et al (2009a) of 293 (116 exposed, 177 not exposed) sawmill workers who had worked at least one year in the timber industry from 1970 to 1990 found that 10 percent had high exposure (mixing PCP). Only 5 percent had worked in the industry for at least 10 years.

Workers who had been exposed to PCP reported increased prevalence of chronic respiratory disease (including TB, pleurisy and pneumonia) and recurrent diarrhoea. Of 17 neuropsychological symptoms, palpitations and sweating for no reason were more prevalent.

Neurological examination of 13 signs found exposed workers had more difficulty with straight leg raising. Non-statistically significant increases were found in exposed workers for diabetes, impaired liver function, unexplained persistent fevers, recurrent nausea, depression, frequent mood changes without reason and cranial nerve function deficit.

A significant dose-response trend was seen for chronic respiratory disease and cranial nerve function deficit; duration of employment and thyroid disorders and some neuropsychological symptoms (often going back to check things, low libido, palpitations) and frequent mood changes without reason.

Cumulative exposure was associated with frequent mood changes without reason, low libido, palpitations, the number of neuropsychological symptoms reported and difficulty with straight leg raising (McLean et al 2009a).

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