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General Information about Dioxins

What are Dioxins?

The term “dioxins” refers to a group of environmentally persistent chemicals that share similar chemical structures and mechanism of toxicity. These compounds belong to three closely related families – the polychlorinated dibenzo-p-dioxins (PCDD), polychlorinated dibenzofurans (PCDF), and certain polychlorinated biphenyls (PCBs). Dioxins exist in the environment as complex mixtures.

Dioxins in the environment are largely the result of formation as unintentional by-products of combustion and industrial processes. There are a few natural sources of dioxins, such as forest fires and volcanic activity, but generally these have emitted comparatively little dioxins into the environment compared with man made sources. Cigarette smoke also contains small amounts of dioxins.

Seventeen of the dioxins 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.

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 via atmospheric deposition onto soil and plant surfaces and subsequent ingestion by grazing animals. With the exception of Cucurbitaceae (e.g. zucchini, pumpkin), plants take up only very small amounts of dioxins via their roots. Small amounts of exposure occur from inhalation, skin absorption, and ingestion of contaminated soil or dust.

Historic sources of dioxins included leaded petrol, pentachlorophenol (PCP), PCBs and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T). Advances in chemical and environmental management practices since the late 1980s have resulted in a reduction in dioxins emissions in New Zealand.

Body Burden of Dioxins

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 reaches the mother’s level after about six months of breastfeading (Smith and Lopipero 2001). Modelling shows that by about 10 years of age the level of dioxins in breastfed children is similar to that of formula-fed children (US EPA 2000).
The half-life of TCDD in humans is uncertain but an average of 7 -11 years is generally accepted. Generally, children, men and those with less body fat have a shorter half-life. Half-life also depends on concentration with an initial phase of rapid elimination with shorter than average half-lives at high concentrations (Aylward et al 2005a; Kerger et al 2006). The mechanism underlying the rapid elimination phase is unknown.

Typically lower levels of dioxins are found in people from less industrialised countries and in younger people. Possible reasons for higher levels in older people include higher exposure several decades ago, differences in metabolism and amount of body fat, and ongoing accumulation.

Levels for the New Zealand general population are at the low end of the range of levels reported internationally. Body burdens of dioxins are declining e.g. from 1988 to 1998 dioxins in breast milk of New Zealand women decreased by about 70 percent (Bates et al 2001). A further breast milk study is currently being undertaken.

**Reducing Dioxin Exposure**

There is no generally accepted treatment to get rid of dioxins now in people. Everyone has some dioxins in their body although levels in the general population are decreasing. Reduction in the amount of animal fat in the diet reduces dioxin exposure. It is not recommended that all fat is eliminated from the diet as a moderate amount is part of a healthy balanced diet.

**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 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 from 1973 on significantly reduced the TCDD produced. TCDD was not a contaminant in other chemicals known to have been manufactured at the plant.

Incineration of liquid waste occurred on site from 1975 until 1979, and in 1985 and 1986. In 1981 a solid waste incinerator was established. Since 1986 this has operated on a non-continuous basis. Under the Clean Air Act 1972 (implemented in 1974 and 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 continues to operate, but is regularly monitored by the Taranaki Regional Council. Current emissions are below the limit set in their resource consent and accepted international emission standards. Whilst the incinerator would have contributed some of the residential exposure demonstrated in the Paritutu serum dioxins study, the study’s report suggests it was very unlikely to be the primary source (Fowles et al 2005).

Two chemical release incidents are known to have occurred. In November 1972 there was an explosion in the plant manufacturing the herbicide 4-(4-chloro-2-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 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 current procedures should be extended to include the pilot plant facility, the functions of which included clean up of plant wastes and recovery of 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 Ltd (ESR) to investigate non-occupational exposure to dioxins among current and former Paritutu residents. Community consultation occurred which resulted in majority agreement to proceed with 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 for those with at least 15 years residence (14.7 pg/g lipid; 2.4 pg/g lipid expected) and for 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 and serum dioxins studies of IWD workers have been undertaken by Massey University ('t Mannetje et al 2005) and the University of Otago and Dow AgroSciences (McBride et al 2008, Collins et al 2008a). A morbidity study of IWD workers is currently being undertaken by Massey University.

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 (Ah) receptor which regulates gene expression. The mechanisms of toxic action are unknown. Whether adverse effects occur or not depends on what biological responses follow. These responses differ among and within species, and among tissues in individual species. It is currently 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 dioxin the person is exposed to and for how long is important as well as individual susceptibility.

Dioxins differ in toxic potential and the toxicity of individual dioxins is added in order to evaluate the mixtures to which people are exposed. The term toxic equivalence (TEQ) refers to 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 (e.g. 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, and cancer in some people. The range of TCDD body burdens that result in chloracne in humans is 436 to 13,600 pg/g lipid (DeVito et al 1995). DeVito et al (1995) estimated TCDD body burdens 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 2008).

Animal studies show immune, reproductive and developmental effects. Reproductive and developmental toxicity has been seen in all of the animal species tested and most of these species respond at similar doses. Although the evidence for these non-cancer effects in people is to date limited, these animal studies have been used internationally to establish health-based guidelines for exposure to dioxins in soil, air and food.

There are differences 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, concomitant 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.

Most data indicate that TCDD is not genotoxic. There is some evidence 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. It is therefore plausible that a carcinogenic response to TCDD exposure in humans depends upon exposure to other initiators such as cigarette smoking.

Institute of Medicine Evaluation of Studies on Dioxins and Health

As a result of the (US) Agent Orange Act of 1991, the IOM of the National Academy of Sciences has carried out reviews of scientific evidence about health effects of exposure to dioxin-and
other chemical compounds in herbicides used in Vietnam and any of their components or contaminants such as dioxin. This information is provided to the US 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, occupationally exposed, and environmentally exposed populations. Distinctions among categories are based on statistical association not causation. The most recent review was published in 2009.

The list of specific diseases and conditions has been developed from the literature, concerns of Vietnam veterans and requests by the US Department of Veterans Affairs. The IOM review committee is neutral for those conditions for which association with the chemicals of interest is still unaddressed in the literature.

Those conditions that have been accepted in the sufficient evidence of health effects category by the IOM are Hodgkin’s disease (HD), non-Hodgkin’s lymphoma (NHL), soft tissue sarcoma (STS), chronic lymphocytic leukaemia (CLL) and chloracne. 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 transient peripheral neuropathy, porphyria cutanea tarda, Type 2 diabetes, hypertension, AL amyloidosis, Parkinson’s disease, ischaemic heart disease (IHD), and spina bifida in offspring. Ischaemic heart disease and Parkinson’s disease were added to this category as a result of the latest review. This review also clarified that CLL includes all chronic B-cell leukaemias e.g. hairy cell leukaemia. A number of other conditions, including other birth defects, have been suggested but there is insufficient or inadequate evidence to confirm these as being caused by exposure to dioxin (Table 1) (IOM 2009).

Table 1: Health outcomes and herbicides exposure

<table>
<thead>
<tr>
<th>Hierarchy by Strength of Association</th>
<th>Health Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sufficient evidence</td>
<td>Chloracne</td>
</tr>
<tr>
<td></td>
<td>Soft tissue sarcoma</td>
</tr>
<tr>
<td></td>
<td>Non-Hodgkin’s lymphoma</td>
</tr>
<tr>
<td></td>
<td>Hodgkin’s disease</td>
</tr>
<tr>
<td></td>
<td>Chronic lymphocytic leukaemia</td>
</tr>
<tr>
<td>Limited/Suggestive evidence</td>
<td>Respiratory cancers (larynx, trachea, lung, bronchus)</td>
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<tr>
<td></td>
<td>Prostate cancer</td>
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<tr>
<td></td>
<td>Multiple myeloma</td>
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<tr>
<td></td>
<td>Early-onset transient peripheral neuropathy</td>
</tr>
<tr>
<td></td>
<td>Porphyria cutanea tarda</td>
</tr>
<tr>
<td></td>
<td>Type 2 diabetes</td>
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<tr>
<td></td>
<td>Spina bifida (in offspring)</td>
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<tr>
<td></td>
<td>AL amyloidosis</td>
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<tr>
<td></td>
<td>Hypertension</td>
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<tr>
<td></td>
<td>Ischaemic heart disease</td>
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<tr>
<td></td>
<td>Parkinson’s disease</td>
</tr>
<tr>
<td>Inadequate/Insufficient evidence</td>
<td>Cancers of oral cavity, pharynx or nasal cavity</td>
</tr>
<tr>
<td></td>
<td>Cancers of pleura, mediastinum, and other unspecified sites within respiratory system and intrathoracic organs</td>
</tr>
</tbody>
</table>

1 2,4-D, 2,4,5-T, TCDD, cacodylic acid and picloram.
Oesophageal cancer
Stomach cancer
Colorectal cancer
Hepatobiliary cancers
Pancreatic cancer
Bone and joint cancer
Cancers of reproductive organs (cervix, uterus, ovary, testis, penis)
Renal cancer
Bladder cancer
Leukaemia (other than CLL)
Melanoma
Non-melanoma skin cancers
Breast cancer
Cancers of brain and nervous system incl eye
Endocrine cancers
Cancers at other and unspecified sites
Infertility
Spontaneous abortion (other than for paternal TCDD exposure)
Birth defects (other than spina bifida)
Neonatal/infant death and stillbirth
Low birth weight
Childhood cancer in offspring incl AML
Neurobehavioural disorders
Neurogenerative disorders excl Parkinson’s disease
Chronic peripheral nervous system disorders
Gastrointestinal, metabolic and digestive disorders
Immune system disorders
Circulatory disorders (other than hypertension and IHD)
Respiratory disorders
Endometriosis
Effects on thyroid homeostasis

| Limited/suggestive evidence of no association | Spontaneous abortion and paternal TCDD exposure |

Source: IOM 2009

In their 2000 review the IOM concluded that there was limited/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/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 data correction 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.

The 2008 IOM review committee also concluded that emerging understanding of epigenetic mechanisms means paternally-mediated transgenerational effects are more plausible than previously considered. However they identified and recommended further research in this area.
Cancer

The first evidence that dioxin caused cancer was 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 US National Toxicology Program in 1999.

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

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 maternally toxic, results in hydronephrosis and cleft palate (Smith and Lopipero 2001). Studies in several rodent species also show that administration of a single maternal dose of TCDD produces malformations of female external genitalia. Animal studies of potential male-mediated birth defects following TCDD exposure are too limited for conclusions to be made (IOM 2009).

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.

Since 1996 the IOM has concluded that there is suggestive evidence that paternal exposure to TCDD and herbicides used in Vietnam is associated with spina bifida in veterans’ children and insufficient or inadequate evidence for any other birth defect (IOM 2009).

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 which 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 following two babies born with neural tube defects within a month of one another from adjacent Waikato farms (Sare and Forbes 1972). A Department of Health report reviewed the toxicology and epidemiology of 2,4,5-T and investigation into 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 (Department of Health 1977). The Department of Health 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 woman 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 during 1960-1977 were compared with densities of aerial 2,4,5-T spraying in the same areas and 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% 2,4-D and 50% 2,4,5-T) exposure in Vietnam shows an increased risk of birth defects (RR² 1.95; 95% CI 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 (13 of 22) of the studies included have not been published in a peer-reviewed journal and 11 of the 13 Vietnamese studies included are unpublished. Commentary on this study by Schecter and Constable (2006) who have published research relating to dioxin exposure in Vietnam states:

"However 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 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."

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 which included internal comparisons and detailed exposure assessments³, dose-related increases in IHD mortality were found in all four studies reporting 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, the most heavily exposed zone, within 10 years of exposure which Bertazzi et al (2001) hypothesised resulted from psychosocial stress.

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

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² RR relative risk
³ 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 i.e. the healthy worker effect.
Occupational Studies

Four highly exposed occupational cohort studies each show small increases in mortality from all cancers combined (SMR4 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 US Dow Chemical Company workers exposed to dioxins from 1940 -1983 and followed up to 1994 was the same as the background level (SMR 1.0; 95% CI 0.8-1.1). This cohort was the largest in the IARC cohort and has the longest follow up. Eleven percent of this cohort had developed chloracne but this group had lower than expected all cancer mortality (SMR 0.5; 95% CI 0.3-1.0) (Bodner et al 2003).

In New Zealand production workers along with sprayers5 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), NHL 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 to 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 workers6 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. Lymphohaemopoietic 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 handling 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)7 found 196 deaths among the 1134 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 NHL (SMR 1.6; 95% CI 0.3-4.7) and lower than expected mortality from lung cancer. Diabetes mortality was less 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 2008).

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4 SMR standardised mortality ratio
5 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.
6 Employed for at least one month from January 1969 to December 1984.
7 Employed for at least one day from January 1969 to November 1988. 1 November was the last day of 2,4,5-T use.
Almost 30 years after Vietnam service, US Army veterans who sprayed herbicides showed significantly higher risks of diabetes (OR 1.5; 95% CI 1.15-1.95), heart disease (OR 1.52; 95% CI 1.08-1.94), hypertension (OR 1.32; 95% CI 1.08-1.61) and chronic respiratory diseases (OR 1.62; 95% CI 1.28-2.05) compared to non-sprayers. Odds ratios for these outcomes were also elevated for Vietnam veterans compared to 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 to non-Vietnam veterans (OR 1.46; 95% CI 1.02-2.10) but not when comparing spraying status among Vietnam veterans. Odds ratios were adjusted for factors including age and current smoking status (Kang et al 2006). An association between diabetes and spraying herbicides has also been found among US Air Force Ranch Hand veterans.

Seveso Studies

An explosion at a TCP plant in Seveso, Italy in 1976 resulted in 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 reported in the 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.

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 been followed up to serve as the reference population.

Findings for various health outcomes are given below.

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

- 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 incident among all people aged 0-19 years living in any of the three exposure zones at the time of the incident. The three zones were grouped given 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).

- 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 lymphohaemopoietic (includes HD, NHL and leukaemia) cancer mortality. These results are for the two most exposed zones combined. Increased chronic cardiovascular and respiratory disease mortality occurred in the 5-10 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 of note was the finding of excess lymphohaemopoietic 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 mortality among men only (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).

- 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 which 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 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 (i.e. increased females) with increasing paternal serum TCDD levels. This effect occurred from about 100 pg/g. Fathers exposed when they were less than 19 years old had 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 (SWHS) was initiated in 1996 to study the effects of TCDD on reproductive health. The study cohort (n=981) comprises women who were one 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. Results have been published about menstrual cycle characteristics, age at menarche and menopause, breast cancer, endometriosis, ovarian function, uterine leiomyoma (fibroids) and birth outcomes. Differing exclusion criteria such as age and oral contraceptive use applied to various components of the SWHS.

About 300 women participated in the survey on menstrual function (women were excluded for reasons such as age over 44, 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 premenarcheal at the time of the incident was associated with slightly longer (less than a day) reported menstrual cycle and reduced odds of scanty flow. There was no change in other menstrual cycle characteristics (Eskenazi et al 2002a), 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 incident 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 (e.g. from 10 to 100 pg/g) in serum TCDD. The authors considered this to be an early finding as the cohort was relatively young (mean age at interview was 41 years) and the number of cases small (Warner et al 2002).
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 2002b).

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).

A retrospective study of pregnancy outcome 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 (TCDD results are for blood taken shortly after the explosion and before conception). Associations for TCDD and lowered birth weight and gestational age were stronger though non-significant for pregnancies occurring within the first half-life (i.e. 8 years) after the incident. Within the first year after the incident about a 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 that it is possible 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).

Since animal evidence suggests prenatal exposure may have more significant effects for some reproductive health outcomes, Eskenazi et al (2003) consider follow up of the younger women in the SWHS and female offspring of the cohort are vital.

- Other

Results from a recent Seveso study suggest maternal TCDD exposure has an effect on neonatal thyroid function. Mean neonatal thyroid-stimulating hormone (b-TSH) levels of children born between 1994 and 2005 to women from Seveso zones A and B (resident at the time of the incident or moved into the area up to the end of 1979) were significantly higher compared to the level of children of women from the surrounding non-contaminated area. After further testing, two children of women from the contaminated zones and none from the non-contaminated area were diagnosed with congenital primary hypothyroidism. Neonatal TSH levels were highest in the children whose mothers had the highest plasma TCDD levels. These findings are consistent with animal studies showing maternal TCDD exposure induces elevated b-TSH and neonatal primary hypothyroidism (Baccarelli et al 2008).

### 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).
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 or TEQ in breast milk in different countries and in some instances different areas within countries. Outside the European region the lowest TEQ levels were reported from New Zealand, Thailand and north Vietnam (Hanoi). The highest TEQ values were reported in some areas of south Vietnam although large differences were reported between areas of Vietnam. Large differences for TCDD levels were also reported between areas of Vietnam, including within south Vietnam. Table 2 shows the TCDD results for New Zealand in comparison with some other countries including areas of Vietnam (Yrjanheikki 1989).

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

<table>
<thead>
<tr>
<th>Country</th>
<th>TCDD (pg/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vietnam (Song Be)</td>
<td>17</td>
</tr>
<tr>
<td>Belgium</td>
<td>9.7</td>
</tr>
<tr>
<td>Vietnam (Ho Chi Minh)</td>
<td>7.1</td>
</tr>
<tr>
<td>Netherlands</td>
<td>5.3</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>5.5</td>
</tr>
<tr>
<td>Poland</td>
<td>3.6</td>
</tr>
<tr>
<td>USA</td>
<td>3.3</td>
</tr>
<tr>
<td>Vietnam (Hanoi)</td>
<td>2.2</td>
</tr>
<tr>
<td><strong>New Zealand</strong></td>
<td><strong>1.4</strong></td>
</tr>
<tr>
<td>India</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Thailand</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

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.

A further national breast milk study which includes participation in a WHO breast milk survey is currently being undertaken in New Zealand.

**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 the mean TCDD serum level (53.3 pg/g) in 1988 was almost 10 times that for 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).
A television news programme, TV One Close Up @ 7, had blood from three former IWD workers and one former IWD worker’s spouse tested for TCDD in 2004 (TV One Close Up @ 7; 16 December 2004) which were compared with results from the 1996-7 Ministry for the Environment’s (MfE) serum study (Table 3).

Table 3: Blood TCDD results of IWD workers

<table>
<thead>
<tr>
<th>Age group</th>
<th>TCDD (pg/g lipid)</th>
<th>MfE mean TCDD (pg/g lipid)</th>
</tr>
</thead>
<tbody>
<tr>
<td>male 50-64 yrs</td>
<td>5.4</td>
<td>2.5</td>
</tr>
<tr>
<td>male 65+ yrs</td>
<td>2.3</td>
<td>3.0</td>
</tr>
<tr>
<td>female 65+ yrs</td>
<td>11.6</td>
<td>5.9</td>
</tr>
<tr>
<td>female 50-64 yrs</td>
<td>34.8</td>
<td>3.6</td>
</tr>
</tbody>
</table>

Two of the workers had been involved in 2,4,5-T manufacture, only one of whom had a TCDD level above the mean expected for his age group and gender. Although the workers’ TCDD levels were less than what would be expected based on overseas occupational studies the small number tested means no conclusions about the TCDD levels of former workers can be made.

During 2005-7, serum samples were collected from 241 of 1,134 IWD workers who were employed during the period 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 accidental release. These workers spent an average of 32.5 months in a job with potential TCDD exposure. Current mean serum TCDD was 9.9 pg/g.

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 not 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, mechanics and transport and professional personnel had levels generally consistent with many continuous exposure jobs (Table 4). The lowest TCDD levels were found for laboratory workers with the exception of the TCDD laboratory (5.9 pg/g) (Collins et al 2008a).

Measured current serum TCDD levels of former IWD workers are relatively low compared to other occupational cohorts with a similar time period between blood collection and last occupational exposure (Aylward et al 2008).
Table 4: Mean TCDD levels of IWD workers by department and exposure level (pg/g lipid)

<table>
<thead>
<tr>
<th>Department</th>
<th>Estimated exposure level</th>
<th>Serum TCDD Level</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Continuous exposure</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>trichlorophenol</td>
<td>low</td>
<td>23.4</td>
</tr>
<tr>
<td></td>
<td>high</td>
<td>21.9</td>
</tr>
<tr>
<td>phenoxy</td>
<td>low</td>
<td>12.4</td>
</tr>
<tr>
<td></td>
<td>medium</td>
<td>13.9</td>
</tr>
<tr>
<td></td>
<td>high</td>
<td>17.9</td>
</tr>
<tr>
<td>formulations</td>
<td>very low</td>
<td>8.6</td>
</tr>
<tr>
<td></td>
<td>low</td>
<td>5.9</td>
</tr>
<tr>
<td>herbicides</td>
<td>low</td>
<td>6.6</td>
</tr>
<tr>
<td>pilot plant</td>
<td>high</td>
<td>7.5</td>
</tr>
<tr>
<td><strong>Intermittent exposure</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>construction &amp; maintenance</td>
<td>very infrequent</td>
<td>8.4</td>
</tr>
<tr>
<td></td>
<td>infrequent</td>
<td>13.1</td>
</tr>
<tr>
<td></td>
<td>monthly</td>
<td>13.9</td>
</tr>
<tr>
<td>mechanics &amp; transport</td>
<td>very infrequent</td>
<td>6.6</td>
</tr>
<tr>
<td></td>
<td>infrequent</td>
<td>19.1</td>
</tr>
<tr>
<td></td>
<td>monthly</td>
<td>22.1</td>
</tr>
<tr>
<td>phenoxy laboratory</td>
<td>daily</td>
<td>3.6</td>
</tr>
<tr>
<td>TCDD laboratory</td>
<td>daily</td>
<td>5.9</td>
</tr>
<tr>
<td>other laboratories, R&amp;D</td>
<td>very infrequent</td>
<td>3.7</td>
</tr>
<tr>
<td></td>
<td>infrequent</td>
<td>3.5</td>
</tr>
<tr>
<td></td>
<td>monthly</td>
<td>3.9</td>
</tr>
<tr>
<td>professional personnel (incl engineering &amp; manufacturing)</td>
<td>very infrequent</td>
<td>15.8</td>
</tr>
<tr>
<td></td>
<td>infrequent</td>
<td>6.2</td>
</tr>
<tr>
<td></td>
<td>monthly</td>
<td>10.0</td>
</tr>
<tr>
<td></td>
<td>daily</td>
<td>17.5</td>
</tr>
<tr>
<td><strong>Accident</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1986 release</td>
<td>NA</td>
<td>37.9</td>
</tr>
<tr>
<td><strong>Unexposed workers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never exposed</td>
<td>NA</td>
<td>4.9</td>
</tr>
</tbody>
</table>

NA not applicable

Source: Collins et al 2008a

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 (Table 5). 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 2009a).

Exposed workers worked in a sawmill known to have cut *Pinus radiata* as mixing PCP concentrate, dip bath operator, timber grader, green table hand or green chain puller, yardhand, order man or boron diffusion plant operator.
Table 5: Mean levels of selected dioxin congeners in former sawmill workers (pg/g lipid)

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

Source: McLean et al 2009a

Serum results from 23 members of Sawmill Workers Against Poisons (SWAP) tested by the Accident Compensation Corporation 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 (Table 6). SWAP members worked at the Whakatane sawmill.

Table 6: Levels of selected dioxin congeners in SWAP members (pg/g lipid)

<table>
<thead>
<tr>
<th>Congener</th>
<th>Mean</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>2,3,7,8-TCDD</td>
<td>3.58</td>
<td>0.62-9.25</td>
</tr>
<tr>
<td>1,2,3,7,8-PeCDD</td>
<td>14.84</td>
<td>5.97-28.4</td>
</tr>
<tr>
<td>1,2,3,4,7,8-HxCDD</td>
<td>9.82</td>
<td>2.37-18.3</td>
</tr>
<tr>
<td>1,2,3,6,7,8-HxCDD</td>
<td>95.26</td>
<td>21.5-285</td>
</tr>
<tr>
<td>1,2,3,7,8,9-HxCDD</td>
<td>9.95</td>
<td>2.71-27.4</td>
</tr>
<tr>
<td>1,2,3,4,6,7,8-HpCDD</td>
<td>83.96</td>
<td>9.27-200</td>
</tr>
<tr>
<td>OCDD</td>
<td>917.60</td>
<td>184-2200</td>
</tr>
<tr>
<td>WHO-TEQ</td>
<td>37.74</td>
<td>13.7-77.7</td>
</tr>
</tbody>
</table>

Source: McLean et al 2009

- 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, 1,000 to 2,400 pg/g, and 345-3,890 pg/g (Smith and Lopipero 2001).

The mean serum TCDD level of 30 US Dow Chemical Company workers exposed to chlorophenols was estimated to be 582 pg/g, assuming a 7-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
  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 two kilometre radius east and one kilometre 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 (i.e. 3.8-fold increase). Expected background TCDD levels in 2004 were extrapolated from the MfE’s national serum organochlorines study carried out in 1996-7 (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 7 and 8 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 to 1987 was important in terms of whether participants had an elevated TCDD level or not. The mean TCDD level for those with at least 15 years residence was 14.7 pg/g (n=14) compared to an expected mean of 2.4 pg/g, whereas for those with less than 15 years residence it was 3.6 pg/g (n=38) compared to an expected mean of 1.5 pg/g.

Table 7: Mean serum TCDD levels for Paritutu and New Zealand

<table>
<thead>
<tr>
<th>Age Group</th>
<th>N</th>
<th>Paritutu TCDD (pg/g lipid) Mean (95% CI)</th>
<th>Projected TCDD (pg/g lipid) from MfE study Mean (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19-24 yrs</td>
<td>4</td>
<td>1.4 (0.8 - 2.1)</td>
<td>0.6 (0.5 - 0.7)</td>
</tr>
<tr>
<td>25-34 yrs</td>
<td>4</td>
<td>1.3 (1.0 - 1.6)</td>
<td>0.9 (0.8 - 1.1)</td>
</tr>
<tr>
<td>35-49 yrs</td>
<td>7</td>
<td>5.3 (2.3 – 8.3)</td>
<td>1.4 (1.3 - 1.6)</td>
</tr>
<tr>
<td>50-64 yrs</td>
<td>11</td>
<td>6.0 (3.1 – 8.9)</td>
<td>2.4 (1.9 - 2.8)</td>
</tr>
<tr>
<td>65+ yrs</td>
<td>4</td>
<td>17.8 (9.9 - 25.7)</td>
<td>4.1 (3.5 - 4.6)</td>
</tr>
<tr>
<td>Total</td>
<td>30</td>
<td>6.2 (3.8 - 8.6)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25-34 yrs</td>
<td>2</td>
<td>1.7 (0.7 - 2.7)</td>
<td>0.6 (0.5 - 0.7)</td>
</tr>
<tr>
<td>35-49 yrs</td>
<td>3</td>
<td>1.9 (1.3 - 2.5)</td>
<td>1.1 (1.0 - 1.2)</td>
</tr>
<tr>
<td>50-64 yrs</td>
<td>12</td>
<td>6.1 (2.3 –10.0)</td>
<td>1.5 (1.4 - 1.7)</td>
</tr>
<tr>
<td>65+ yrs</td>
<td>5</td>
<td>14.0 (4.1 - 24.0)</td>
<td>1.9 (1.7 - 2.1)</td>
</tr>
<tr>
<td>Total</td>
<td>22</td>
<td>6.9 (3.5 –10.3)</td>
<td></td>
</tr>
<tr>
<td>All ages</td>
<td>52</td>
<td>6.5 (4.6 - 8.6)</td>
<td>1.7 (1.5 - 1.9)</td>
</tr>
</tbody>
</table>

Source: Fowles et al 2005

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

For study participants who lived in Paritutu at least 15 years the peak increase in serum TCDD above background at the time production ceased in 1987 (or earlier if they left the area) is crudely estimated to have been between 39 and 77 pg/g assuming average half lives of 7.1 and

---

8 95% CI = lower and upper 95% confidence interval around the mean.
9 The MfE stratum was for 15-24 year olds.
11 years. For the total study group the mean past peak TCDD level is estimated to have been between 17 and 35 pg/g above background.

Subsequent to the publication of this study the study’s principal investigator re-examined the data using toxicokinetic information about half-lives that was not published at the time the ESR study was completed. This suggests that exposure was most significant in the years 1965 to 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 to 1973, in particular 1964 and 1967 to 1973 (Fowles et al 2004).

Table 8: 2004 Paritutu Serum TCDD concentrations (pg/g lipid)

<table>
<thead>
<tr>
<th>Age Group (in 1997)</th>
<th>N</th>
<th>Range</th>
<th>Mean</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19-24 yrs</td>
<td>4</td>
<td>0.9-2.1</td>
<td>1.4</td>
<td>1.3</td>
</tr>
<tr>
<td>25-34 yrs</td>
<td>4</td>
<td>0.9-1.7</td>
<td>1.3</td>
<td>1.2</td>
</tr>
<tr>
<td>35-49 yrs</td>
<td>7</td>
<td>1.2-13.5</td>
<td>5.3</td>
<td>5.1</td>
</tr>
<tr>
<td>50-64 yrs</td>
<td>11</td>
<td>1.8-17.9</td>
<td>6.0</td>
<td>4.5</td>
</tr>
<tr>
<td>65+ yrs</td>
<td>4</td>
<td>8.3-25.4</td>
<td>17.8</td>
<td>18.8</td>
</tr>
<tr>
<td>Total</td>
<td>30</td>
<td>0.9-25.4</td>
<td>6.2</td>
<td>3.4</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15-24 yrs</td>
<td>2</td>
<td>1.1-2.2</td>
<td>1.7</td>
<td>1.7</td>
</tr>
<tr>
<td>25-34 yrs</td>
<td>3</td>
<td>1.3-2.4</td>
<td>1.8</td>
<td>1.9</td>
</tr>
<tr>
<td>35-49 yrs</td>
<td>12</td>
<td>1.6-24.3</td>
<td>6.0</td>
<td>3.7</td>
</tr>
<tr>
<td>65+ yrs</td>
<td>5</td>
<td>4.3-33.3</td>
<td>14.0</td>
<td>11.8</td>
</tr>
<tr>
<td>Total</td>
<td>22</td>
<td>1.1-33.3</td>
<td>6.9</td>
<td>3.7</td>
</tr>
<tr>
<td>All ages</td>
<td>52</td>
<td>0.9-33.3</td>
<td>6.5</td>
<td>3.7</td>
</tr>
</tbody>
</table>

Source: Fowles et al 2009

- International

With the exception of Australia, the TCDD levels in Table 9 may not be representative of the general population of these geographical areas.

The US mean TCDD level of 1.9 pg/g is based on four studies totaling 588 blood samples collected from 1996-2001 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 e.g. the TEQ for all dioxins for Germany is similar to US and two areas (Binh Hoa, Dong Nai) in south Vietnam despite lower TCDD levels (Schecter et al 1994).
Table 9: Blood TCDD levels in selected countries

<table>
<thead>
<tr>
<th>Country</th>
<th>TCDD (pg/g lipid)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Germany</td>
<td>3.6 (n= 102; whole blood)</td>
<td>Schecter et al 1994</td>
</tr>
<tr>
<td>Vietnam:</td>
<td></td>
<td>Schecter et al 1994</td>
</tr>
<tr>
<td>Binh Hoa (sth)</td>
<td>28 (pooled n=50; whole blood)</td>
<td></td>
</tr>
<tr>
<td>Dong Nai (sth)</td>
<td>12 (pooled n=33; whole blood)</td>
<td></td>
</tr>
<tr>
<td>Ho Chi Minh City (sth)</td>
<td>3.4 (pooled n=50; whole blood)</td>
<td></td>
</tr>
<tr>
<td>Hanoi (nth)</td>
<td>&lt;2.4 (pooled n=32; whole blood)</td>
<td></td>
</tr>
<tr>
<td>Australia</td>
<td>0.9</td>
<td>Harden et al 2004</td>
</tr>
<tr>
<td>United States</td>
<td>1.9</td>
<td>Patterson et al 2004</td>
</tr>
</tbody>
</table>

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 occurred from 1965 - 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 10.

Table 10: Blood TCDD levels in Central Vietnam, 1999

<table>
<thead>
<tr>
<th></th>
<th>Male (n)</th>
<th>Female (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huong Lam</td>
<td>17 (n=31)</td>
<td>5.3 (n=29)</td>
</tr>
<tr>
<td>Hong Thuong</td>
<td>21 (n=43)</td>
<td>12 (n=37)</td>
</tr>
<tr>
<td>Hong Van</td>
<td>ND&lt;sup&gt;10&lt;/sup&gt; (n=37)</td>
<td>ND (n=27)</td>
</tr>
</tbody>
</table>

Source: Dwernychuk et al 2002

At the time of the Seveso incident 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 1,770-10,400 pg/g for nine adults with no chloracne (Bertazzi et al 1998).

In 1992-3 blood was also taken from randomly selected people over 20 years and TCDD levels back-calculated to 1976 assuming a half-life of 7.1 years (Table 11).

<sup>10</sup> ND = not detected
Table 11: Back-calculated Seveso TCDD results by zone

<table>
<thead>
<tr>
<th>Exposure zone</th>
<th>Mean</th>
<th>Median</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>333.8</td>
<td>388.7</td>
<td>6</td>
</tr>
<tr>
<td>B</td>
<td>111.4</td>
<td>76.6</td>
<td>52</td>
</tr>
<tr>
<td>R</td>
<td>5.3</td>
<td>5.5</td>
<td>52</td>
</tr>
</tbody>
</table>

Source: Bertazzi et al 1998

TCDD results close to the time of the incident 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 which decreased with age until about 13 years and then were constant. Zone of residence and age were the strongest predictors of serum TCDD. Other factors related to serum TCDD were chloracne, nearby animal mortality, being outdoors at the time of the incident and consumption of home-grown produce (Eskenazi et al 2004).

In 1996 (i.e. 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 in zone B. This compares to 4.9 pg/g 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 of a community in Louisiana, US concerned about exposure from nearby chemical industries found a mean TCDD level of 7.6 pg/g. Study participants had an 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 limiting consumption because of chemical contamination had been issued (Orloff et al 2001).

The US Dow Chemical Company funded the University of Michigan to undertake a dioxin exposure study in response to public concern that dioxins contamination from its plant in Midland, Michigan of areas of the city and the river flood plain may have resulted in elevated serum dioxins levels.

Serum testing of randomly selected adults with at least five years residence from five areas including a control area in 2005 found significantly elevated mean TCDD levels of 3.7 pg/g in the flood plain (n=243), 3.2 pg/g near the flood plain (n=205), 3.4 pg/g in the plume area downwind of the Dow plant (n=43) and 3.6 pg/g outside of the flood plain and plume areas (n=204) compared to the control area (1.8 pg/g, n=251). Age, gender and body fat were the most important contributors to population variation in both serum TEQ and TCDD. Eating fish and game particularly from contaminated areas was also a contributor whereas living on contaminated soil, living in the region and contaminated household dust were very small contributors (University of Michigan Dioxin Exposure Study 2006).

Paritutu TCDD Levels in Comparison to Other Non-occupational Studies

The mean Paritutu serum TCDD result of 6.5 pg/g in 2004 (i.e.17 years after 2,4,5-T manufacture ceased) is lower than the mid-range exposed zone of Seveso 20 years after the incident, and 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 US community close to chemical plants but higher than that found near the US Dow plant.

The mean serum TCDD result of 14.7 pg/g in 2004 for those who lived in Paritutu at least 15 years from 1962 to 1987 is slightly higher than the mid-range exposed zone of Seveso 20 years after the incident 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 soil study in 2002 undertaken for the MfE found TCDD at all Paritutu sites investigated, but all but one result was below the most conservative residential guidelines set to protect people’s health that exist internationally (Pattle Delamore Partners 2002).

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

Concentrations tend to be highest close to the former IWD plant, and drop off rapidly within 800 to 1000 metres from 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. Consequently, it is considered unlikely that historical TCDD soil levels on residential properties would have been significantly higher than the levels measured in this study and would have exceeded the health-based soil guidelines.

**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 to indicate that their health had been adversely affected by their work. This 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 prior to employment at IWD (Department of Health 1980a).

A cancer mortality atlas using 1974-1978 mortality data found a higher rate of NHL and HD in New Plymouth compared to 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 were reported by a former midwife to have had a birth defect. 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). No difference in cancer registrations (1990-1997), a lower rate of birth defects notifications (1988-1999) and six percent (within the range of variation expected by chance) higher cancer mortality (1988-1997) was found compared to the New Zealand population. The results do not exclude a small increased cancer risk. Data for multiple sclerosis\(^{11}\) were insufficient to draw conclusions about comparative incidence rates of the disease (O’Connor 2001).

O’Connor investigated the incidence of neural tube defects since the historically available labour ward records mention only major defects and there is suggestive evidence of an association between spina bifida and exposure to TCDD. 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 significant difference this is uncertain given uncertainties with the data and the definition of the study area (O’Connor 2002).

In late 2005 the Ministry of Health released the findings of a study of all cancer and HD, NHL, STS, and CLL incidence and mortality in New Plymouth from 1970 to 2001. This study found excess all cancer (SIR\(^{12}\) 111; 95% CI 104-119), NHL (SIR 175; 95% CI 121-246) and CLL (SIR 251; 95% CI 144-408) incidence for 1970-1974 compared to 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 the cause was TCDD, the period of exposure would have been 1960-1964, which is partially outside of the 2,4,5-T manufacturing period and before TCP was manufactured on site. Annual 2,4,5-T production was also low during 1962-1964 compared to 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).

The Health of the Paritutu Population

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

\(^{11}\) Multiple sclerosis had been raised as a concern by the community.
\(^{12}\) SIR standardised incidence ratio
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 to date from the more highly exposed IARC occupational cohort and the Seveso cohort it is 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 in the most exposed areas (i.e. 1 km to the east and about 400 m to the south) at least 15 years during the 2,4,5-T manufacturing years or possibly in the period 1965-1968.

**Serum Dioxins Testing**

Individual blood dioxins testing is not recommended. The results only indicate if the person has been exposed to dioxins and cannot be used to predict 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 which take account of evidence that TCDD elimination is dose-dependent show using a first-order elimination model based on an average half-life (e.g. 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 and depending on the detection limit a large volume of blood is required e.g. 90 ml.

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 uninformative result.

**Pentachlorophenol**

Pentachlorophenol is another chemical that was widely used in New Zealand which was contaminated with dioxins. Use in New Zealand differed from overseas where it was mainly used as a PCP in oil timber preservative. Its predominant use was as an antisapstain fungicide in the treatment of *Pinus radiata* either by spraying or more commonly dipping 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 dermal absorption was used as a timber preservative. 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 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. Results of a serum dioxins study of former New Zealand sawmill workers are given in Table 5. 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. Toxic Equivalent Factors 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 dioxin contaminants.

Although PCP has acute health effects these are not discussed here as use no longer occurs 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).

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 in humans. No consistent association between PCP exposure and cancer has been found. Up to 64 years of follow up of 773 PCP manufacturing workers from the Dow Chemical Company’s Midland, Michigan plant found a higher NHL mortality rate than expected (SMR 2.4; 95% CI 1.0-4.7) but no trend with TEQ exposure level. No excess mortality was found for other selected cancers or all cancers (SMR 1.0; 95% CI 0.8-1.2). Mortality results were similar when 196 workers who also had TCP exposure were excluded – for NHL, SMR 2.8; 95% CI 1.1-5.7 (Collins et al 2008b).

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 from the work and task history of the participants. 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 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 to non-exposed workers (McLean et al 2007).

A morbidity study by McLean et al (2009b) of 293 (116 exposed, 177 not exposed) sawmill workers who worked at least one year in the timber industry from 1970 to 1990 found 10 percent had high exposure (mixing PCP). Only 5 percent had worked in the industry for at least 10 years. Exposed workers worked in a sawmill known to have cut Pinus radiata as mixing PCP concentrate, dip bath operator, timber grader, green table hand or green chain puller, yardhand, order man or boron diffusion plant operator.

Workers who had been exposed to PCP reported increased prevalence of chronic respiratory disease (including TB, pleurisy and pneumonia) and recurrent diarrhea. Of 17 neuropsychological symptoms, palpitations and sweating for no reason were more prevalent. Neurological examination of 13 signs found difficulty with straight leg raising was elevated among exposed workers. 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 deficit in cranial nerve function.

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 2009b).
References and Bibliography

For detailed information on dioxins see:


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