Evaluation of the toxicity of dioxins and dioxin-like PCBs: A health risk appraisal for the New Zealand population

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Authors

Allan H Smith, MB, ChB, PhD
Peggy Lopipero, MPH

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About the authors: See inside back cover

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Executive summary

This report is submitted to the Ministry for the Environment as an independent appraisal of the health risks posed to the New Zealand population by polychlorinated dibenzo-p-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs) and the dioxin-like polychlorinated biphenyls (PCBs). Collectively, these three groups of closely related chemicals are generically referred to as 'dioxin-like compounds'.

The Ministry for the Environment has collected information on the sources and environmental levels of dioxin-like compounds in New Zealand, and on population exposures to these chemicals, including data on dietary intakes and concentrations in serum. These, and other data collected by the Ministry of Health on PCDD/F body burdens of New Zealanders, have been used in this health risk appraisal. This report also presents a concise review of our current understanding of the health risks associated with exposure to dioxin-like compounds, and reviews various health guidelines that have been established by other jurisdictions.

From consideration of the New Zealand exposure data, and a review of the published scientific literature on dioxin-like compounds, the following observations and conclusions can be made.

ES1 New Zealand exposure data

For the general population, over 90% of exposure to dioxin-like compounds is through the diet, with foods of animal origin such as meats, dairy products and fish usually the main source. Unborn children are exposed to dioxin-like compounds *in utero*, and nursing infants are exposed to these contaminants present in breast milk.

Based on a dietary study for dioxin-like compounds (Buckland *et al.*, 1998c), the level of dietary intake of these chemicals for the New Zealand population is lower than exposures reported for any other country where a comparable study has been undertaken. For adult males with a median energy diet, the intake is estimated as 0.37 pg TEQ/kg bw/day, and for adolescent males with a high energy (90^{th} centile) diet, the intake is estimated as 0.84 pg TEQ/kg bw/day, where the toxic equivalents (TEQ) are based on the toxic equivalent factors (TEFs) developed in 1997 for dioxin-like compounds by the World Health Organization (WHO) (Van den Berg *et al.*, 1998).

Similarly, the results of the study of dioxin-like compounds present in serum (Buckland *et al.*, 2001) show that levels for the general New Zealand population are at the low end of the scale of levels reported internationally. The mean serum concentration across the population aged 15 years and older was determined as 19.7 ng TEQ kg^{-1} on a lipid-adjusted basis (range: 9.71–38.5 ng TEQ kg^{-1}). From these serum data, body burdens and average lifetime daily exposures (ALDE) were calculated. The mean ALDE for all data was estimated as 1.4 pg TEQ/kg bw/day (minimum of 0.35 pg TEQ/kg bw/day for the population aged 15–24 years; maximum of 3.4 pg TEQ/kg bw/day) for the population aged 65+ years). The higher ALDE estimate compared to the estimated dietary intake is because the ALDE includes historical exposures, which are likely to have been higher than current exposures, as well as intakes from non-dietary exposure pathways.

A study undertaken in the late 1980s measured concentrations of PCDD/Fs in New Zealand mother's milk in the range 6.2–40 ng TEQ kg^{-1} of milk fat. The preliminary indications from a

second study currently underway is that over a 10-year period from 1987/88 to 1997/98, concentrations of PCDD/Fs in breast milk have fallen by about two-thirds.

Whilst noting the comparatively low levels of PCDD/F emissions relative to most other industrialized countries, as documented in the New Zealand dioxin inventory (Buckland *et al.*, 2000), there is no clear evidence to show that the emissions of PCDD/Fs from known sources correlate proportionally with general population exposures. Although the inventory estimates the relative contribution of the various sources to total emissions, the uncertainties in these estimates mean it cannot be assumed that these sources make the same relative contributions to human intakes as calculated. Although unlikely, it is even possible that the major sources of PCDD/Fs in foods are not the sources with the largest fractions of estimated total emissions in New Zealand. However, it is clear that to prevent or minimise general population intakes of dioxin-like compounds, protection of the quality of New Zealand's agricultural lands and aquatic environments used for food production is paramount.

Higher-level exposures, such as may occur in the work place, are normally restricted to smaller groups of people. In New Zealand, historical occupational exposures to PCDD/Fs would probably have been restricted to individuals involved in the handling and use of the pesticides pentachlorophenol (PCP) and 2,4,5-trichlorophenoxyacetic acid. These chemicals are no longer used in New Zealand.

More detailed information on the New Zealand exposure data is provided in Section 3 of this report.

ES2 Toxic effects of dioxin-like compounds and health risk appraisal considerations

The most widely studied of all the dioxin-like compounds is 2,3,7,8-tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD). It has been shown to affect a wide range of organ systems in many animal species, it can induce a wide range of adverse biological responses, and it is extraordinarily potent. Recent animal studies suggest that the most sensitive endpoints of TCDD exposure relate to immunotoxicity, and reproductive and neurobehavioral effects.

Our current knowledge of the mechanisms of TCDD toxicity clearly suggests that binding of TCDD to the aryl hydrocarbon receptor (Ah receptor) is the first step in a series of events that manifest themselves in biological responses, including changes at the biochemical, cellular and tissue level. Binding to the Ah receptor occurs in humans and also in monkeys and rats – the two animals used most in experimental studies. This being the case, it is reasonable to use the results of the animal studies to predict health effects that may not yet have been demonstrated in human studies.

2,3,7,8-TCDD is an extremely potent animal carcinogen. It has been shown to cause both benign and malignant tumors at multiple sites in several animal species. Increases in lung cancer and all-cancers combined have been observed in highly exposed cohorts of workers in industrial settings. From the occupational studies, and an understanding of biological plausibility as shown by animal studies, the International Agency for Research on Cancer has concluded that TCDD is carcinogenic to humans. Although the mechanisms of TCDD carcinogenicity are not fully known,

the available evidence suggests that they do not involve direct damage to cellular DNA. Whatever the precise mechanism of TCDD carcinogenicity, no threshold for effects has been established. It is therefore plausible to include low-dose linearity in the range of possibilities, and for regulatory considerations we believe that the linear model should be the first choice unless it can be shown that it does not adequately fit the data.

The available epidemiological data indicate that dioxin-like compounds produce a variety of biochemical responses in humans, some of which occur at relatively low exposure levels. Enzyme induction, changes in hormonal levels and reduced glucose tolerance are examples of subtle changes that may occur at comparatively low exposures. However, these subtle effects are of unknown clinical significance, and may or may not indicate a toxic response or potential for a toxic response.

Despite the lack of data for toxic effects from dioxin-like compounds other than 2,3,7,8-TCDD, there is reason to infer that biochemical, cellular and tissue-level effects that are elicited by exposure to TCDD are also induced by other chemicals that have a similar structure and that bind to the Ah receptor. There is widespread agreement within the scientific community that the use of TEFs to estimate the relative toxicities of dioxin-like compounds has an empirical basis, is theoretically sound, and is a useful procedure. Furthermore, agencies such as the WHO and the United States Environmental Protection Agency (US EPA) have noted that the derivation and use of TEQ levels is a pragmatic and feasible approach for assessing human health risks from exposure to dioxin-like compounds. We concur with this approach, and endorse the use of the most recent (1997) WHO TEFs (Van den Berg *et al*., 1998), applying the concept of additivity for the PCDDs, PCDFs and dioxin-like PCBs to provide total TEQ estimates.

There are a number of key studies that document a variety of health effects of TCDD toxicity in laboratory animals, and these have been instrumental in establishing human health guidelines for exposure to dioxin-like compounds. Some of these studies are summarized in Table ES.1.

Table ES.1 Key studies used in the derivation of human health criteria

Species	Biological effect	Reference
Sprague-Dawley rats	Cancer	Kociba *et al*., 1978
Long Evans Hooded rats	Decreased sperm count in offspring; increased genital malformations in offspring	Gray *et al*., 1997a Gray *et al*., 1997b
Rats	Immune suppression in offspring	Gehrs *et al*., 1997; Gehrs and Smialowicz, 1998
Rhesus monkeys	Neurobehavioral effects in offspring	Schantz and Bowman, 1989; Schantz *et al*., 1992
Rhesus monkeys	Endometriosis	Rier *et al*., 1993

From these studies, the WHO, the United Kingdom, Germany, Japan and the Netherlands have all set a tolerable daily intake (TDI), and the United States Agency for Toxic Substances and Disease Registry (ATSDR) has set a minimal risk level (MRL) on the basis of the lowest observable adverse effect level (LOAEL) and the application of safety factors. In most cases, based on the non-cancer effects data, the TDI or MRL value set by these jurisdictions is, or falls within the range, 1–4 pg TEQ/kg bw/day. However, we note that the margins of safety used in deriving these

values are very small, and we can have no assurance that some people with the highest exposures may not have deleterious effects even when the overall New Zealand population average intake, based on ALDE estimates, is approximately 1.4 pg TEQ/kg bw/day. It is also noted that, for non-cancer effects, the US EPA does not recommend the derivation of a reference dose (RfD) for dioxin-like compounds, because any RfD that the Agency would set is likely to be 2–3 orders of magnitude below current background intakes and body burdens.

The cancer study of Kociba *et al.* (1978) using Sprague-Dawley rats has been used to assess the carcinogenic risk from exposure to 2,3,7,8-TCDD. From the findings of this study, the US EPA has determined a risk-specific dose (RsD) of 0.006 pg TCDD/kg bw/day for a one in a million lifetime cancer risk. This was derived from an upper bound unit risk estimate of 1.6×10^{-4} (pg/kg bw/day)$^{-1}$ (US EPA, 1985). Further analysis of the Kociba data has derived an oral intake RsD of 0.01 pg TEQ/kg bw/day, corresponding to a unit risk estimate of 1×10^{-4} (pg/kg bw/day)$^{-1}$ (US EPA, 1994b), and most recently the US EPA have proposed an upper bound cancer risk estimate of 1.4×10^{-3} (pg/kg bw/day)$^{-1}$ (US EPA, 2000) based on the Kociba rat data.

Although the evidence has limitations, more recent epidemiological studies in humans have led to TCDD being classified as a human carcinogen, and it is now possible to derive the cancer potency directly from human studies of exposed industrial workers. Thus, the US EPA has recently calculated a cancer potency factor from a meta-analysis of human data from three occupational cohorts of 1×10^{-3} (pg/kg bw/day)$^{-1}$ (US EPA, 2000). This potency turns out to be much higher than initially estimated from the rat studies by the US EPA in their 1985 health assessment report (US EPA, 1985). However, recent reassessment of the Kociba rat study including incorporating the half-life differences between rats and humans has shown that the estimates for human cancer risks derived from this animal study come quite close to those that can be estimated directly from the pertinent studies of TCDD-exposed workers. This information adds to our confidence in recommending the use of the cancer potency estimates derived directly from the human studies to appraise the risks to the New Zealand population from exposure to dioxin-like compounds.

In Section 5, a critique is provided of the following risk assessment methodologies that are applicable to the current study:

- safety factor approach
- low-dose extrapolation
- benchmark dose or point of departure
- public health risk assessment.

The public health risk assessment approach, which takes into account current background exposures as well as allowing for consideration of single point sources of exposure adding to background, is considered to be the most appropriate means by which ongoing sources of dioxin-like compounds to the environment can be managed and exposures to the population reduced in the medium to long-term. Furthermore, we recommend that these chemicals be classified in the 'Class 2' category of the public health risk assessment framework.

Further discussion of the toxic effects of dioxin-like compounds is provided in Section 4, and on health risk appraisal considerations in Section 5 of this report.

ES3 Appraisal of the New Zealand population exposure data

The New Zealand serum data can be used to estimate exposure to dioxin-like compounds by relating body burden to an equivalent human daily intake, or ALDE estimate. Such intake estimates will include dietary intakes and other exposure pathways, such as inhalation. Because of the representative nature of the New Zealand serum study, both in terms of the large number of samples analyzed, and the incorporation of demographic, geographic, age, gender and ethnicity variables into the study design, it is a reasonable assumption that the ALDE estimates derived from the serum data are an accurate reflection of intakes across the population. Furthermore, these estimates of exposure are likely to be more reliable than the intake estimates derived from the comparatively smaller dietary study that were based on model diets.

The New Zealand intakes can be compared against the TDI target value established by the WHO and the MRL set by the ATSDR of 1 pg TEQ/kg bw/day. The average current dietary intake may be somewhat lower than this value (perhaps two times lower). However, the more reliable estimate of intake based on serum concentrations suggests that during approximately the last 25 years the average intake was probably close to 1.4 pg TEQ/kg bw/day. This being the case, about half the population would have exceeded this intake. It should also be noted again that these health criteria set by WHO and ATSDR involve very small margins of safety. Therefore, there would appear to be only a small margin of safety, if any, between New Zealand intakes and some non-cancer effects in animal studies; in particular, effects on the offspring of exposed mothers.

Cancer risk has been assessed by low-dose extrapolation, using both animal and human data. The cancer estimates from the human studies are similar to those from animal studies when the long human half-life is taken into account, and emphasis should therefore be placed on cancer risks derived from the human data. Overall, based on the human potency factors, the current appraisal has estimated that the upper bound lifetime risk for background intakes of dioxin-like compounds for the New Zealand population may exceed one additional cancer per 1000 individuals. This cancer risk estimate is 100 times higher than the value of 1 in 100,000 often used in New Zealand to regulate carcinogenic exposure from environmental sources. Of course, if there were a threshold above current exposures the actual risks would be zero. Alternatively, they could lie in a range from zero to the estimate of 1 in 1000 or more.

When assessing cancer risk using a benchmark dose derived from human data, the margin of safety between the average intake of dioxin-like compounds for the New Zealand population and the concentration estimated to result in a 1 in 100 cancer risk is found to be very small (less than an order of magnitude).

The exposure of breast-fed infants also warrants mention since after about six months of breast feeding, the body concentrations of dioxin-like compounds in infants exceed those in the mother as a consequence of the presence of these contaminants in breast milk. Whether adverse effects will result from this exposure is not known, although it is clearly known that breast feeding is in general beneficial. The concern about dioxin-like compounds in breast milk adds to the reasons for taking a prudent and precautionary approach concerning population exposures to these chemicals.

On the basis of the findings of this risk appraisal, the current background exposures to dioxin-like compounds for the New Zealand population has, in our opinion, an insufficient margin of safety, and steps should be taken to further reduce human exposure.

This report also considers 'special' populations who may be exposed to dioxin-like compounds above background levels, including workers who were occupationally exposed to PCDD/F from the use of PCP in the timber industry. Based on a small number of cases, it is clear that workers who handled PCP have higher PCDD/F body burdens above those of the general New Zealand population. While it is not possible to draw conclusions about health effects from the small number of workers whose blood concentrations have been measured, it is clear that studies are needed of workers with these exposures. If a study is feasible, and would be of sufficient statistical power to assess health effects, we recommend that such a study of former New Zealand timber workers be undertaken.

More detailed information on the health risks to New Zealanders from exposure to dioxin-like compounds is provided in Section 7 of this report.

ES4 Recommendations

In the light of ever-increasing scientific information concerning the toxicity of dioxin-like compounds, and data on body burdens present in the New Zealand population, we make the following recommendations:

1. A precautionary approach should be adopted concerning dioxin-like compounds in New Zealand.
2. A goal of ongoing reduction in population body burdens of dioxin-like compounds should be stated.
3. Identifying a tolerable daily intake is not recommended.
4. A health exposure criterion (HEC) should be established to regulate point sources of exposure.
5. Application of the HEC should involve consideration of the plausible maximally exposed person from the point source activity.
6. The New Zealand population burden of dioxin-like compounds should be monitored periodically, perhaps every 5–10 years.
7. Policies and the HEC should be reviewed after consideration of trends revealed by future population monitoring.

Further information on each of these recommendations is provided in Section 8 of this report.

Disclaimer

This report represents work undertaken by Dr Allan Smith and Ms Peggy Lopipero for the New Zealand Ministry for the Environment. The work has been carried out as a component of the Ministry's Organochlorines Programme. This publication, in particular the Executive Summary along with Sections 4, 5, 7 and 8, represents the final report for Dr Allan Smith and Ms Peggy Lopipero to the Ministry for the Environment.

Sections 1, 2, 3 and 6 of the report were prepared by Dr Simon Buckland of the Ministry for the Environment for incorporation into the report. These sections provide supporting information on dioxin-like compounds relevant to the current risk appraisal.

Every effort has been made to ensure that the information in this report is accurate. The Ministry for the Environment and the authors of this report do not accept any responsibility or liability whatsoever for any error of fact, omission, interpretation or opinion which may be present in this report, however it may have occurred.

The report has been peer reviewed by scientists from the Ministry for the Environment, Ministry of Health and the Institute of Environmental Science and Research. The publication of this report by the Ministry for the Environment does not constitute any endorsement of the conclusions made in the report, and, furthermore, there is no commitment whatsoever to adopt any policy recommendations that the report contains.

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Contents

Tables

Figures

Page

1 Introduction

Polychlorinated dibenzo-p-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs) (commonly known simply as 'dioxins', and referred to throughout this report as PCDD/Fs) are contaminants found in a variety of environmental media, including air, soil, sediment and biota. This class of compounds has caused a great deal of public concern, and been the subject of extensive investigation by the scientific community and regulatory agencies. PCDD/Fs are extremely potent in producing a variety of effects in animals in toxicological studies, at dose levels several orders of magnitude lower than most other chemicals of environmental interest. In addition, epidemiological (human) studies have demonstrated health effects following PCDD/F exposure.

To better understand the situation in New Zealand, the Ministry for the Environment has commissioned an overview of the current scientific understanding of the toxicity of PCDD/Fs and dioxin-like polychlorinated biphenyls (PCBs), an evaluation of health risk assessment methods, and an appraisal of the possible risks to New Zealanders at current background levels of exposure to these chemicals. This work forms one component of the Ministry for the Environment's Organochlorines Programme (see Box 1).

This report presents a health risk appraisal for PCDD/Fs and dioxin-like PCBs in New Zealand. To support this appraisal, the scientific research of the Organochlorines Programme has been summarised in the report, namely:

- a survey of the concentrations and distribution of PCDD/Fs and PCBs in the New Zealand environment (these data have been used in an ecological risk assessment, published by the Ministry for the Environment (Jones and Giesy, 2001))
- a survey of PCDD/Fs and PCBs in foods, and an estimation of the dietary intake for New Zealanders
- a survey of the New Zealand population for levels of PCDD/Fs and PCBs in serum
- an inventory of PCDD/F emissions to air, land and water, and an assessment of reservoir sources.

Information on each of these phases of the Organochlorines Programme is summarized in Section 3 of this report. Full technical reports have been published by the Ministry for the Environment, and are available on the Ministry's web site at: http://www.mfe.govt.nz/issues/waste/organo.htm.

The specific aims of this current project were to:

1. provide a concise review of the current understanding of the established and potential human health effects associated with exposure to PCDD/Fs and dioxin-like PCBs
2. summarize the health risk methodologies that can be used for an assessment of exposure to PCDD/Fs and dioxin-like PCBs
3. review the various health guidelines for PCDD/Fs and dioxin-like PCBs that have been established by other jurisdictions
4. carry out, as far as practicable, an appraisal of the current risks from PCDD/Fs and dioxin-like PCBs to the New Zealand population, incorporating the dietary intake and serum data collected under the Organochlorines Programme, together with other available New Zealand exposure data

5. make recommendations to the Ministry for the Environment aimed at protecting the health of New Zealanders from background exposures to PCDD/Fs and dioxin-like PCBs.

Each of these tasks is addressed separately in this report. In addition, summary background information on PCDD/Fs and dioxin-like PCBs, including the concept and applicability of the use of toxic equivalent factors (TEFs), their mechanisms of action and pharmacokinetics is provided.

Box 1. The Organochlorines Programme

The Organochlorines Programme was initiated in response to a recognition of the need to minimise industrial emissions of PCDD/Fs to air and water, clean-up sites contaminated with organochlorine residues and manage the safe disposal of waste stocks of organochlorine chemicals such as the PCBs and persistent pesticides. The Organochlorines Programme is consistent with current international concerns on persistent organic pollutants (UNEP, 1997).

The Organochlorines Programme as a whole comprises the study of environmental and human levels of organochlorine substances; the development of an inventory of ongoing PCDD/F emissions; and the estimation of the risk posed by these substances. The integration of these and other components of the Organochlorines Programme is shown in Figure 1.1. The outcomes from the overall programme will be:

- National environmental standards for PCDD/Fs and where necessary environmental guidelines or standards for PCBs, organochlorine pesticides and chlorophenols;
- Identified clean-up technologies that can safely and effectively destroy organochlorine wastes;
- An integrated management strategy for PCDD/Fs and other organochlorine contaminants and wastes in New Zealand;
- Identification of issues for the phase-out of organochlorines;
- Informed public input to Government decisions on the management of organochlorines in the New Zealand environment.

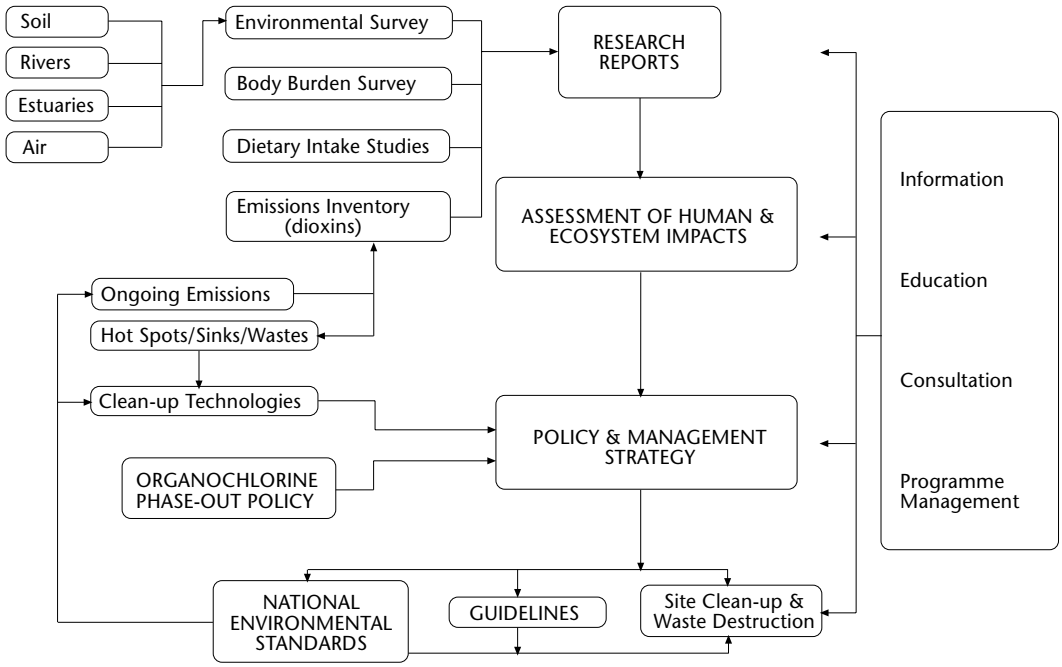

Figure 1.1 Overview of the New Zealand Organochlorines Programme

2 Dioxins and dioxin-like PCBs

2.1 Chemical structure

The PCDD/Fs are chemically classified as halogenated hydrocarbons. They are tricyclic aromatic compounds, comprising two benzene rings joined via either one or two oxygen atoms at adjacent carbons on each of the benzene rings, as shown in Figure 2.1.

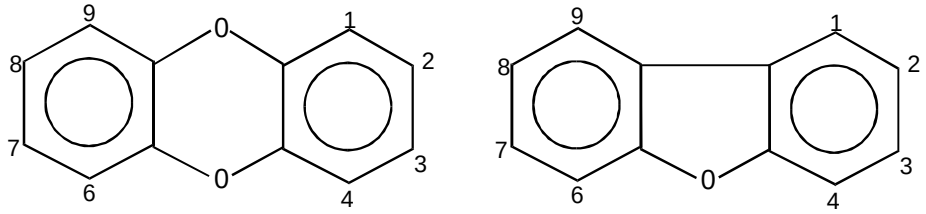

Figure 2.1 Structures of dibenzo-p-dioxin and dibenzofuran

Both groups of chemicals may have up to eight chlorine atoms attached at carbon atoms 1 to 4 and 6 to 9. Each individual compound resulting from this is referred to as a congener. Each specific congener is distinguished by the number and position of chlorine atoms around the aromatic nuclei. In total, there are 75 possible PCDD congeners and 135 possible PCDF congeners. Groups of congeners with the same number of chlorine atoms are known as homologues. The number of congeners in each homologue group is shown in Table 2.1. The most widely studied of the PCDD/Fs is 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). This congener is often generically referred to as 'dioxin', and represents the reference compound for this class of chemicals.

Table 2.1 Homologues and congeners of PCDDs and PCDFs

Abbreviation	Homologue name	No. of possible congeners	No. of possible 2,3,7,8-chlorinated congeners
MCDD	Monochlorodibenzo-p-dioxin	2	0
DiCDD	Dichlorodibenzo-p-dioxin	10	0
TrCDD	Trichlorodibenzo-p-dioxin	14	0
TCDD	Tetrachlorodibenzo-p-dioxin	22	1
PeCDD	Pentachlorodibenzo-p-dioxin	14	1
HxCDD	Hexachlorodibenzo-p-dioxin	10	3
HpCDD	Heptachlorodibenzo-p-dioxin	2	1
OCDD	Octachlorodibenzo-p-dioxin	1	1
MCDF	Monochlorodibenzofuran	4	0
DiCDF	Dichlorodibenzofuran	16	0
TrCDF	Trichlorodibenzofuran	28	0
TCDF	Tetrachlorodibenzofuran	38	1
PeCDF	Pentachlorodibenzofuran	28	2
HxCDF	Hexachlorodibenzofuran	16	4
HpCDF	Heptachlorodibenzofuran	4	2
OCDF	Octachlorodibenzofuran	1	1

Congeners containing one, two or three chlorine atoms are thought to be of no toxicological significance. However, 17 congeners with chlorine atoms substituted in the 2, 3, 7 and 8-positions are thought to pose a risk to human and environmental health. Toxic responses include dermal toxicity, immunotoxicity, carcinogenicity and adverse effects on reproduction, development and endocrine functions. These health effects are discussed in detail in Section 4 of this report. Increasing substitution from four to eight chlorine atoms generally results in a marked decrease in potency.

The PCBs are structurally and chemically similar to the PCDD/Fs, and comprise up to 209 congeners, from the monochloro congener through to the fully chlorinated decachloro congener. The basic aromatic nucleus is shown in Figure 2.2, and the distribution of PCB congeners arising from attachment of chlorine atoms to this nucleus is given in Table 2.2.

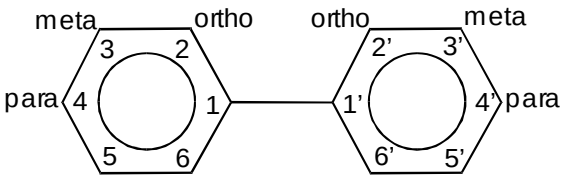

Figure 2.2 Structure of biphenyl

Table 2.2 Distribution of PCB congeners

No. of Cl substituents	Cl_1	Cl_2	Cl_3	Cl_4	Cl_5	Cl_6	Cl_7	Cl_8	Cl_9	Cl_{10}
No. of congeners	3	12	24	42	46	42	24	12	3	1

Like the PCDD/Fs, the biologic and toxic effects of the PCBs are highly dependent both on the degree of chlorination and on the position of the chlorine atoms around the aromatic nuclei (i.e. whether they are *ortho*-, *meta*- or *para*- to the phenyl-phenyl bridge at carbon-1). Certain PCBs (the so called non-*ortho* and mono-*ortho* congeners) are conformationally similar to the PCDD/Fs, and appear to elicit dioxin-specific biochemical and toxic responses through a similar mechanistic action. In this regard, they are often referred to as 'dioxin-like' PCBs.

For the purposes of this report, PCDD/Fs and dioxin-like PCBs are collectively referred to as 'dioxin-like compounds', which are generally agreed to produce dioxin-like toxicity.

2.2 Physiochemical properties

In general, dioxin-like compounds have low water solubility, high octanol-water partition coefficients, low vapor pressure and are resistant to chemical degradation under normal environmental conditions. These properties mean that dioxin-like compounds are extremely persistent in the environment, and their high lipophilicity results in their bioconcentration into biota and biomagnification through the food chain. Physiochemical properties for selected PCDD/F and PCB congeners have been collated and reviewed extensively in a number of publications (US EPA, 1994a; ATSDR, 1998; 1999; IARC, 1997), and will not be discussed further in this report.

2.3 Environmental fate

In soil, sediment, water and (to a lesser extent) ambient air, PCDD/Fs are primarily associated with particulate and organic matter because of their high lipophilicity and low water solubility. The lower chlorinated congeners have a relatively higher vapor pressure, and more readily partition into the gaseous phase. Once adsorbed to particulate matter, PCDD/Fs exhibit little potential for significant leaching or volatilization. The available data indicate that these are extremely stable compounds under most environmental conditions, with environmental persistence measured in decades. The only environmentally significant transformation process for PCDD/F congeners is considered to be their photodegradation in the gaseous phase and at the soil–air or water–air interface. PCDD/Fs entering the atmosphere are removed either by photodegradation or by wet or dry deposition. Although some volatilization of PCDD/Fs on soil does occur, the predominant fate of these chemicals adsorbed to soil is to remain in place near the surface of undisturbed soil, or to move to water bodies with soil erosion. The scouring of surface soil through wind erosion may also lead to the re-suspension of particle-bound PCDD/Fs into the atmosphere. PCDD/Fs entering the water column primarily undergo sedimentation and burial. The ultimate environmental sink of these PCDD/Fs is believed to be aquatic sediments.

Much less specific information is available on the environmental transport and fate of dioxin-like PCBs. However, from what is known of the physiochemical properties of these chemicals, coupled with information on the widespread occurrence and persistence of PCBs in the environment, it is apparent that these PCBs are thermally and chemically stable, and likely to be associated primarily with soils and sediments. Soil erosion, sediment transport in water bodies and emissions to air (via volatilization, dust re-suspension or point source emissions) followed by atmospheric transportation and deposition are believed to be the dominant transport mechanisms responsible for the widespread occurrence of PCBs. Photodegradation to less-chlorinated congeners, followed by aerobic and/or anaerobic biodegradation, is believed to be the principal path for the loss of PCBs from the environment.

2.4 Toxic equivalency factors and toxic equivalents

In environmental media, dioxin-like compounds occur as complex mixtures of congeners, which therefore complicates any environmental or human health risk evaluation. However, because it is widely accepted that the toxicological action of dioxin-like compounds is via a common mechanism of action (in the initial stages, at least), these compounds have been assigned individual toxicity equivalency factor (TEF) values, as agreed by international convention (see, for example, Kutz *et al.*, 1990; Van den Berg *et al.*, 1998). This approach allows the combined toxicity of a complex mixture of congeners to be represented in terms of a single numerical value, or 'toxic equivalents' (TEQ). The TEQ contribution of each congener is calculated by multiplying its concentration by the TEF for that congener. This approach facilitates risk assessment and regulatory control of exposure to these mixtures.

The TEQ method is based on toxicological and *in vitro* biological data, and knowledge of structural similarities among this group of chemicals. In essence, TEFs are estimates of the relative toxicities of dioxin-like compounds compared to the toxicity of 2,3,7,8-TCDD, which as the reference compound for this group of chemicals, is assigned a TEF of 1.0. All 2,3,7,8-PCDD/Fs along with the dioxin-like PCBs have been assigned TEF values, which are generally less than one, reflecting their lower toxic potency. Periodically, these TEFs are revised based on

new toxicological data. The latest internationally accepted TEFs for the dioxin-like compounds, as agreed at a 1997 World Health Organization (WHO) consultation (Van den Berg *et al*., 1998), are shown in Table 2.3. Throughout this report, these TEFs are referred to as the 1997 WHO TEFs. Earlier TEF schemes for the PCDD/Fs (Ahlborg, 1989; Kutz *et al*., 1990) and the PCBs (Ahlborg *et al*., 1994) have been widely used to assess the combined toxicity of these compounds.

Table 2.3 Toxic equivalency factors for dioxin-like compounds for humans and mammals

PCDD/F congener	TEF value	PCB congener	TEF value
2,3,7,8-TCDD	1	Non-*ortho* PCBs	
1,2,3,7,8-PeCDD	1	PCB #81	0.0001
1,2,3,4,7,8-HxCDD	0.1	PCB #77	0.0001
1,2,3,6,7,8-HxCDD	0.1	PCB #126	0.1
1,2,3,7,8,9-HxCDD	0.1	PCB #169	0.01
1,2,3,4,6,7,8-HpCDD	0.01		
OCDD	0.0001	Mono-*ortho* PCBs	
		PCB #105	0.0001
2,3,7,8-TCDF	0.1	PCB #114	0.0005
1,2,3,7,8-PeCDF	0.05	PCB #118	0.0001
2,3,4,7,8-PeCDF	0.5	PCB #123	0.0001
1,2,3,4,7,8-HxCDF	0.1	PCB #156	0.0005
1,2,3,6,7,8-HxCDF	0.1	PCB #157	0.0005
2,3,4,6,7,8-HxCDF	0.1	PCB #167	0.00001
1,2,3,7,8,9-HxCDF	0.1	PCB #189	0.0001
1,2,3,4,6,7,8-HpCDF	0.01		
1,2,3,4,7,8,9-HpCDF	0.01		
OCDF	0.0001		

Source: Van den Berg *et al*., 1998.

The use of TEFs assumes that the toxicity of the various congeners acts in an additive fashion. The toxic potency of a mixture of dioxin-like compounds (i.e. the TEQ) is the sum of the products of the concentration of each congener present in the mixture and that congener's TEF, as given by the following equation:

$$TEQ = \sum([PCDD_a] \times TEF_a) + \sum([PCDF_a] \times TEF_a) + \sum([PCB_a] \times TEF_a)$$

Thus, TEQs represent 2,3,7,8-TCDD toxic equivalents for mixtures of PCDD/Fs and dioxin-like PCBs.

Throughout this document, concentrations of this group of chemicals will be presented as TEQs. At times, data may be presented as concentrations of 2,3,7,8-TCDD because the study in question may have considered this particular congener alone.

2.5 Applicability of the TEQ concept

The concept of toxic equivalents in evaluating mixtures of PCDD/Fs and dioxin-like PCBs is fundamental to many of the conclusions reached in this health risk appraisal. This is because most

data on the health effects of PCDD/Fs are for 2,3,7,8-TCDD. Nevertheless, estimates of the New Zealand population exposures, as summarized in Section 3.3.3, suggest that more than 85% of the total intake of dioxin-like compounds, measured as TEQs, is from congeners other than 2,3,7,8-TCDD.

The TEQ approach involves assessing the comparative effects of individual PCDD/F and PCB congeners on various biological endpoints, and deriving TEFs based on the upper range of potency data for these effects. The key assumptions unifying the diverse types of data that are considered in the derivation of TEFs are that:

- the compound must show a structural relationship to TCDD
- the compound must bind to the aryl hydrocarbon receptor (Ah receptor), and elicit Ah receptor-mediated biochemical and toxic responses
- the toxic effects of individual congeners in mixtures are additive.

Whilst there are empirical bases for the TEFs assigned to dioxin-like compounds relative to 2,3,7,8-TCDD, they generally represent order-of-magnitude estimates of relative toxicity, and are not meant to be used precisely. The potency for most, if not all, of the toxic endpoints is determined by the number of chlorine atoms and their position on the dioxin-like molecule. The molecules structure, in turn, affects its relative ability to bind to a specific cellular protein receptor (the Ah receptor), which mediates most, and possibly all, of the toxic endpoints of this class of compounds.

In addition to the idea of 'relative ranking', there is a second critical aspect to the TEQ approach. This is the concept of additivity. The TEQ approach assumes that the toxicity of a mixture of PCDD/Fs and dioxin-like PCBs can be estimated by adding together the products of the concentrations of the individual congeners with their TEFs. Generally, the majority of studies that have evaluated the interactions of dioxin-like compounds to cause toxicity have found that the interactions do not deviate significantly from linearity, at least at current levels of environmental exposures, and consequently there is widespread acceptance within the scientific community of the concept of additivity.

At a general level, the use of TEQs can be justified on a practical basis, because of the magnitude of the task of attempting to conduct appropriate evaluations of all toxic endpoints for all of the PCDD, PCDF and dioxin-like PCB congeners, separately.

However, confounding the concept of additivity when using TEQs for health risk assessment is people's exposure, via the diet, to Ah receptor agonists. These include indole-3-carbinol and related compounds that are present in vegetables, which may compete with the PCDD/Fs and dioxin-like PCBs for the Ah receptor. This may reduce the toxic effect of the dioxin-like compounds, because the antagonist compounds bind without inducing the toxic effects. Even if the binding affinities of these molecules are much lower than those of the dioxin-like compounds, as dietary components these compounds are likely to be present at much higher concentrations than the dioxin-like molecules and therefore may still have a significant influence on dioxin-like toxicity. Because such Ah antagonists are likely to prevent toxic effects of PCDD/Fs, the use of the additivity concept in risk assessment would be protective from a public health perspective.

The TEQ approach also has a number of other shortcomings. One problem is that very few data may be available for estimating the TEF for a congener, and, from what data are available, there may be a wide range of relative potency estimates derived from the published studies. A further problem is the need to adequately incorporate pharmacokinetic differences between the other congeners and 2,3,7,8-TCDD, because differences in absorption and metabolism modulate the relative potencies of these chemicals.

Nevertheless, by and large, the international scientific community has agreed that the use of TEFs to predict relative toxicities of mixtures of PCDD/Fs and PCBs has an empirical basis, is theoretically sound, and, in the absence of more complete data on the toxicity of individual congeners, is a useful procedure. Furthermore, whilst recognizing the uncertainties associated with the use of TEFs, agencies such as the WHO and the United States Environmental Protection Agency (US EPA) have noted that, pragmatically, the derivation and use of TEQ levels for human health risk assessment is the most feasible approach to adopt (Van Leeuwen and Younes, 2000; US EPA, 2000).

2.6 Mode of action

A wide variety of data, primarily on TCDD but also on other members of the dioxin family of compounds, has shown the importance of the Ah receptor in mediating the biological effects of dioxin-like compounds. These data have been collected in many experimental studies across several species – including humans. Whilst the precise chain of molecular events associated with dioxin toxicity is not yet fully understood, it is thought to proceed via ligand-receptor complexes, in which the dioxin-like compound binds to the Ah receptor. This, in turn, induces a cascade of biochemical changes at the cellular level. These alterations in biochemical and cellular functions are thought to form the basis of dioxin toxicity. Because humans are believed to be polymorphic with respect to the Ah receptor structure and function, it is reasonable to expect that people may differ from one another in their susceptibilities to dioxin-like compounds.

The evidence currently available indicates that the Ah receptor participates in most, and possibly all, biological responses to TCDD (IARC, 1997). For example, findings from laboratory experiments, using inbred mouse strains in which TCDD binds with lower affinity to the Ah receptor, demonstrate a lack of, or decreased, acute toxicity to TCDD in comparison to other strains. The evidence also indicates that the formation of a ligand-receptor complex depends on both the concentration of TCDD and the receptor in the cell, and the binding affinity of the receptor for TCDD. In principle, some TCDD-receptor complexes will form even at very low levels of exposure. However, in practice, at some finite concentrations of TCDD, the formation of TCDD-receptor complexes may be insufficient to elicit detectable effects. In other words, there may be a threshold of effect. Recent studies have indicated no evidence of a threshold for some relatively simple biochemical responses to TCDD, although this should not be interpreted as an absence of a threshold.

There is sufficient evidence that 2,3,7,8-TCDD is a carcinogen in animals, and epidemiological data from occupational exposure studies show that exposure to TCDD causes an increase in human cancers. This is discussed further in Section 4.2. Whilst the mechanism of TCDD carcinogenicity has not been fully elucidated, there is considerable evidence to suggest that it does not involve direct damage to DNA through formation of DNA adducts (i.e. TCDD is a non-genotoxic

carcinogen). Rather, it is believed that TCDD carcinogenicity is due to its promoting activities following initiation by other carcinogens. An extensive review of the published literature on the mechanisms of dioxin toxicity for both cancer and non-cancer endpoints has been published by the US EPA (1994b) and the ATSDR (1998).

In summary, based on our current understanding of the mechanisms of dioxin toxicity, it is evident that interaction with the Ah receptor is necessary, that humans are likely to be sensitive to the effects of dioxin-like compounds, and that there is likely to be variation between and within species, and between tissue in individual species based on different responses to receptor binding. Although thresholds may exist for some of these responses, they have yet to be demonstrated.

2.7 Pharmacokinetics

An understanding of the pharmacokinetics of dioxin-like compounds – covering their absorption, distribution in body tissue, metabolism and excretion – is important in evaluating the health effects and risks posed by these contaminants to humans. Detailed reviews on their pharmacokinetics, primarily for TCDD, in humans and experimental animals have been published (ATSDR, 1998; IARC, 1997; US EPA, 1994b), from which the following summary has been prepared.

2.7.1 Absorption

Dioxin-like compounds are absorbed through the gastrointestinal tract, skin and lungs. The degree of absorption varies with each congener, the route of absorption and the medium. For the general population, oral intake of trace levels of these contaminants in foods accounts for 90% or more of the total intake. Findings of studies in experimental animals indicates that oral exposure to TCDD in the diet or in an oil vehicle results in the absorption of > 50%, and often closer to 90%, of the administered dose. More soluble congeners are almost completely absorbed, whilst extremely insoluble congeners, such as octachlorodibenzo-p-dioxin (OCDD) are very poorly absorbed. Limited data from a single human volunteer suggest a high level (> 85%) of absorption of TCDD in corn oil from the gastrointestinal tract. The oral intake of PCDD/Fs on various environmental matrices, such as contaminated soil, can lead to a significant reduction in absorption, with bioavailability depending strongly on the properties of the particles. For example, absorption via contaminated soil may be about half or less than half the amount absorbed when administered dissolved in plant oil. Again, the more highly chlorinated congeners, such as the heptachlorodibenzo-p-dioxins and OCDD, are significantly less bioavailable than TCDD.

Dermal exposure of humans to dioxin-like compounds usually occurs as a complex mixture of these contaminants in soils and similar environmental media, and is found to depend on the nature of the medium and the duration of contact. Although slow dermal absorption does occur in experimental animals, it is much more limited than uptake after oral ingestion. Similarly, direct exposure by inhalation is usually low as a percentage of overall intake.

2.7.2 Distribution

Studies in animals show that following oral exposure, TCDD is distributed via the blood, principally to the liver and adipose tissue as well as to the skin and muscles. Both the liver and adipose are the primary deposition sites, although in certain species the skin can also act as an

important storage site. Dioxin-like compounds are also distributed to human milk, and in this medium can be transferred to newborn infants via breast feeding.

The distribution of the PCDD/Fs between the liver and adipose tissue is found to vary with congener and dose, with studies in rodents showing that the pentachlorinated and hexachlorinated congeners have a higher hepatic retention than TCDD. Similarly, the liver/adipose tissue ratio has been found to be time dependent, the ratio falling with increasing time following exposure. This variation over time is believed to be due to the redistribution of TCDD between the two storage sites and/or hepatic metabolism and subsequent excretion.

Transport in the blood occurs through binding to plasma lipids and lipoproteins. It has been shown that serum TCDD levels are strongly correlated with adipose tissue TCDD levels when both are expressed on a lipid weight basis. This relationship appears to hold over a wide concentration range above background levels, and indicates that serum TCDD, coupled with the measurement of serum lipid content, provides a valid estimate of TCDD concentration in adipose tissue under steady-state, low-dose conditions. Consequently, the population exposure data for New Zealanders summarized in Section 3.3.3 are presented on a lipid-adjusted basis.

2.7.3 Metabolism and excretion

Although TCDD is highly resistant to biotransformation, low levels of metabolites, including hydroxylated and sulfur-containing metabolites, have been identified in rodent studies. In addition, conjugation appears to be important for the elimination of dioxin-like compounds from the body, as many TCDD metabolites are present as glucuronide adducts in the bile. Direct intestinal excretion of the parent compound, which is not regulated by metabolism, is another route for excretion of PCDD/Fs and dioxin-like PCBs.

Dioxin-like compounds are mainly excreted in the faeces, with only small amounts excreted in the urine. There are large species differences in the rate of elimination from the body. The half-life of TCDD in rats is approximately 17 to 31 days, depending on the strain and the experimental conditions. Lactation has been shown to be a very efficient route of elimination. With increased numbers of chlorine atoms in the 2,3,7,8- positions, elimination is much slower, and half-lives between 75 days and several years have been estimated from rat studies. The half-life of TCDD in primate species is much longer than in rodent species, averaging about one year for adult female Rhesus monkeys.

From a single human volunteer who orally ingested TCDD, an elimination half-life of 5.8 years was calculated up to 125 days after dosing. In a follow-up evaluation five years after dosage, a half-life of 9.7 years was determined. A median half-life of 7.1 years was estimated for TCDD in a group of Ranch Hand veterans, based on the decline in serum concentrations over a five-year period. The individual half-lives varied from 2.9 to 26.9 years. Subsequently, a larger study of Vietnam veterans suggested a half-life of 11.3 years, which on reanalysis was revised to 8.7 years. The half-life estimate of 8.7 years included additional measurements of serum TCDD levels and controls for potential biases.

In a group of workers occupationally exposed to PCDD/Fs in a herbicide-producing plant, in Germany, a median half-life for TCDD of 7.2 years has been calculated. In a separate occupationally exposed cohort, also in Germany, estimated half-lives for TCDD of 5.1 and

8.9 years were determined for individuals with 20% and 30% body fat respectively. Several other studies have found correlations between percent of body fat and TCDD elimination half-lives. A half-life of 8.2 years has been estimated for Seveso residents with elevated TCDD serum levels above background. Overall therefore, there is good agreement in TCDD half-life estimates from four different populations (Vietnam veterans, two industrial cohorts, and Seveso residents). There are much fewer data available on the elimination of other PCDD/F congeners in humans. From occupational cohort studies, estimates of half-lives between 3.5 and 15.7 years have been made.

The WHO, in the 1998 re-evaluation of their tolerable daily intake (TDI), used a half-life of 7.5 years to estimate human intakes from animal body burden data (van Leeuwen *et al*., 2000; Van Leeuwen and Younes, 2000). In the current risk appraisal, we have adopted the half-life value used by the WHO of 7.5 years, and this is used to calculate daily intakes of dioxin-like compounds from body burden estimates, and to estimate risks for the New Zealand population for exposure to these contaminants (see Section 7).

3 Dioxins and dioxin-like PCBs in New Zealand

To undertake an appraisal of the health risks posed to the New Zealand population by dioxin-like compounds, it is necessary to understand the sources of these compounds, their levels in the environment, in food, and in the New Zealand population. This section briefly describes the New Zealand-specific research that has been undertaken in each of these areas, with a particular focus on the more recent research undertaken as part of the Organochlorines Programme.

The exposure data are summarized in the TEQ concentrations provided in the original source publication. Generally, for the PCDD/Fs, these are in units of International TEQs (I-TEQs) (Kutz *et al*., 1990), and for the PCBs in TEQs based on the TEFs of Ahlborg *et al*. (1994). Where the exposure data are used in this risk appraisal (e.g. the New Zealand dietary intake data), the TEQ levels have been recalculated using the 1997 WHO TEFs for the PCDD/Fs and PCBs (Table 2.3; Van den Berg *et al*., 1998). In these instances, both the original and recalculated TEQ data are presented. In every case, the TEQ data reported include half the limit of detection (LOD) for non-quantified congeners. The use of half the LOD for estimating levels of exposure is considered a reasonable but conservative approach to follow.

3.1 Sources

3.1.1 Overview

PCDD/Fs are unintentional products of thermal processes involving organic matter and chlorine as a result of incomplete combustion or chemical reactions. Internationally, the manufacture and use of chlorinated aromatic chemicals have been major sources of PCDD/Fs in the environment. Most notable examples include the wood preservative and biocide pentachlorophenol (PCP), the herbicide 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), and the PCBs. Of these, only 2,4,5-T was manufactured in New Zealand. Other processes, such as the production of chlorine-bleached pulp, have also led to environmental contamination by PCDD/Fs.

Combustion processes are recognized as another important source of PCDD/Fs. Most thermal reactions that involve the burning of organic material in the presence of a chlorine source result in the formation of these substances. PCDD/Fs have been detected in emissions from the incineration of various types of wastes, particularly municipal, medical and hazardous wastes; from fossil fuel plants, domestic coal and wood fires; and from automobile engines (especially when using leaded fuels) as well as accidental fires. Metallurgical production, including the production of iron and steel as well as non-ferrous metals, and metal processing and refining, especially the secondary processing of scrap metals, can also lead to the formation and release of PCDD/Fs.

Although natural, non-anthropogenic, combustion sources (like forest fires) have probably always been a source of PCDD/Fs, the background levels associated with pre-industrial processes (before the 1930s/1940s) are negligible when compared to those resulting from more recent industrial activities.

An extensive review of PCDD/F sources has been published by Fiedler *et al*. (1990), and more recently by the United States Environmental Protection Agency (US EPA, 1998). A compilation

of source inventories for a number of industrialized countries, primarily Northern Hemisphere countries, has also been published (UNEP, 1999).

3.1.2 Emissions in New Zealand

A comprehensive inventory of PCDD/F emissions to air, land and water, and an assessment of PCDD/F reservoir sources has been published as one component of the Organochlorines Programme (Buckland *et al*., 2000). This inventory has estimated that, for the reference year of 1998, the total quantity of PCDD/Fs released to the environment was in the range 41–109 g I-TEQ (Table 3.1).

Table 3.1 PCDD/F emissions to air, land and water

Receiving environment	Annual release estimate (g I-TEQ yr^{-1})[1]
Air	14–51
Land	26–54
Water	0.56–3.9
Total emissions	41–109

1. PCDD/Fs as I-TEQ (Kutz *et al*., 1990). Includes half LODs for non-detected congeners.

The inventory further estimated that industrial sources account for approximately 60% of the total PCDD/F emissions, with non-industrial (predominantly domestic) sources accounting for the remaining 40%. The major industrial emissions to air were from landfill fires (estimated between 10–15 g I-TEQ yr^{-1}), the burning of wood and coal as fuels in industrial appliances (0.88–6.4 g I-TEQ yr^{-1}), the burning of clinical, pathological and quarantine waste (0.38–3.5 g I-TEQ yr^{-1}) and ferrous and non-ferrous metal production (0.23–3.3 g I-TEQ yr^{-1}). Comparatively lower amounts of PCDD/Fs were emitted from cement and lime manufacture (0.10–0.81 g I-TEQ yr^{-1}), crematoria (0.0080–0.45 g I-TEQ yr^{-1}) and from coal-fired power generation (0.059–0.11 g I-TEQ yr^{-1}). Emissions from a number of other industrial processes were also assessed in the New Zealand inventory, including hazardous waste incineration and wastewater solids incineration, and found to be negligible sources of PCDD/Fs.

Non-industrial emissions to air included domestic wood burning and coal burning for space heating (0.71–8.7 g I-TEQ yr^{-1} and 0.36–0.59 g I-TEQ yr^{-1} respectively), the domestic burning of waste in backyard fires (0.54–6.4 g I-TEQ yr^{-1}), and the inadvertent and uncontrolled burning of buildings and vehicles (0.37–2.8 g I-TEQ yr^{-1}). The use of unleaded petrol and diesel for land transport was estimated to emit 0.11–1.2 g I-TEQ yr^{-1}.

Solid waste streams from the burning of coal, wood and waste were identified as significant contributors to the release of PCDD/Fs to land, primarily to landfill. The deposition of industrial and domestic refuse at landfills was estimated to account for about 20 g I-TEQ of PCDD/Fs released to land each year.

Since the late 1980s, advances in environmental and chemical management practices are believed to have resulted in a reduction in the release of PCDD/Fs to the New Zealand environment. Reasons for this include:

- many smaller, poorly designed and/or operated, hospital waste incinerators have closed

- leaded petrol (which emits more PCDD/Fs than unleaded petrol) has been phased out of use in New Zealand's land transport fleet
- the use of PCP in the timber industry ceased in 1988, and it was deregistered[1] in 1991
- 2,4,5-T manufacture ceased in 1987, and, once existing stocks were exhausted, its widespread use ceased
- upgrades at New Zealand's two bleached kraft pulp mills have seen both mills convert to elemental chlorine-free technology
- through regulations under the Toxic Substances Act (1979), the import of PCBs was prohibited from January 1987 and their use has been prohibited since January 1994.

Nevertheless, past industrial practices have created PCDD/F reservoirs. Generally these are localized sites of contamination in which the levels of PCDD/Fs are elevated compared to typical background levels in the wider general environment. Such reservoirs create the potential for the redistribution and circulation of the contaminants into the wider environment. The inventory has estimated that the quantity of PCDD/Fs contained within reservoir sources in New Zealand is 1450–1700 g I-TEQ, primarily arising from historical 2,4,5-T use (620–860 g I-TEQ) and the past use of PCP (310 g I-TEQ), as well as from PCDD/Fs associated with refuse deposited to landfills (500 g I-TEQ).

Whilst the New Zealand PCDD/F inventory has been based on the assessment of individual sources, there is no clear evidence showing that the emissions of PCDD/Fs from known sources correlate proportionally with general population exposures. Although the emissions inventory estimates the relative contribution of the various sources to total emissions, there are uncertainties in these estimates and it cannot be assumed that these sources make the same relative contributions to human intakes.

There has been no comparable inventory of emissions of dioxin-like PCBs, either in New Zealand or worldwide.

3.2 Environmental levels

PCDD/Fs and PCBs have been found throughout the world in practically all media, including air, soil, water and sediment, and biotic media such as birds, fish, shellfish and marine mammals. Although high levels of these compounds may occur in soil and sediment, generally the highest levels are found in biota. Top-of-food-chain predators in particular, such as marine mammals, bioaccumulate these chemicals so that they are often present at higher levels compared to their surrounding environment. The widespread occurrence of the PCDD/Fs, particularly within industrialized countries in the Northern Hemisphere, can be readily explained by the numerous sources that emit these compounds into the atmosphere and their overall persistence in the environment due to a resistance to biotic and abiotic transformation.

In New Zealand, considerable research has been undertaken to characterize the presence of dioxin-like compounds in the environment. As a result, there is a reasonable understanding of the levels

[1] Importation, manufacture or sale prohibited, though existing stocks can be used.

of these chemicals and their distribution in various environmental compartments, including ambient air (Buckland *et al*., 1999), soil (Buckland *et al*., 1998a), sediment (Scobie *et al*., 1998), water and biota (both avian and aquatic) (Buckland *et al*., 1998b; Jones *et al*., 1999; Reid, 2000; Scobie *et al*., 1998). A summary of the environmental concentrations measured in New Zealand is given in Table 3.2, with an emphasis on the data collected from the environmental survey of the Organochlorines Programme. To date, this survey represents the only national assessment of environmental levels of dioxin-like compounds undertaken in New Zealand. Because of the bioaccumulative nature of these contaminants, the greatest concentrations may be found in the higher trophic level species, such as harrier hawks and the inshore-dwelling marine mammal Hector's dolphin.

Table 3.2 Concentrations of PCDD/Fs and PCBs in the New Zealand environment

Environmental compartment[1]	PCDD/Fs	PCBs	Reference
Ambient air[2] (fg TEQ m^{-3})			Buckland *et al*., 1999
Reference sites	0.77–7.48	0.54–3.45	
Agricultural sites	0.94–31.7	0.11–1.88	
Urban residential sites	6.15–262	1.29–13.1	
Urban industrial site	40.3–1170	9.52–33.1	
Soil[2] (ng TEQ kg^{-1}, dry wt)			Buckland *et al*., 1998a
Reference soils	0.17–1.99	0.065–0.29	
Agricultural soils	0.17–9.14	0.065–0.15	
Urban soils	0.54–33.0	0.067–1.33	
Sediment[2] (ng TEQ kg^{-1}, dry wt)	0.081–2.71	0.065–0.62	Scobie *et al*., 1998
Finfish[2] (ng TEQ kg^{-1}, fillet wt)	0.016–0.39	0.069–1.39	Buckland *et al*., 1998b
Shellfish[2] (ng TEQ kg^{-1}, wet wt)	0.015–0.26	0.065–0.60	Scobie *et al*., 1998
Marine mammals (ng TEQ kg^{-1}, wet wt)			Jones *et al*., 1999
Inshore species (Hector's dolphin)	81.4 (includes the PCBs)		
Open ocean species (various)	0.77–15.7 (includes the PCBs)		
Harrier hawks (ng TEQ kg^{-1}, wet wt)	1.15–18.3	2.46–29.4	Reid, 2000

1. PCDD/Fs as I-TEQ (Kutz *et al*., 1990); PCB TEQ from Ahlborg *et al*., 1994. TEQ levels include half LODs for non-detected congeners.
2. Data from the environmental survey of the Organochlorines Programme.

Overall, these data show that the concentrations of dioxin-like compounds in the New Zealand environment are generally lower than levels for comparable environments in the Northern Hemisphere. For the PCDD/Fs, this finding is consistent with the estimated comparatively low level of emissions for New Zealand compared to emission estimates made for other industrialized countries (see Section 3.1).

An ecological risk assessment of the New Zealand environmental data has reported that, for the most part, the current background concentrations of most persistent organochlorine chemicals are significantly less than the threshold for effects for most wildlife species (Jones and Giesy, 2001). However, there are indications that the dioxin-like compounds are bioaccumulating in top-of-food-chain predators to levels where effects may occur, and in such situations future assessment and management may be warranted.

3.3 Human exposure and population levels

Human exposure to PCDD/Fs and PCBs is generally of two kinds: background exposures, of the entire population, and additional exposures that are normally restricted to smaller groups of people, such as may occur in particular workplaces.

3.3.1 Exposure for the general population

Everyone is exposed to small background levels of dioxin-like compounds when they consume food and, to a much lesser extent, when they breathe air or have skin contact with dioxin-contaminated materials. For the general population, over 90% of exposure to PCDD/Fs and PCBs is through the diet, with foods of animal origin such as meats, dairy products and fish usually the main source. Unborn children are exposed to dioxin-like compounds *in utero*, and nursing infants are exposed to these contaminants present in breast milk.

PCDD/Fs in our food mainly result from its deposition from air onto pasture and its uptake by grazing animals, which results in the contamination of animal meat and milk. Another exposure pathway results from the discharge of effluent containing PCDD/Fs and PCBs to waterways, where these compounds can then bioaccumulate in fish and shellfish. The application of waste materials, such as sewage sludge, to agricultural land might also enhance the entry of dioxin-like compounds into food produce.

3.3.2 Accidental and occupational exposure

Some people are exposed to PCDD/Fs and PCBs in their work places, and sometimes people have been exposed to very high levels from industrial accidents, or accidental poisonings such as the Yusho incident in Japan or the Yu-Cheng incident in Taiwan. Occupational exposures have generally been associated with the manufacture or use of industrial chemicals contaminated with PCDD/Fs, including chlorophenols and the herbicide 2,4,5-T.

In New Zealand the past use of PCP in the timber industry has resulted in occupational exposure to PCDD/F contaminants for some timber workers. Analysis of four plasma samples, collected in 1995, from former timber workers showed TEQ levels in the range 10.6–53.9 ng I-TEQ kg^{-1} lipid, which were up to four times higher than levels that have been reported for the general New Zealand population (see Section 3.3.3.2). Some congeners were particularly elevated, most notably 1,2,3,6,7,8-HxCDD. Congener-specific data for these occupationally exposed samples are reported in Table A1 (Appendix). No follow-up study has been undertaken to verify this initial finding, which is discussed further in Section 7.3.2 of this report. Similarly, a study published in 1992 reported that the blood serum 2,3,7,8-TCDD levels of New Zealand pesticide applicators involved for many years in ground-level spraying of 2,4,5-T were significantly higher than those of a comparison group (Smith *et al*., 1992).

PCBs were never manufactured in New Zealand, and consequently occupational exposures similar to those observed at manufacturing plants overseas (ATSDR, 1999; Swanson *et al*., 1995) would not have occurred here. However, the handling of PCB-containing equipment, particularly within the electrical industry where PCB-filled capacitors and transformers were once used, is likely to have resulted in human exposure. Inhalation and dermal contact would have been the most likely routes of exposure (Wolff, 1985). Whilst some monitoring of New Zealand electrical industry

employees' blood have been undertaken for PCBs, we are not aware of any published data on the concentrations found.

3.3.3 Relevant New Zealand studies on background exposures

A number of important studies have been undertaken on background exposures to PCDD/Fs and PCBs in New Zealand which are relevant to an appraisal of the health risks posed by these chemicals. These studies are briefly summarized in the following sections.

3.3.3.1 Dietary study

The New Zealand dietary study was undertaken as a component of the Organochlorines Programme. Here, 391 food samples, representing 53 different types of food (including meat, dairy, poultry, fish and cereal produce) were purchased in 1997 at retail outlets from five New Zealand towns and cities (Buckland *et al*, 1998c). These samples were made into 22 composite food groups for analysis. Concentrations of PCDD/Fs and PCBs determined are summarised, both on a wet weight and fat weight basis, in Table 3.3.

Table 3.3 Concentrations of PCDD/Fs and PCBs in New Zealand retail foods

Foods	PCDD/F (ng I-TEQ kg^{-1})[1]		PCBs (ng TEQ kg^{-1})[1]	
	Wet weight basis	Fat weight basis	Wet weight basis	Fat weight basis
Meats and meat products	0.0076–0.090	0.072–0.57	0.0048–0.068	0.045–0.43
Milk and dairy products	0.0021–0.075	0.056–0.26	0.0020–0.12	0.10–0.15
Fish	0.021–0.12	0.41–1.82	0.028–0.16	0.77–2.42
Eggs and poultry	0.0072–0.012	0.12–0.29	0.0036–0.010	0.11–0.14
Bread and cereal products	0.0059–0.0099	0.19–0.66	0.0027–0.0040	0.051–0.45
Potatoes and hot chips, snack foods, and vegetable fats and oils	0.016–0.044	0.041–0.42	0.0025–0.014	0.016–0.066

1. PCDD/Fs as I-TEQ (Kutz *et al*., 1990); PCB TEQ from Ahlborg *et al*., 1994. TEQ levels include half LODs for non-detected congeners.

Source: Buckland *et al*., 1998c

To assess the dietary intakes of dioxin-like compounds, model diets for two types of New Zealander were developed (Buckland *et al*., 1998c; Hannah, 1997). These diets were for:

- adult males, 80 kg weight, 25–44 years of age, consuming 10.8 MJ daily (a median energy intake)
- adolescent males, 70 kg weight, 15–18 years of age, consuming 21.5 MJ daily (a 90^{th} centile energy intake).

Diets for adult and adolescent females were not developed because proportionally they have a lower energy intake than males. Consequently, their dietary intakes of PCDD/Fs and PCBs are expected to be less (Hannah, 1997). The male diets are therefore likely to represent worst-case intakes for these age groups. The estimated intakes of PCDD/Fs and PCBs from this assessment are summarized in Table 3.4.

Table 3.4 Dietary intake for an adult and adolescent male New Zealander

	Adult male (pg TEQ/kg bw/day)	Adolescent male (pg TEQ/kg bw/day)
PCDD/F I-TEQ[1]	0.18	0.44
PCB TEQ[1]	0.15	0.32
Total TEQ (PCDD/F + PCB TEQs)	0.33	0.76

1. PCDD/Fs as I-TEQ (Kutz *et al*., 1990); PCB TEQ from Ahlborg *et al*., 1994. TEQ levels include half LODs for non-detected congeners.

Source: Buckland *et al*., 1998c

Recalculating the contaminant concentrations for each food group using the 1997 WHO TEFs (Van den Berg *et al*., 1998) results in approximately a 10% increase in TEQ levels. This increase agrees well with the predicted estimated increase identified by the WHO for recalculating TEQ levels (van Leeuwen *et al*., 2000). Using the recalculated data, the dietary intake of dioxin-like compounds is estimated at 0.37 pg TEQ/kg bw/day for an adult male and 0.84 pg TEQ/kg bw/day for an adolescent male (Table 3.5). The recalculated concentrations of PCDD/Fs and PCBs, for each composite food group, and the corresponding daily dietary intake, are reported in Tables A2 and A3 (Appendix) for adult and adolescent males respectively.

Table 3.5 Dietary intake for an adult and adolescent male New Zealander using the 1997 WHO TEFs

	Adult male (pg TEQ/kg bw/day)	Adolescent male (pg TEQ/kg bw/day)
PCDD/F TEQ[1]	0.22	0.53
PCB TEQ[1]	0.15	0.31
Total TEQ (PCDD/F + PCB TEQs)	0.37	0.84

1. TEQ levels include half LODs for non-detected congeners.

3.3.3.2 Body burden studies

Three major body burden studies have been undertaken to measure, respectively, the levels of organochlorine chemicals in serum (Bates *et al*., 1999; Buckland *et al*., 2001), plasma (Hannah *et al*., 1994) and breast milk (Bates *et al*., 1990; 1994).

Serum study

This study was undertaken as a component of the Organochlorines Programme (Bates *et al*., 1999; Buckland *et al*., 2001). It involved a cross-sectional survey of a representative sample of New Zealanders, aged 15 years and older, living in households throughout New Zealand. The serum study 'piggy-backed' onto the Ministry of Health's National Nutrition Survey, and took advantage of the sampling frame, procedures and technical support provided by this much larger survey (Quigley and Watts, 1997). Blood samples were collected during the period December 1996 to November 1997 from 2925 individuals. From each participant up to 10 mL of blood was collected, which was processed to provide serum for analysis.

Of the total samples, 1834 (approximately 0.05% of the New Zealand population) were from non-occupationally exposed participants, and provided sufficient volume of serum for inclusion in the study. Because PCDD/F analysis required a greater volume of serum than could be collected from

any one individual, the serum was pooled according to stratification criteria of age, ethnicity, sex and geographic region. A total of 60 pooled serum samples were analyzed for organochlorine residue levels. Concentrations of PCDD/Fs and PCBs, as TEQ calculated using the 1997 WHO TEFs (Van den Berg *et al*., 1998), on a lipid weight basis, are reported in Table 3.6. These concentrations are also reported, stratified by age, in Table 3.7, and Tables A4 and A5 (Appendix).

Table 3.6 Concentrations of PCDD/Fs and PCBs in the serum of New Zealanders

	Concentration (ng TEQ kg^{-1} lipid weight basis)[1]		
	Minimum	**Maximum**	**Mean**
PCDD/F TEQ	5.05	26.7	12.8
PCB TEQ	4.29	11.9	6.86
Total TEQ[2]	9.71	38.5	19.7

1. TEQs calculated using the 1997 WHO TEFs. Data reported includes half LODs for non-detected congeners.
2. This does not correspond to a summation of the PCDD/F TEQ and PCB TEQ levels reported in the table, because the minimum PCDD/F TEQ and PCB TEQ are for different samples, and similarly the maximum PCDD/F TEQ and PCB TEQ are for different samples.

For appraising the health risks of dioxin-like compounds to New Zealanders, it is useful to also consider the concentrations of these contaminants normalized to body weight. Body burdens (as ng TEQ/kg bw) for the PCDD/Fs plus the dioxin-like PCBs, for male and female for each age group are presented in Table 3.7.

Table 3.7 Concentrations of PCDD/Fs and PCBs for male and female New Zealanders

Sex	**Age (years)**	**Serum concentration (ng TEQ kg^{-1} lipid)**		**Body burden (ng TEQ/kg bw)**	
		Maximum	**Mean**	**Maximum**	**Mean**
Male	15–24	15.7	12.9	2.02	1.66
	25–34	17.1	14.3	2.76	2.32
	35–49	22.8	18.7	4.47	3.66
	50–64	27.0	23.1	5.62	4.80
	65+	31.3	25.3	5.85	4.73
Female	15–24	13.4	12.4	3.34	3.10
	25–34	18.7	15.5	5.11	4.25
	35–49	22.9	19.5	7.11	6.06
	50–64	35.1	24.3	11.3	7.80
	65+	38.5	33.9	12.0	10.6

Body burdens were calculated using average body weights and fat content for each of the age groups. Body weights were measured as part of the National Nutrition Survey, and fat content was calculated from skinfold measurements, also obtained from the Survey. The conversion of the serum concentration data to body burdens is summarized in Table A6 (Appendix).

The body burden data (Table 3.7) show a strong sex differentiation, with on average an 84% (range of 62–125%) higher body burden in females compared to males for the same age group.

Generally, serum concentrations were similar for males and females of the same age group, except for the older age group, where women appear to have higher concentrations. The higher body burden in women therefore appears to be primarily influenced by their higher body fat content compared to that of men. As shown in Table A6 (Appendix), body fat is on average 68% (range of 54–94%) higher in women compared to men for the same age group.

Whilst the serum study is an important assessment of levels of dioxin-like compounds in the New Zealand population, it has a number of limitations. In particular, by pooling samples, it is not possible to examine the distribution of contaminant levels among individuals. Nevertheless, the study has enabled the following conclusions to be made.

1. National averages: The national average serum concentration for dioxin-like compounds was 19.7 ng TEQ kg^{-1} on a lipid-adjusted basis, or 0.15 ng TEQ L^{-1} on a serum volume basis.

2. Age variations: Serum concentrations were found to increase with age. Thus, the mean serum concentration of PCDD/Fs ranged from 6.69 ng TEQ kg^{-1} lipid for the 15–24 years age group, to 20.7 ng TEQ kg^{-1} lipid for the 65 years and older age group. For the PCDD/Fs and dioxin-like PCBs combined, the mean serum concentration ranged from 12.5 ng TEQ kg^{-1} lipid for the 15–24 years age group to 29.9 ng TEQ kg^{-1} lipid for the 65 years and older age group.

Similarly, when normalized to body weight, serum concentrations increased with age. Thus the mean body burdens for the PCDD/Fs and dioxin-like PCBs combined ranged from 1.66 ng TEQ/kg bw for 15–24-year-old males to 4.73 ng TEQ/kg bw for 65+ males, and from 3.10 ng TEQ/kg bw for 15–24-year-old females to 10.6 ng TEQ/kg bw for 65+ females. The higher serum concentrations measured in older people are likely to reflect higher historical exposures to dioxin-like compounds, and the fact that these compounds are only slowly metabolized and excreted from the body.

3. Geographic variations: Small geographical variations were observed, with serum concentrations tending to be marginally higher in the two most northern regions (Northland/Auckland and Waikato/Bay of Plenty) compared to the two most southern regions (Lower North Island and South Island) of New Zealand.

4. Ethnic variations: No clear differences in serum concentrations were found on the basis of race.

5. Sex variations: Generally, no clear differences in serum concentrations were found between males and females, although women from the oldest age group (65+ years) appear to have higher concentrations than men aged 65 years and older. However, when expressed as body burdens normalized to body weight, women consistently had higher amounts of dioxin-like compounds per kilogram of body weight (i.e. ng TEQ/kg bw) than men for the same age group.

The study also found that, on average, the dioxin-like PCBs accounted for approximately 15–30% of the total TEQ associated with general population exposures to dioxin-like compounds.

Plasma study

This study analyzed the levels of PCDD/Fs in 28 self-selected males and females aged between 20 and 60 years. Samples were collected from a single region of New Zealand in November and December 1992. Concentrations of individual PCDD/F congeners and I-TEQ data on a lipid weight basis, by sex and age group, are reported in Tables A7 and A8 (Appendix). TEQ levels, recalculated using the 1997 WHO TEFs (Van den Berg *et al*., 1998), are summarized in Table 3.8.

Table 3.8 Concentrations of PCDD/Fs in the plasma of New Zealanders

Sex	Age (years)	Concentration (ng TEQ kg^{-1}, lipid weight basis)[1]		
		Minimum	Maximum	Mean
Male	20–29	4.63	14.1	9.02
	30–39	9.60	17.9	14.3
	40–60	8.12	22.5	13.4
Female	20–29	5.27	14.6	9.10
	30–39	7.72	23.5	15.2
	40–60	8.65	44.6	20.6

1. TEQs calculated using the 1997 WHO TEFs. Data reported includes half LODs for non-detected congeners.

The data shows generally similar PCDD/F concentrations for males and females, with increasing plasma concentrations with increasing age.

As this study was comparatively limited in scope (both in terms of the small number of samples collected and the localized geographical coverage) and the concentrations of PCDD/Fs measured were similar to the levels measured in the Organochlorines Programme serum study (compare data reported in Table 3.8 and Tables A8 and A9 [Appendix] with the data reported in Table A4 [Appendix]), data from this plasma study are not considered further in the current risk appraisal.

Breast milk study

During 1987/88 the Department of Health commissioned a study to determine the extent to which New Zealanders have been exposed to persistent organochlorine chemicals, and to compare the levels found with those in other countries. To carry out the study, the researchers looked at levels in mothers' milk.

The study involved the collection of 38 breast milk samples from primiparous mothers between 20 and 30 years of age from two urban centers (Auckland and Christchurch) and two rural regions (Northland and North Canterbury) of the country. All samples were analyzed for PCBs and persistent organochlorine pesticides, and 37 of the samples were analyzed for PCDD/Fs (Bates *et al*., 1990; 1994). The concentrations of PCDD/Fs measured, reported as Nordic TEQs[2] (Ahlborg, 1989), are summarized in Table 3.9.

Table 3.9 Concentrations of PCDD/Fs in the breast milk of New Zealand women from the 1987/88 breast milk study

	Concentration		
	Minimum	Maximum	Mean
PCDD/F (ng Nordic-TEQ L^{-1}, whole milk)[1]	0.19	2.3	0.60
PCDD/F (ng Nordic-TEQ kg^{-1}, milk fat)[1]	5.0	32	17

1. TEQ levels include half LODs for non-detected congeners.

[2] TEF values in the Nordic scheme are identical to those for the WHO scheme given in Table 2.3, except that in the Nordic scheme the factor for 1,2,3,7,8-PeCDF is set at 0.01, 1,2,3,7,8-PeCDD is set at 0.5 and OCDD and OCDF are set at 0.001.

Recalculating this PCDD/F data using the 1997 WHO TEFs results in an approximately 15–20% increase in TEQ levels. These recalculated TEQ levels are summarized in Table 3.10 and reported by geographic region in Table A9 (Appendix).

Table 3.10 Concentrations of PCDD/Fs in the breast milk of New Zealand women from the 1987/88 breast milk study, recalculated using the 1997 WHO TEFs

	Concentration		
	Minimum	**Maximum**	**Mean**
PCDD/F (ng TEQ L^{-1}, whole milk)[1]	0.24	3.0	0.72
PCDD/F (ng TEQ kg^{-1}, milk fat)[1]	6.2	40	21

1. TEQ levels include half LODs for non-detected congeners.

PCB analysis of the breast milk samples was undertaken for only a limited number of congeners. These did not include the non-*ortho* congeners, or, with the exception of PCB congener #118, the mono-*ortho* congeners, which have since been assigned TEF values. Consequently, PCB TEQ levels were not calculated for any of the samples reported in the original publications. Total PCB concentrations, measured as the sum of the congeners analyzed, were however reported, and these are summarized in Table 3.11.

Table 3.11 Concentrations of PCBs in the breast milk of New Zealand women from the 1987/88 breast milk study

	Concentration		
	Minimum	**Maximum**	**Mean**
Sum of PCBs (μg L^{-1}, whole milk)[1]	1.7	26	4.6
Sum of PCBs (μg kg^{-1}, milk fat)[1]	52	940	143

1. PCB congeners determined: PCB#28, #74, #118, #146, #153, #138, #183, #185, #187, #171, #174, #177, #170, #180 and ∑octas.

From this study, and based on advice from the WHO at the time, the Department of Health concluded that despite the presence of these chemicals in human milk, breast feeding should be encouraged and promoted on the basis of convincing evidence of the benefits of human milk to the overall health and development of the infant.

A second breast milk study is currently being undertaken by the Institute of Environmental Science and Research, funded by the Ministry of Health (Ministry for the Environment, 1998). The preliminary indication from this study is that over the 10-year period from 1987/88 to 1997/98, the New Zealand PCDD/F levels have fallen by about two-thirds (Institute of Environmental Science and Research, 2001).

4 Health effects of dioxins

The available literature indicates that dioxin-like compounds may induce a wide spectrum of biological responses at the biochemical, cellular and tissue level. This section reviews the cancer and non-cancer health effects of 2,3,7,8-TCDD, based on data from laboratory animal studies and the available human data from occupational cohort studies. The information covered focuses on those studies considered to be the most significant in elucidating the most sensitive endpoints of TCDD. More comprehensive reviews on the health effects of dioxin-like compounds are available from a number of sources (ATSDR, 1998; IARC, 1997; US EPA, 1994b).

4.1 Non-cancer health effects of TCDD

The main focus of initial attention concerning the health effects of dioxin concerned cancer. Cancer remains an important area of concern regarding human exposure to TCDD, but recent animal studies have suggested that TCDD might also have sensitive non-cancer effects at low dose.

4.1.1 Non-cancer health effects in animals

TCDD has been shown to affect most organ systems in several animal species and is extraordinarily potent (ATSDR, 1998; IARC, 1997; US EPA, 1994b). Acute effects include excessive body weight loss; thymic atrophy; hypertrophy and hyperplasia of the liver, gastrointestinal tract, urogenital and cutaneous epithelia; impaired liver structure and function; subcutaneous edema; and systemic hemorrhage (ATSDR, 1998; IARC, 1997). Changes in heart weight, pathophysiological effects, and degenerative changes to the cardiovascular system have also been observed in exposed animals at or near lethal doses of TCDD (ATSDR, 1998). Exposure to low doses of TCDD has resulted in suppression of both cell-mediated and humoral immunity in several species and can decrease resistance to infection in exposed mice (ATSDR, 1998; IARC, 1997; Kerkvliet, 1994). Route and rate (single exposure versus repeated daily) of exposure appears to have little influence on the effects seen following exposure to TCDD (DeVito and Birnbaum, 1994). Rather, the toxicity is dependent on body burdens. Because reproductive and developmental effects resulting from TCDD exposure are the most sensitive health effects seen in experimental systems, more emphasis is placed on these results in the following discussion.

TCDD has been shown to cause a variety of reproductive and developmental effects in fish, birds and mammals (ATSDR, 1998; Theobald and Peterson, 1994; US EPA, 1994b). The effects seen in adult animals generally require overt toxic doses, while some studies suggest that toxicity to the developing organism can occur at doses as much as 100 times lower than these (US EPA, 1994b). The most sensitive developmental effects in mammals resulting from perinatal exposure to TCDD include reproductive system abnormalities, neurobehavioral effects and immunotoxicity (ATSDR, 1998; US EPA, 1994b). Reproductive effects are the most extensively studied in animals, and involve a number of different outcomes.

Reproductive effects induced by TCDD in adult animals include reduced testis and accessory sex organ weights, abnormal testis structure, decreased spermatogenesis, reduced fertility, decreased testicular testosterone synthesis, reduced plasma androgen concentrations, and altered regulation

of pituitary luteinizing hormone secretion (ATSDR, 1998; Theobald and Peterson, 1994; US EPA, 1994b). Effects on the adult female reproductive system include signs of ovarian dysfunction and alterations in hormone levels, decreased fertility, inability to maintain pregnancy, decreased litter size, and decreased uterine weights in mice, rats, and primates. TCDD exposure has been shown to alter menstrual and estrus cycles in these species and is considered to have antiestrogenic effects. A dose-related increase in the incidence and severity of endometriosis has been reported in monkeys chronically exposed to TCDD in the diet (Rier *et al*., 1993), which is discussed in more detail in Section 4.1.4.4. Surgically induced endometriosis was exacerbated by TCDD exposure in rodents (Cummings *et al*., 1996).

Teratogenic effects of TCDD have been demonstrated in several species, the mouse being the most sensitive (ATSDR, 1998; Theobald and Peterson, 1994; US EPA, 1994b). Structural malformations including cleft palate formation and hydronephrosis have been demonstrated in mice exposed to TCDD during gestation at doses that are not maternally toxic (US EPA, 1994b). Induction of cleft palate in this species can reach 100% (Birnbaum *et al*., 1987ab). In rats (Schwetz *et al*., 1973) and hamsters (Olson and McGarrigle, 1992) cleft palate was observed in offspring only at doses toxic to the dam and fetus. The maximum incidence of cleft palate in these species was 10–20%. Gestational exposure to TCDD can cause an increased incidence of extra ribs in the rabbit and intestinal hemorrhage in the rat (ATSDR, 1998; Theobald and Peterson, 1994). Malformations of the external genitalia have also been reported in female rats, resulting from prenatal exposure to low levels of TCDD (Gray *et al*., 1997b; see Section 4.1.4.2.).

Decreased spermatogenesis is one of the most sensitive toxic effects of perinatal exposure to TCDD on the male rat reproductive system (ATSDR, 1998; Theobald and Peterson, 1994). Other effects in exposed male offspring include alterations in testosterone levels, demasculinization and feminization of sexual behavior, and feminization of the regulation of LH secretion. Accelerated onset of constant estrus, shortened reproductive lifespan, reduced ovarian weight, and cystic hyperplasia of the endometrium have been observed in female rats exposed to TCDD during gestation (Gray and Ostby, 1995). Developmental effects in monkeys exposed to TCDD during gestation and lactation include impaired object learning (Schantz and Bowman, 1989) and behavioral changes (Schantz *et al*., 1992), and these are discussed further in Section 4.1.4.3. Prenatal exposure to TCDD causes thymic atrophy in all species tested and this effect occurs at doses well below those that induce maternal or fetal toxicity (US EPA, 1994b). Alterations in cell-mediated immunity and changes in lymphocyte surface cell markers have also been observed in rodents (ATSDR, 1998).

4.1.2 Non-cancer health effects in humans

The most widely recognized effect following high dose exposure to TCDD is chloracne (ATSDR, 1998; US EPA, 1994b). The condition can disappear after termination of exposure or can persist for many years. Other effects on the skin include hyperpigmentation and hirsutism (Ashe and Suskind, 1950; Suskind and Hertzberg, 1984). Neurological symptoms observed in TCDD-exposed workers include lassitude, weakness of the lower limbs, muscular pains, increased perspiration, loss of appetite, headaches, nervousness, anxiety, irritability, and loss of libido (Ashe and Suskind, 1950; Jirasek *et al*., 1974; 1976; Moses *et al*., 1984; Oliver, 1975; Pazderova-Vejlupkova *et al*., 1981; Suskind, 1985). In certain instances, effects persisted for several years. Increased levels of hepatic enzymes and slight alterations in lipid profile have been reported in humans exposed to high levels of TCDD (ATSDR, 1998), although the effects were mild and

often transient. Temporary enlargement of the liver has also been observed (US EPA, 1994b). TCDD can cause long-term alteration in glucose metabolism (Henriksen *et al.*, 1997; Pesatori *et al*., 1998) and slight changes in thyroid function (Zober *et al*., 1994). Effects on the respiratory system, manifested mainly as upper respiratory tract irritation, have resulted from acute high exposure to TCDD (ATSDR, 1998). Other irritant effects resulting from acute exposure include conjunctivitis with red and irritated eyes, and blepharitis (US EPA, 1994b). The information regarding the toxicity of TCDD to the immune system is scant and inconsistent (ATSDR, 1998; US EPA, 1994b). Natural killer cells were increased in a population of chemical workers exposed to TCDD examined 17 years after termination of exposure (Jennings *et al*., 1988). There is some suggestive evidence of toxicity to the cardiovascular system (ATSDR, 1998; Steenland *et al*., 1999) and limited information regarding body weight effects in humans (ATSDR, 1998).

The majority of studies on human reproductive and developmental effects concern paternal exposure to TCDD, and have evaluated its potential toxicity long after a high exposure had occurred (IARC, 1997). Studies of the risk of spontaneous abortion involving occupational and environmental herbicide exposure have generally not found increased risks (ATSDR, 1998; IARC, 1997; Institute of Medicine, 1994; Sweeney, 1994; US EPA, 1994b). Findings from studies of Vietnam veterans suggested an effect with increasing estimated (self-reported or inferred) Agent Orange exposure (Institute of Medicine, 1994). However, the inconsistency with results of the occupational and environmental exposure studies and the marginal magnitude of the increased risk make these results suspect (Institute of Medicine, 1994). Most studies of spontaneous abortion have suffered from a high degree of exposure and outcome misclassification, small sample sizes, lack of data on TCDD levels at the time of conception, and differences in case definition. Similarly, results from human studies of developmental effects and exposure to herbicides or TCDD have been inconclusive (ATSDR, 1998; Institute of Medicine, 1994; Sweeney, 1994; US EPA, 1994b). The studies have been limited due to small sample sizes (for specific birth defects), potential biases in the findings, and uncertainties regarding the assessment of exposure.

Egeland *et al*. (1994) demonstrated that current and half-life serum dioxin levels were positively and significantly related to luteinizing and follicle stimulating hormones and inversely related to testosterone levels in male workers from the National Institute for Occupational Safety and Health (NIOSH) cohort. Vietnam veterans were found to have a significantly lower sperm concentration relative to non-Vietnam veterans (CDC, 1989). The ability to produce children was not affected, and with the exception of Ranch Hand veterans, Vietnam veterans did not have increased body burdens of TCDD. No associations between TCDD exposure and hormone levels or sperm characteristics were observed among Ranch Hand veterans (Henriksen *et al*., 1996). The investigators noted that the members of this cohort were exposed to lower levels of TCDD and for shorter duration than the workers followed by Egeland *et al*.

Epidemiological investigations of populations exposed occupationally or environmentally to TCDD do not demonstrate increased all-cause or non-cancer mortality among these groups (Bertazzi *et al*., 1989; Cook *et al*., 1986; 1987; Fingerhut *et al.* 1991ab; Ott *et al.* 1980; 1987; Wolfe *et al*., 1995; Zack and Suskind, 1980). Likewise, no excess overall mortality was reported in workers exposed to TCDD as a result of the accident at the BASF facility in Germany (Ott and Zober, 1996; Thiess *et al*., 1982; Zober *et al*., 1990). However, increased cancer mortalities have been observed in some of these studies, and these are discussed further in Section 4.2.4. The all-cause, all-cancer and non-cancer mortality from those cohorts with quantitative exposure data for TCDD are presented in Table 4.1.

Table 4.1 All-cause, all-cancer and non-cancer mortality from three occupational cohort studies

Cohort	Deaths observed	Deaths expected	SMR
Boehringer-Ingelheim, Germany (Flesch-Janys *et al*., 1998)			
All-cause	413	357.7	1.2
All-cancer	124	88.1	1.4
Non-cancer	289	269.6	1.1
BASF, Germany (Ott and Zober, 1996)			
All-cause	92	102.2	0.9
All-cancer	31	25.8	1.2
Non-cancer	61	76.4	0.8
NIOSH, USA (Fingerhut *et al*., 1991ab)			
All-cause	1052	1062.6	1.0
All-cancer	265	230.4	1.2
Non-cancer	787	832.2	1.0

4.1.3 Causal inference regarding reproductive and developmental effects of TCDD

The available epidemiological evidence is insufficient or inadequate to determine whether an association exists between exposure to TCDD and changes in hormonal levels, altered sperm parameters or infertility, spontaneous abortion, and birth defects in humans (ATSDR, 1998; IARC, 1997). Some of the problems with the studies conducted to date include inadequate statistical power and limited assessment of the exposure. Furthermore, the epidemiological studies have focused on paternal rather than maternal exposure to TCDD and its resulting effects on offspring.

The toxicological literature shows that exposure to TCDD is associated with a number of reproductive and developmental effects in experimental animals. The levels of TCDD associated with such toxicity are lowest among animals perinatally exposed (ATSDR, 1998). Gray *et al*. (1997b) have cautioned against concluding that fetal animals are exposed to levels that are only one to four times higher than human fetal levels, for several reasons. First, it is unclear if TCDD is transferred from the maternal/placental compartment to the human fetus to the same extent as seen in the rat. Second, the bioavailability of TCDD to the fetus at a given maternal body burden may differ depending upon whether TCDD was administered as a single exposure (gavage or 'bolus' dose) or by long-term low-level exposure. Only the studies in Rhesus monkeys have approximated long-term chronic exposure as would occur in most human populations. A comparison of animal and human body burdens of TCDD for various toxic endpoints is presented and discussed in a Section 4.3.

4.1.4 Key studies of non-cancer health effects of TCDD

Evidence from animal studies suggests that the most sensitive effects of TCDD exposure result in abnormal reproductive system development, and neurobehavioral and immunotoxicity effects in offspring. In this section, the results from the studies demonstrating the most sensitive adverse

effects as identified by a WHO consultation (Van Leeuwen and Younes, 2000) and the Agency for Toxic Substances and Disease Registry (ATSDR, 1998) are summarized (Table 4.2).

Table 4.2 Animal body burdens of TCDD and related human estimated daily intakes

Response (LOAELs)	Maternal body burden[1] (ng/kg bw)	Related human EDI[2] (pg/kg bw/day)	Reference
Rats			
Decreased sperm count in offspring	28	14	Gray *et al.*, 1997a
Immune suppression in offspring	50	25	Gehrs *et al.*, 1997; Gehrs and Smialowicz, 1998
Increased genital malformations in offspring	73	37	Gray *et al.*, 1997b
Monkeys			
Neurobehavioral (object learning) effects in offspring	42	21	Schantz and Bowman, 1989
Endometriosis	42	21	Rier *et al.*, 1993

1. Increment above background.
2. Human estimated daily intake (EDI) as reported by van Leeuwen *et al.* (2000), and Van Leeuwen and Younes (2000).

4.1.4.1 Immune system effects in offspring

Gehrs and Smialowicz (1998) and Gehrs *et al*. (1997) studied the persistence of delayed-type hypersensitivity (DTH) suppression in rat offspring exposed to TCDD on gestational day 14. DTH suppression was determined by measuring the DTH response to bovine serum albumin in the 4- and 14-month-old offspring of dams exposed by gavage to 0, 0.1, 0.3 or 1.0 μg TCDD kg^{-1}. The lowest maternal dose that produced DTH suppression was 0.1 μg TCDD kg^{-1} in males at 14 months of age. DTH suppression occurred in female offspring of the same age at 0.3 μg TCDD kg^{-1}. There were only four to seven animals per dose group, and the investigators did not report numbers of animals affected per dose group.

4.1.4.2 Reproductive effects in offspring

Gray *et al*. (1997a) investigated reproductive effects of gestational Day 15 TCDD administration in male Long Evans Hooded rat offspring. Day 15 in the rat corresponds to the onset of the endocrine-sensitive phase of sexual differentiation. Pregnant dams were dosed by gavage with 0, 0.05, 0.20 or 0.80 μg TCDD kg^{-1} in corn oil. Male offspring (10 to 12 animals per dose group) were monitored for viability, growth, and reproductive function. Accelerated eye opening was observed in all dose groups versus controls (50% of the animals in the low and mid-dose groups and 79% in the high-dose group). Reduced pup survival and growth retardation were observed in offspring from the highest dose group. Percentage of pup survival on days 3 to 22 ranged from 82% to 93% for the high-dose group. Percentage of survival in all other dose groups (including controls) was 99% to 100%. The most sensitive adverse effect was a 25% reduction in ejaculated sperm numbers at the lowest dose tested (0.05 μg TCDD kg^{-1}). The number of animals affected was not reported.
Gray *et al*. (1997b) also investigated reproductive effects of gestational day 15 TCDD administration in female Long Evans Hooded rat offspring (18 to 24 pups per dose group). Delayed vaginal opening was observed in progeny exposed to 0.80 μg TCDD kg^{-1}. The mean

distance from urethral to vaginal opening was 6.8 mm in the high-dose group versus 11.03 mm in the control group. A dose-related increase in the percentage of females with a temporary or persistent vaginal thread was observed from 15% in control animals to 97% in the highest exposure group. The threads were permanent in 2.5% of controls, as compared to 10%, 27%, and 92% of treated animals, at 0.05, 0.20 and 0.80 μg TCDD kg^{-1}, respectively. At the two highest dose levels, the increases in response rates were statistically significant. Partial to complete clefting of the phallus was displayed in offspring at dose levels of 0.20 (20% of offspring) and 0.80 μg TCDD kg^{-1} (75% of offspring). Other morphological changes in animals from these dose groups were increased length of the urethral slit, increased distance from the urethral opening to the tip of the phallus, and decreased distance from the urethral opening to the vaginal orifice. Time to pregnancy was delayed in females from the highest dose group, though fertility rate was not affected. Histopathological changes in the ovary, cervix, and vagina were observed in animals necropsied at 20 months of age. The investigators noted that the dosing period they used (gestational day 15) may not have been the most sensitive for the detection of ovarian alterations, endometrial hyperplasia, and a shortened reproductive life span.

4.1.4.3 Neurobehavioral effects in offspring

Schantz and Bowman (1989) studied the cognitive effects of perinatal exposure to TCDD in Rhesus monkeys. Efficiency of discrimination-reversal learning (RL) and delayed spatial alternation (DSA) were the two cognitive paradigms used in the evaluation of behavioral effects. After seven months of oral exposure, eight 5 ng kg^{-1}, eight 25 ng kg^{-1} TCDD-exposed and seven control females were bred. Six of the eight 5 ng kg^{-1} dosed females delivered viable offspring (Cohort I). Only one viable pup was born to a female from the 25 ng kg^{-1} dose group. This animal was not studied behaviorally. All offspring were born after approximately 16 months of maternal exposure to TCDD. The females were dosed during nursing of their offspring until weaning at four months of age. After a total of 26 months of exposure, the 5 ng kg^{-1} dosed females were bred a second time. The second group of offspring (Cohort II) were born after 36.3 months of maternal TCDD exposure and were further exposed to TCDD via lactation until weaned. In total, 10 TCDD-exposed monkeys (five from Cohort I and five from Cohort II) and 10 controls were evaluated in the cognitive effects study. Both groups of TCDD-exposed offspring exhibited impaired ability to learn a shape RL problem but not spatial or color RL problems. TCDD-exposed offspring took 47.4 trials to reach criterion for RL (shape) versus 27.4 trials in control animals. No effects on DSA performance were observed in exposed offspring relative to controls.

Schantz *et al*. (1992) studied the effect of perinatal TCDD exposure on the behavior of monkeys in peer groups. The same group of offspring exposed to 5 ng kg^{-1} TCDD (Cohort I) (16 months of maternal exposure and four months *post partum*) were investigated. The total maternal intake at the end of exposure was estimated at 59.6 ng kg^{-1}. The offspring were four months old at this time. At 8.6 months of age, offspring were placed in peer groups of four animals each, 1½ hours per day, five days per week for a total of 36 sessions in nine weeks. Animals were allowed to interact without interference. Testers were blinded to the treatment conditions of the monkeys. Investigators stated that a total of 21 behaviors occurred with sufficient frequency to warrant statistical analysis, whereas four behaviors (aggression, threat, fear grimace, and contact cling) occurred infrequently and were not analyzed. TCDD-exposed monkeys exhibited more rough-tumble play, retreated less during play, were less often displaced from preferred positions in the playroom, and showed increased levels of self-directed behavior. No clinical symptoms of toxicity or significantly decreased birth weights or weaning weights were observed in exposed

animals as compared to controls. The investigators noted that the TCDD-exposed offspring were reared by TCDD-exposed mothers. Consequently, it was possible that the peer group behavioral changes were indirect effects related to differences in the early socialization of the infants rather than direct effects of TCDD exposure. Schantz *et al*. (1986) had previously reported that TCDD-exposed mother-infant dyads spend more time than control dyads in close social contact and that these early behavioral changes might account for some or all of the peer group behavioral changes observed later. It was further stated that the effects observed were quite subtle and that long-term follow-up studies were needed to assess any permanent effects on the exposed infants' social adjustment.

4.1.4.4 Endometriosis

After five years of exposure to TCDD as reported by Schantz *et al*. (1986; 1992), Rier *et al*. (1993) observed a dose-dependent increase in the incidence and severity of endometriosis in the same Rhesus monkeys. The disease was first documented in TCDD-exposed animals seven years after the termination of treatment. Endometriosis was present in 71% and 86% of the females in the 5 and 25 ng kg^{-1} TCDD exposure groups, respectively. The incidence of disease was 33% in animals from the control group. Three of seven animals exposed to 5 ng kg^{-1} TCDD and five of seven animals in the 25 ng kg^{-1} dose group had moderate to severe endometriosis. Moderate to severe disease was not observed in control animals. The investigators noted that the background incidence of endometriosis in monkeys is 30% compared to 10% in humans (Wheeler, 1992), and that the disease in monkeys resembles human endometriosis both anatomically and clinically (Fanton and Golden, 1991; MacKenzie and Casey, 1975; McClure, 1979).

4.2 Carcinogenicity of TCDD

4.2.1 Cancer effects in animals

TCDD has been shown to cause both benign and malignant tumors at multiple sites in several species of both rats and mice (ATSDR, 1998; Huff, 1994; IARC, 1997; US EPA, 1994b). Neoplasms have also been induced in the hamster (Pour *et al*., 1976). This species is considered the most resistant to the acute toxic effects of TCDD (US EPA, 1994b). All long-term bioassays have produced positive results (Huff, 1994; US EPA, 1994b). Target organs include the liver, thyroid, lung, skin, oral and nasal cavities, adrenal glands, connective and soft tissues, and the haematopoietic system. A more detailed review of TCDD carcinogenicity in animals is available from ATSDR (1998) and IARC (1997).

4.2.2 Key study of carcinogenicity in animals

The results of the two-year carcinogenesis bioassay conducted by Kociba *et al*. (1978) have been the most often utilized for cancer risk assessment of TCDD. Rats of both sexes were fed 0, 1, 10 and 100 ng TCDD/kg bw/day. Increased incidences of hepatocellular carcinomas and hepatomas along with a decreased incidence in several endocrine tumors in females were observed. Tumors of the nasal turbinates, hard palate and lung were also observed in exposed females. Tumors of the tongue, nasal turbinates, and hard palate were induced in males. Male rats were found to be less susceptible to the carcinogenic effects of TCDD than females. Exposure at 100 ng TCDD/kg bw/day was associated with a statistically significant increase in hepatocellular carcinomas in female rats. At 10 ng TCDD/kg bw/day, a significant increase in liver nodules and alveolar

hyperplasia were observed. Re-evaluation of the liver pathology has shown some quantitative differences, however. The lowest detectable effect was for the induction of liver tumors, which consistently occurred at the 10 ng TCDD/kg bw/day dose (IARC, 1997; US EPA, 1994b).

4.2.3 Cancer effects in humans

The body of literature concerning cancer mortality resulting from exposure to TCDD has been extensively reviewed (ATSDR, 1998; IARC, 1997; Institute of Medicine, 1994; 1996). Case-control and cohort studies of dioxins and cancer have been conducted among chemical manufacturing and processing workers, herbicide sprayers, pulp and paper mill workers, accidental exposures among industry- and community-based cohorts, and Vietnam veterans exposed to Agent Orange. Few of these studies have provided individual exposure estimates, and in some instances, such as with short-term spraying of herbicides, no increased body burden of dioxins occurs. The epidemiological studies of cancer resulting from exposure to TCDD usually have populations with concomitant exposure to other compounds, raising the possibility of confounding. Other problems with many of the studies include low statistical power to detect an adverse effect if one exists, lack of well-defined exposures, and inadequate latency. As a result of these limitations, the overall interpretation of the studies has been difficult and controversial.

The situation is made much clearer by focusing on those studies involving the highest exposures. The cohort studies among chemical manufacturing and processing workers offer the most reliable results in view of the higher TCDD exposures, large numbers of individuals studied, longer follow-up, and the availability of at least some biological confirmation of TCDD exposure, including measures of blood concentrations of TCDD and the presence of chloracne among some workers as a result of their TCDD exposure. In general, an excess relative risk for all-cancers combined has been observed. Thus, the overall relative risk for all-cancers combined calculated by the IARC working group from four industrial populations was 1.4 (95% confidence interval [CI] = 1.2–1.6) for the most highly exposed groups (IARC, 1997) (Table 4.3). Although the magnitude of the increased risks is generally low, dose-response relationships have been reported in several of the studies. Similarly, the IARC (1997) reported increased relative risk (SMR = 1.2, 95% CI = 1.1–1.3) for all-cancers from the combined international cohort (Kogevinas *et al.*, 1997) (Table 4.3).

Although few epidemiological studies have investigated lung cancer as a specific endpoint, either because of small sample sizes or because investigators had other *a priori* hypotheses, increased risks of respiratory cancers have consistently been found in the largest cohorts where TCDD exposures were high and of sufficient latency. The combined relative risk for lung cancer for the industrial populations as estimated by the IARC working group was 1.4 (95% CI = 1.1–1.7) (IARC, 1997) (Table 4.3). Confounding by smoking and exposure to other occupational carcinogens could possibly contribute to some of the elevation in cancer risks. However, the overall evidence supports the conclusion that the increased cancer risks are real, and are due to TCDD.

An increased risk of soft-tissue sarcoma (STS) has often been an *a priori* hypothesis in epidemiological studies involving exposure to herbicides assumed to be contaminated with TCDD. The suggestion of an association of TCDD exposure and STS has come from a series of Swedish case-control studies involving exposure to phenoxy herbicides (Ericksson *et al.*, 1981, 1990; Hardell and Eriksson, 1988; Hardell and Sandstrom, 1979; Hardell *et al.*, 1991). However, no increase in TCDD body burden has been associated with short-term exposure among herbicide

sprayers (Smith *et al*., 1992), so these studies cannot be used as evidence that TCDD causes soft-tissue sarcoma. Indeed, the puzzling findings from these studies in the absence of meaningful exposure to TCDD counts against causal evidence for TCDD itself.

Table 4.3 Summary of the combined international cohort and selected industrial cohort studies with high TCDD exposure levels

Cohort	All-cancer deaths			Respiratory cancer deaths			References
	Obs.	SMR	95% CI	Obs.	SMR	95% CI	
International cohort	394	1.2	1.1–1.3	127	1.2	1.0–1.4	Kogevinas *et al*., 1997
Industrial populations (high-exposure sub-cohorts)							
NIOSH, USA	114	1.5	1.2–1.8	40	1.4	1.0–1.9	Fingerhut *et al*., 1991ab[1]
Plants producing phenoxy herbicides and chlorophenols, Germany	105	1.3	1.0–1.5	33	1.4	1.0–2.0	Becher *et al*., 1996[2]
Plant producing phenoxy herbicides and chlorophenols, Netherlands	51	1.5	1.1–1.9	14	1.0	0.5–1.7	Hooiveld *et al*., 1996
BASF, Germany	18	1.9	1.1–3.0	7	2.4	1.0–5.0	Ott and Zober, 1996[3]
Total	288	1.4	1.2–1.6	94	1.4	1.1–1.7	

1. ≥ 20 years latency and ≥ 1 year exposure.
2. Boehringer-Ingelheim cohort plus one other German industrial cohort.
3. Chloracne subgroup, ≥ 20 years latency.

Source: IARC, 1997.

A nested case-control study from the IARC international cohort found a dose-response trend for STS with estimated TCDD exposure (Kogevinas *et al*., 1995; 1997). However, the dose-related increase was also observed with estimated exposure to 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-T. The large US industry-based cohort of Fingerhut *et al*. (1991ab) found an increase in mortality from STS based on six cases, while no deaths from STS were reported in the chemical industry cohorts in Germany (Becher *et al*., 1996) and Holland (Hooiveld *et al*., 1996). Given the uncertainty as to whether TCDD or phenoxy herbicides themselves are associated with STS, the small number of deaths observed, problems of misclassification and misdiagnosis, and the inconsistency of the results, we consider the available evidence regarding an excess risk of STS from TCDD exposure to be inadequate. This form of cancer will not be considered further in this document.

4.2.4 Key epidemiological studies of cancer mortality resulting from exposure to TCDD

The key epidemiological studies of TCDD exposure and cancer mortality are Fingerhut *et al*. (1991ab); Flesch-Janys *et al.* (1995; 1996) and Ott and Zober (1996). These cohort studies were conducted among chemical manufacturing and processing workers with high TCDD exposures. They involved the study of a large numbers of individuals, and had both longer follow-up and the availability of some quantitative exposure information. The results of each study provide dose-response evidence supporting a causal association between TCDD exposure and mortality from all-cancers combined. Fingerhut *et al.* (1991ab) and Ott and Zober (1996) also evaluated

respiratory cancer mortality and found similar increased relative risks for this site with increasing dose. Each study is summarized in detail below.

4.2.4.1 NIOSH cohort, USA

Fingerhut *et al.* (1991ab) conducted a retrospective cohort mortality study from 1942 through to 1984 among 5172 male workers in 12 plants across the United States that produced chemicals contaminated with TCDD. Mortality was followed from first exposure through to 1987. Only 2% of the cohort was lost to follow-up. Vital status was determined by death certificate, and the US population was used as the reference group since the facilities were located in 11 different states.

Occupational exposure to substances contaminated with TCDD was documented by a review of process descriptions and job duties, as well as through serum TCDD levels as adjusted for lipids in 253 surviving members of the study cohort from two plants. The serum TCDD levels ranged up to 3400 ng kg^{-1} fat, and were highly correlated with years worked in TCDD contaminated processes ($r = 0.72$, $p < 0.0001$). Based on this correlation, the sample was divided into a high-exposure group (defined as those exposed for more than one year) and a low-exposure group (those exposed for less than one year). The mean level of serum TCDD in a group of 79 unexposed workers was 7 ng kg^{-1} fat, with a maximum value of 19 ng kg^{-1} fat. The entire cohort worked a mean of 2.7 years in TCDD-contaminated processes and an average of 12.6 years at the plants. Individuals from the high-exposure sub-cohort (≥ one year exposure) and with ≥ 20 years latency were employed a mean of 6.8 years in TCDD-exposed processes and worked an average of 19.2 years. Mean serum TCDD was 462 ng kg^{-1} fat for this group. Workers with less than one year exposure and ≥ 20 years latency had a mean serum TCDD level of 78 ng kg^{-1} and worked in TCDD-contaminated processes for an average of 0.3 years with a total mean employment of 10.7 years.

The TCDD serum levels were extrapolated to the dates when the individuals were last employed in TCDD-contaminated jobs. The mean level for the 253 workers was 2000 ng kg^{-1} fat, ranging up to 32000 ng kg^{-1} fat assuming an elimination half-life of 7.1 years (Pirkle *et al*., 1989). The workers from the low-exposure group and with over 20 years of latency had a mean back-extrapolated TCDD serum level of 640 ng kg^{-1} fat. The average of the half-life extrapolated levels for the individuals from the high-exposure group and with ≥ 20 years of latency was 3600 ng kg^{-1} fat.

Salvan *et al*. (1994) estimated the dose rates expressed as average daily intakes for the sub-cohort of 253 workers based on the individual measurements of serum TCDD concentrations. The data were extrapolated to the total amount of TCDD in body fat using an estimate of the amount of body fat. It was also assumed that there is a linear relationship between body mass index (BMI) and body fat, that TCDD in body fat follows first order elimination kinetics for a single compartment, and that there was a constant occupational intake rate during employment in exposed jobs. The dose rate estimates for the 253 workers ranged over four orders of magnitude at all values of assumed TCDD half-life, and were sensitive to varying TCDD half-life, as shown in Table 4.4. The median dose rate varied three-fold between 7.1 and 14.1 years for TCDD half-life.

Table 4.4 Distribution of estimates of dose rate (average daily intake) by TCDD half-life in a sample from two plants in the NIOSH cohort

Dose rate (pg/kg bw/day)	TCDD half-life (years)			
	7.1	10	11.3	14.1
Mean (n = 253)	1730	870	720	540
Median	530	270	230	170

Deaths from cancers previously associated with TCDD exposure (stomach, liver, nasal cancer, Hodgkin's disease, and non-Hodgkin's lymphoma) were not significantly increased. Mortality from STS was increased (SMR = 3.38, 95% CI = 0.92–8.65), but was based on only four deaths. Mortality from all-cancers combined was slightly but significantly increased in the entire cohort based on 265 deaths (SMR = 1.15; 95% CI = 1.02–1.30). All-cancer mortality was increased in 9 of the 12 plants included in the study. For workers in the high-exposure sub-cohort and with greater than or equal to 20 years of latency (mean half-life extrapolated serum level of 3600 ng TCDD kg^{-1} fat), the SMR for all-cancer deaths was 1.46 (95% CI = 1.21–1.76) based on 114 deaths, as shown in Figure 4.1 (Fingerhut *et al*., 1991ab). Similarly, increased risks for respiratory tract cancers were observed in the same sub-cohort based on 43 deaths (SMR = 1.42, 95% CI = 1.03–1.92). When respiratory cancer mortality was excluded from the analysis, mortality from all remaining cancers combined was still higher than expected in the overall cohort (SMR = 1.17, 95% CI = 1.00–1.36) and in the high-exposure sub-cohort (SMR = 1.50, 95% CI = 1.18–1.89).

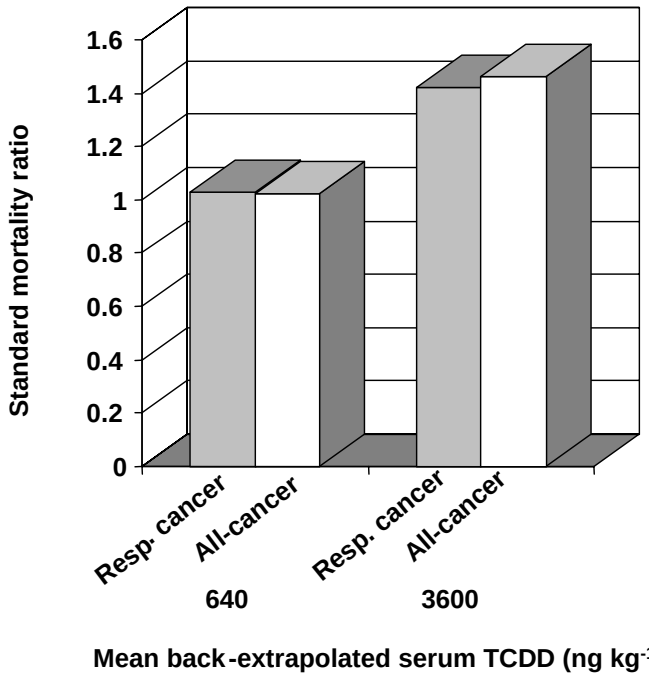

Figure 4.1 Respiratory and all-cancer mortality for sub-cohort of workers with 20 years latency

Source: Fingerhut *et al*.,1991ab. [640 ng TCDD kg^{-1} = < 1 yr exposure and ≥ 20 yrs latency; 3600 ng TCDD kg^{-1} = ≥ 1 yr exposure and ≥ 20 yrs latency.]

To assess the effect of smoking on the observed increase in lung cancer mortality, the expected number of lung cancer deaths was adjusted by the smoking prevalence found in lifetime histories obtained in 1987 among 223 workers from two plants. The adjusted expected lung cancer deaths rose by 5% in the overall cohort and by 1% in the high-exposure sub-cohort. The adjusted SMR for lung cancer mortality decreased to 1.05 (95% CI = 0.85–1.30) in the overall cohort. The smoking status of a sample of 87 workers with more than one year of exposure and more than 20 years of latency was 27.6% non-smokers, 13.8% former smokers, and 58.6% smokers. The age-adjusted smoking status of US males in 1965 included 23.5% non-smokers, 19.4% former smokers and 57.1% smokers. The adjusted SMR for lung cancer in the high-exposure cohort decreased to 1.37 (95% CI = 0.98–1.87).

The year 1965 was chosen for comparison because it was the approximate midpoint of the observation period for the cohort mortality study, and because age-stratified smoking status was available for the national population in the 1965 Health Promotion Survey (National Center for Health Statistics, 1981). The investigators also noted that there was no increase in non-malignant respiratory disease, which is strongly related to smoking. It was therefore concluded that smoking is unlikely to explain the increased respiratory cancer risks, particularly in the high-exposure sub-cohort, although confounding by occupational exposures other than TCDD cannot be ruled out. It was noted that asbestos may have contributed to the increase in lung cancer mortality, since two deaths due to mesothelioma were observed.

Steenland *et al.* (1999) have recently reported results from further follow-up of the NIOSH cohort through 1993. Dose-response trends were estimated for the largest and most highly exposed cohort of workers exposed to TCDD. Statistically significant positive linear trends for all-cancer and lung cancer mortality with increasing exposure were found. The SMRs for all-cancers combined and lung cancer in the highest exposure group were 1.60 and 1.65, respectively. The investigators stated that the TCDD levels in the highest exposed workers were likely to have been 100 to 1000 times higher than those experienced by the general population, and similar to TCDD levels used in animal studies.

4.2.4.2 Boehringer-Ingelheim cohort, Hamburg, Germany

The Boehringer-Ingelheim cohort consisted of 1189 male workers in a chemical plant which produced phenoxy herbicides, chlorophenols, and other herbicides and insecticides known to be contaminated with TCDD. Workers were employed for at least three months between 1952 and 1984, when the plant closed. The latest follow-up of the cohort covered the period 1952 through 1992 (Flesch-Janys *et al*., 1995; 1996). The reference group consisted of workers from a gas supply company from the same region of Germany as the chemical workers. No exposure to PCDD/F was known to have occurred in the reference group and the socio-economic status of both groups was said to be comparable.

PCDD/F levels above background in blood fat were estimated for all members of the cohort. These estimations were based on PCDD/F levels in various processes of the facility, duration of employment in each department, and concentration of PCDD/F in adipose tissue or whole blood. The blood and tissue measurement data were obtained from a subgroup of 190 male workers. The investigators utilized the standard assumption of a one-compartment first-order kinetic model, and half-life estimates were calculated from an elimination study conducted in 48 workers from the cohort (Flesch-Janys *et al*., 1994). A TEQ variable was also constructed for all PCDD/Fs. The

mean estimated TCDD level for the cohort was 141.4 ng kg^{-1} blood fat (median, 38.2 ng kg^{-1}). The TEQ level (including TCDD) was 296.5 ng TEQ kg^{-1} fat (median, 118.3 ng kg^{-1}).

A pattern of increasing risk for all-cancer mortality was associated with both increasing TCDD and TEQ levels (Figures 4.2 and 4.3 respectively). The relative risk for all-cancer in the highest TCDD exposure group (344.7 to 3890.2 ng kg^{-1} blood fat) was 3.30 (95% CI = 2.05–5.31) (Flesch-Janys *et al.*, 1995). The relative risk of total cancer in the highest TEQ exposure group (545.1 to 4361.9 ng TEQ kg^{-1} blood fat) was 2.69 (95% CI = 1.67–4.35) (Flesch-Janys *et al.*, 1996). Similar increases in all-cancer mortality were observed across TCDD and TEQ dose levels when the lowest exposure groups were combined and used as an internal reference. The relative risk estimates were lower and the trends were not as marked when compared to the analysis using the unexposed reference cohort (Flesch-Janys *et al.*, 1995).

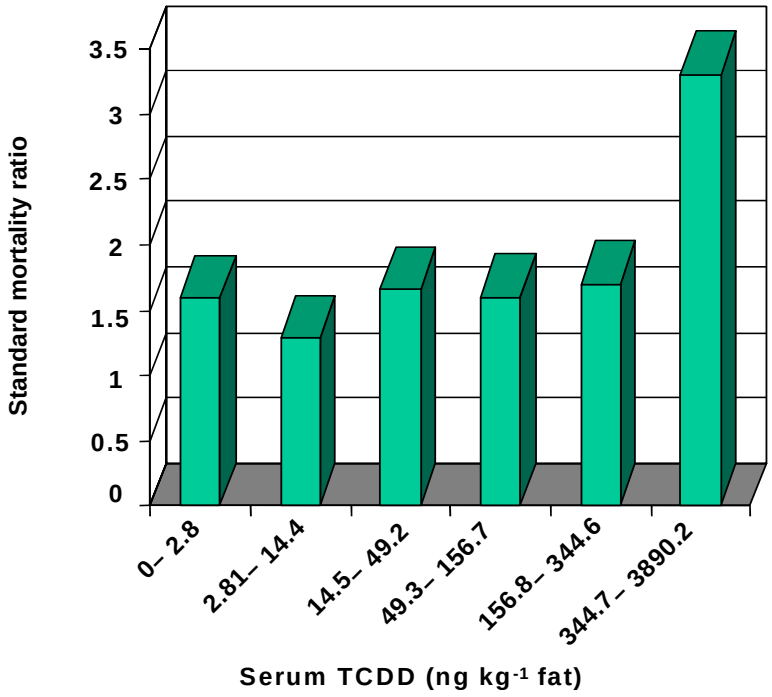

Figure 4.2 SMRs for all-cancer mortality by TCDD levels at the end of exposure above median background levels

Source: Flesch-Janys *et al.*, 1995.

Smoking data were available from a subgroup of the study cohort. The prevalence of smoking in the PCDD/F exposed workers and the reference group was similar: 73% of the chemical workers were smokers or ex-smokers versus 76% among gas workers. The correlation between TCDD levels and smoking status (ever versus never) was $r = 0.065$. The investigators stated that this small association indicated that smoking is unlikely to have seriously biased the relationship between PCDD/F exposure and mortality.

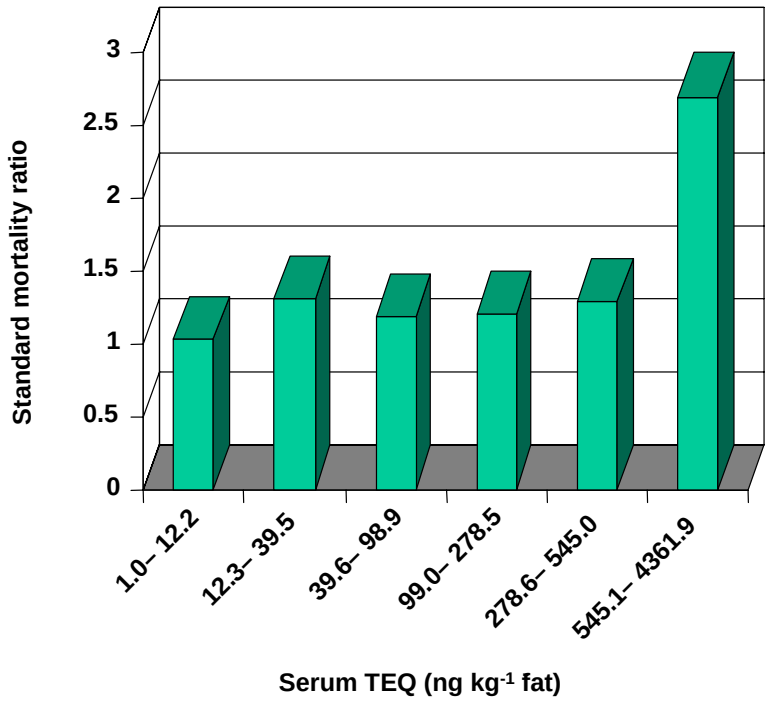

Figure 4.3 SMRs for all-cancer mortality by total TEQ levels at the end of exposure above median background levels
Source: Flesch-Janys *et al.*, 1996.

4.2.4.3 BASF cohort, Ludwigshafen, Germany

Cause-specific mortality and cancer incidence were evaluated among 243 male employees exposed to 2,3,7,8-TCDD after an uncontrolled decomposition reaction occurred in a trichlorophenol (TCP) production unit of a BASF chemical plant in Ludwigshafen, Germany in 1953 (Ott and Zober, 1996). Within days of the reactor accident, workers involved in the clean-up developed chloracne as well as other signs and symptoms of TCDD exposure. TCDD was not, however, identified as the responsible agent until four years later (Kimmig and Schulz, 1957; Schulz, 1957). Further confirmation that exposure to TCDD had occurred was provided by biomonitoring data collected more than 30 years after the incident. Health surveillance of the exposed workers has been conducted on a regular basis since 1953. Vital status was traced through 1992 and there was no loss to follow-up.

Two determinants of past exposure to TCDD were analyzed: the chloracne status of the workers and the estimated cumulative dose of TCDD in units of µg/kg bw. In order to express the dose in µg/kg bw, internal estimates of the half-life of TCDD were obtained from repeated sampling of 29 workers whose initial TCDD concentration ranged from 29 to 553 ng kg^{-1} blood lipid. A mean half-life of 5.8 years was calculated. In addition, percentages of body fat were estimated from body mass index (BMI) as in Wolfe *et al.* (1994). The results of the regression modeling gave half-life estimates of 5.1 and 8.9 years for workers with 20% and 30% body fat, respectively. In addition to the serum measurements, data were obtained on smoking history, BMI at the time of first exposure, and history of occupational exposure to aromatic amines (namely, beta-naphthylamine) and asbestos.

Mortality was assessed by comparison with national rates. All-cancer and respiratory cancer mortality were increased for the entire cohort. The investigators noted that no cancer deaths occurred during the first 10 years after exposure, seven deaths were observed during years 10 through 19, and 23 deaths occurred 20 or more years after exposure. Overall mortality and non-cancer mortality were not elevated for the sub-cohort of men with a history of chloracne.

The SMRs for all-cancer mortality ranged from 0.8 (95% CI = 0.4–1.6) for workers with TCDD body burdens less than 0.1 µg/kg bw, to 1.2 (95% CI = 0.5–2.3) for workers in the mid-dose group (0.1–0.99 µg/kg bw), to 1.6 (95% CI = 0.9–2.6) in the highest exposure group (TCDD ≥1 µg/kg bw) (Figure 4.4). The total number of all-cancer deaths in the three dose groups were eight, eight, and 15 respectively. SMRs for respiratory cancer were 1.0 (95% CI = 0.2–2.9) in the low-dose group, 0.5 (95% CI = 0.0–2.7) in the mid-dose group, and 2.4 (95% CI = 1.0–5.0) in the highest dose group. The number of respiratory cancer deaths per exposure level were three, one, and seven, respectively. Among the 11 cases of respiratory cancer, only one worker was a non-smoker. The highest TCDD dose estimate for any respiratory cancer was 2.4 µg/kg bw.

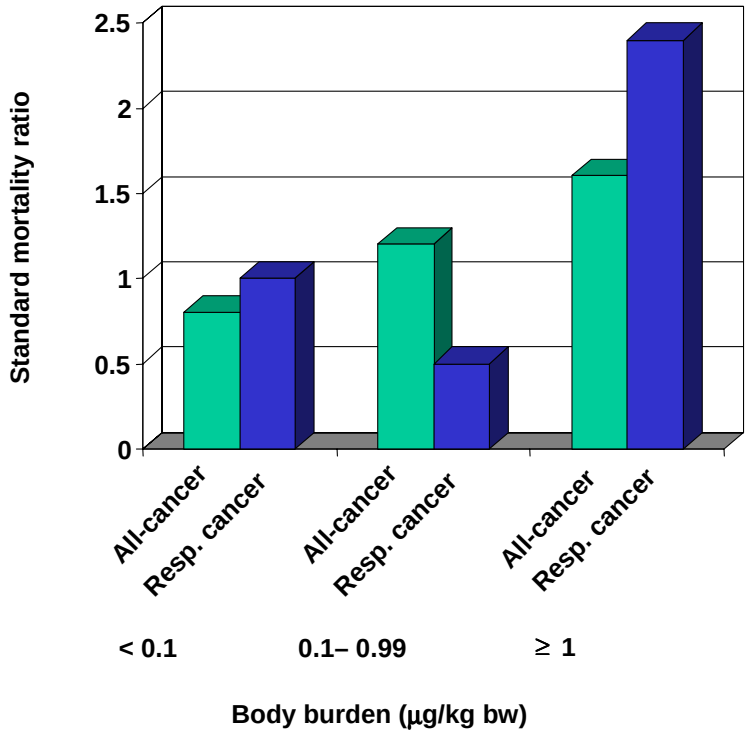

Figure 4.4 SMRs for all-cancer and respiratory cancer mortality, by TCDD dose group
Source: Ott and Zober, 1996.

4.2.5 Criteria for causal inference concerning human cancer

4.2.5.1 Bias

Confounding bias

Confounding by smoking may affect the relationship between TCDD exposure and respiratory and all-cancer mortality. However, confounding by smoking is unlikely to account entirely for the

increased risks. Fingerhut *et al*. (1991ab) and Manz *et al.* (1991) found that smoking rates were only slightly different in a sample of workers from their study populations relative to the comparison groups. Fingerhut *et al.* (1991ab) also found that other diseases caused by smoking were not elevated in this cohort. Mortality from non-malignant respiratory disease was lower than expected. These investigators adjusted the SMRs for respiratory tract cancer mortality in the entire cohort according to smoking rates in a small subset of workers. The adjusted SMR for the high-exposure subcohort decreased slightly, from 1.42 (95% CI = 1.03–1.92) to 1.37 (95% CI = 0.98–1.87).

Studies of cancer risk among individuals exposed to TCDD have often included individuals exposed to other possible carcinogenic agents. Most of the 12 chemical plants in the NIOSH cohort produced thousands of chemicals. Workers were concurrently exposed to chlorophenols and phenoxy herbicides contaminated with TCDD, in addition to exposure to numerous other chemicals. Chemical production workers are also often exposed to asbestos. However, these exposures will vary in different industrial settings. Since several industrial cohorts have consistently demonstrated overall increases in mortality from respiratory cancer and all-cancers combined in the most highly TCDD-exposed workers, this consistency of effect in different industrial settings suggests that confounding is unlikely to explain the increased risks.

Information bias

Information bias concerns exposure and disease misclassification. Exposure misclassification is a common potential problem across all studies of cancer mortality and TCDD exposure. Exposure is presumed predominantly on the basis of job classification and there are only a few studies where serum levels of TCDD were available. Assuming this misclassification bias is non-differential in both the exposed and non-exposed groups, the relative risk estimates will result in under-estimations of the contribution of TCDD to cancer risk.

Selection bias

Selection bias in the studies of TCDD exposure and cancer risk is primarily manifested as the healthy worker effect. For example, Fingerhut *et al.* (1991ab) found low mortality from circulatory disease among the cohort of chemical production workers relative to the general population and suggested that these results might be a reflection of the healthy worker effect. This potential source of selection bias would tend to under-estimate the risks of TCDD exposure in cohort studies with external comparison populations.

4.2.5.2 Chance

In order to assess the probability that findings among studies of cancer in TCDD-exposed populations are due to chance, we cite the meta-analysis of the IARC working group (IARC, 1997). The pooled summary for all-cancer mortality in selected industrial cohort studies with high exposure levels (Becher *et al*., 1996, Fingerhut *et al*., 1991ab; Hooiveld *et al*., 1996, Ott and Zober, 1996) was estimated at 1.4 (95% CI = 1.2–1.6) with a p-value of less than 0.001 (Table 4.3). The pooled result for respiratory cancer relative risks from the same studies was 1.4 (95% CI = 1.1–1.7). The p-value was less than 0.01. Based on these results, we conclude that the findings for increased all-cancer and respiratory cancer mortality among TCDD-exposed workers are unlikely to be due to chance.

4.2.5.3 Consistency of the results

The studies with the largest cohorts, highest exposures and longest periods of follow-up have demonstrated a consistent increase in respiratory tract and all-cancer mortality (Becher *et al.*, 1996; Fingerhut *et al.*, 1991ab; Kogevinas *et al.*, 1997; Ott and Zober, 1996) (Table 4.3).

4.2.5.4 Strength of the association

Strength of association is one criterion for causal inference, yet it is not absolute. It is easier to make causal inference in the presence of strong associations (i.e. large relative risks), and more difficult to reach causal conclusions if the exposure is associated with small relative risks. As a result, when reaching causal conclusions about agents that result in small relative risks, it is better to have large studies and/or a larger number of studies than when making causal inference about an agent that results in large relative risks. Despite this, 'weak associations' in epidemiology have been useful as a basis for causal inference. For example, several large international reviews of the evidence have concluded that environmental tobacco smoke causes lung cancer in non-smokers, even though most pooled relative risks are in the range of about 1.2 to 1.9 (National Research Council, 1986; US Department of Health and Human Services, 1986; National Institutes of Health, 1993).

The observed effect measures for respiratory and all-cancer mortality among TCDD-exposed cohorts are generally low, with pooled risk estimates of 1.4 for both endpoints (IARC, 1997). Effect measures of this magnitude weaken the evidence for causality due to the possibility of uncontrolled confounding or other sources of bias producing the findings. However, repeated and consistent findings that are unlikely to be due to chance, as is the case here, support causal inference in spite of small relative risk.

4.2.5.5 Evidence for dose-response relationships

Only a few of the epidemiological studies have quantified TCDD exposure via blood samples (Fingerhut *et al.*, 1991ab; Flesch-Janys *et al.*, 1995; Ott and Zober, 1996). Each of these studies demonstrated an increasing risk for all-cancer mortality with increasing serum TCDD concentration.

The available dose-response data for all-cancer and/or respiratory cancer mortality are shown in Figures 4.1 through 4.4. The results of Flesch-Janys *et al.* (1995; 1996) demonstrated a dose-response relationship for all-cancers combined, both with TCDD (Figure 4.2) and TEQ (Figure 4.3), with a clear elevation for the highest exposure group. This highest exposure group involved workers with a markedly higher blood and fat TCDD level than for the other categories (SMR = 3.30, 95% CI = 2.05–5.31). Ott and Zober (1996) divided workers into three categories based on blood TCDD levels (Figure 4.4). An increasing trend was observed for all-cancer mortality with TCDD exposure, up to an SMR of 1.6 (95% CI = 0.9–2.6). Increasing linear trends for all-cancer and respiratory cancer mortality were not observed with increasing duration of exposure or with length of employment in the NIOSH cohort (Fingerhut *et al.*, 1991ab). However, mortality increased with increasing latency for both outcomes. When workers were stratified according to exposure (under and over one year of exposure) and latency (under and over 20 years of latency), increases in both all-cancer and respiratory cancer deaths were observed for those with both higher exposure and longer latency (Figure 4.1).

The results from the aforementioned studies provide dose-response evidence supporting a causal relationship between TCDD exposure and mortality from all-cancers combined. The evidence is less strong for cancers of particular sites, with the exception of respiratory cancer.

4.2.5.6 Temporality of the association

Known human carcinogens generally have a latent period of at least 10 years after the initial exposure before their effects become manifest. For many, the latency appears to be 20 years or more. The key studies of TCDD exposure and mortality (Fingerhut *et al*., 1991ab; Flesch-Janys *et al*., 1996; Ott and Zober, 1996; Saracci *et al*., 1991) were of sufficient length to allow for a biologically appropriate timeframe for the development of cancer, including malignancies of the respiratory tract.

4.2.5.7 Biological plausibility

The basic hypothesis of this review – that TCDD can induce cancer at multiple sites including the respiratory system – is biologically plausible. TCDD has been shown to act as a multi-site carcinogen in laboratory animals (Huff, 1994; IARC, 1997) and has been considered the most potent carcinogen ever tested in animal studies (US EPA, 1985). Dose-dependent increases in tumors in multiple target organs have been induced in both sexes of rats and mice. Some of the cancers developed following exposure to TCDD at doses well below the maximally tolerated dose. TCDD has also been shown to cause cancer in hamsters (Rao *et al*., 1988). This species is considered the most resistant to the acute toxic effects of TCDD.

TCDD is not directly genotoxic and its toxic effects, including carcinogenicity, are believed to be mediated through its interaction with the Ah receptor (Huff, 1992; IARC, 1997; Shu *et al*., 1987). This receptor exists in both humans and animals (IARC, 1997). TCDD also affects the regulation of growth factors and other steroid hormone receptors (Huff, 1994). Interactions with mutagens or with endogenous regulators of cell differentiation and proliferation may explain the carcinogenic effects of dioxins (Grassman *et al*., 1998; Huff, 1994).

4.2.6 Conclusions concerning causal inference

In summary:

- Well-designed epidemiological studies with sufficient size, latency, and exposure classification have found increased risks of respiratory and all-cancers combined among individuals exposed to TCDD.
- The pooled relative risk estimates indicate that the apparent increased risks are unlikely to be due to chance.
- The strengths of the associations are small, with pooled risk estimates of 1.4 for both respiratory cancer and all-cancers combined. Such small relative risk estimates increase the likelihood for bias and make causal inference more problematic.
- The possibility that the results may be explained by confounding bias cannot be totally dismissed. However, the evidence supports the view that the increased risks in the key studies are not due to confounding.

- It is unlikely that information bias would act to produce increased relative risk estimates for respiratory cancers and all-cancers combined. In fact, most of the studies are likely to suffer from non-differential exposure misclassification, which would tend to bias results towards the null.
- The results of studies with good quantitative exposure data demonstrate an increasing exposure-response trend.
- The temporal association between TCDD exposure and cancer in the key studies involves appropriate latency.
- On the basis of the results from animal cancer bioassays, the hypothesis that TCDD may lead to cancer at multiple sites, including respiratory cancer, is biologically plausible.

Considering all of the above, we conclude that respiratory cancer and all-cancer mortality are increased in individuals exposed to TCDD.

4.3 Comparison of human and animal body burdens for various toxicological endpoints

The ranges of blood concentrations of TCDD from the three industrial cohorts that demonstrated increased cancer risks are shown in Table 4.5, together with the body burden of TCDD in animals associated with various toxic effects.

Table 4.5 Human and animal body burdens for various toxicological endpoints

Response	Species	Concentration (ng TCDD kg^{-1})	Reference
Cancer	Human	2000 (mean) up to 32000	Fingerhut *et al*., 1991ab
	Human	1000–2400	Ott and Zober, 1996
	Human	345–3890	Flesch-Janys *et al*., 1995
	Rat	5000–10000	Kociba *et al*., 1978[1]
Benign tumors	Rat	1500–2000	Kociba *et al*., 1978[1]
Decreased sperm count in offspring	Rat	28 (maternal body burden)[2]	Gray *et al*., 1997a[3]
Immune suppression in offspring	Rat	50 (maternal body burden)[2]	Gehrs, *et al*., 1997[3]; Gehrs and Smialowicz, 1998[3]
Increased genital malformations in offspring	Rat	73 (maternal body burden)[2]	Gray *et al*., 1997b[3]
Neurobehavioral effects in offspring	Monkey	42 (maternal body burden)[2]	Schantz and Bowman, 1989[3]; Schantz *et al*., 1992
Endometriosis	Monkey	42 (maternal body burden)[2]	Rier *et al*., 1993[3]
Decreased testosterone	Human	496–1860	Egeland *et al*., 1994
	Human	42 (NOAEL)	Henriksen *et al*., 1996
Background TCDD	Humans	2–3	IARC, 1997

1. As reported by IARC (1997).
2. Units are ng TCDD/kg bw.
3. Maternal body burden as reported by van Leeuwen *et al.* (2000) and Van Leeuwen and Younes (2000).

The blood lipid levels of TCDD from the NIOSH cohort estimated at the last time of exposure were 2000 ng kg^{-1}(mean) up to 32000 ng kg^{-1}((Fingerhut *et al.*, 1991ab; IARC, 1997). The concentrations in the dose groups which exhibited elevated all-cancer mortality were 1000 to 2400 ng kg^{-1} in the BASF cohort (Ott and Zober, 1996) and 345 to 3890 ng kg^{-1} in the Boehringer-Ingelheim cohort (Flesch-Janys *et al.*, 1995). As noted by IARC (1997), these concentrations of serum TCDD in workers at the time of last exposure were of the same order as those blood levels from the two-year carcinogenicity study in rats of Kociba *et al.* (1978). Hepatocellular carcinomas and squamous cell carcinomas of the lung were observed in rats exposed to 100 ng TCDD/kg bw/day. Blood levels were estimated at 5000 to 10000 ng kg^{-1} TCDD. Rats exposed to 10 ng TCDD/kg bw/day developed hepatocellular nodules and focal alveolar hyperplasia. The corresponding TCDD blood levels were estimated at 1500 to 2000 ng kg^{-1} TCDD. These results demonstrate similar tumorigenic responses to high levels of TCDD in both humans and rats (IARC, 1997). Note that the estimated background levels of TCDD of 2–3 ng kg^{-1} are 100 to 1000 times lower than those levels observed in the rat and human studies.

For non-cancer endpoints, effects in offspring have been observed for maternal body burdens of TCDD in animals in the range 28 ng/kg bw (decreased sperm count in rat offspring) to 73 ng/kg bw (increased genital malformations in rat offspring) (Table 4.5; see also Section 4.1.4). These correspond to estimated daily intakes for humans of 14–37 pg/kg bw/day (see Table 4.2 and Section 5.1.1). The WHO has used these equivalent human intake estimates in their most recent consultation on the re-evaluation of their TDI (van Leeuwen *et al.*, 2000; Van Leeuwen and Younes, 2000). There are no available findings of studies in the epidemiological literature of these effects in humans exposed perinatally (maternal exposure) to TCDD.

As discussed in Section 4.1.2, the only epidemiological evidence to date regarding decreased hormone levels (testosterone) in adult males exposed to TCDD occurred at serum concentrations ranging from 496 to 1860 ng kg^{-1} (Egeland *et al.*, 1994). No changes in reproductive hormone levels were found in the Ranch Hand cohort. Low- and high- exposure categories were defined as being below or above 42 ng TCDD kg^{-1} fat at current levels (rather than levels at the end of the veterans' tour of duty in Vietnam) (Henriksen *et al.*, 1996).

5 Approaches to risk assessment

Ultimately, the purpose of investigating the health effects resulting from exposure to various substances is to determine what are 'safe' or 'acceptable' levels of exposure. Decisions on these matters, combined with information on the extent to which various uses or levels of emissions lead to exposures of people or the environment, drive public policy. In the case of organochlorines, decisions may be made on what (if any) are appropriate uses of these chemicals, or how emissions, such as discharges from incinerators, should be restricted and controlled. The process of arriving at 'acceptable' levels of human exposure is a very complex one. Often the available information is very limited or open to varying interpretation. As new information emerges, it may be necessary to revise estimates of risk associated with particular levels of exposure. This has particularly been the case with PCDD/Fs, where 'acceptable' levels of exposure have consistently been revised downwards as more data on the health effects of these compounds have become available.

Most of the information on which risk estimates are based is of two types: toxicological studies using laboratory animals, and epidemiological studies of human populations. Both types of study are important and both have their strengths and weaknesses. Animal studies have the advantage that they are carried out in controlled laboratory environments where very precise estimates of dose and comprehensive measures of the effects of those doses can be obtained. They can also be carried out on chemicals to which no humans have yet been exposed. However, they have the major disadvantage that the effects of particular chemicals on animals may be completely different to the effects in exposed humans. Even when the effects are the same, the risks in humans may be different to those seen in laboratory animals. Animal bioassays, of necessity, usually involve very small numbers of animals at much higher exposures than those experienced by humans. Effects experienced at high doses may not occur at lower doses if there is a threshold of effect. Another disadvantage of the use of animal data is that laboratory animals are genetically homogeneous, while the human population is not.

Epidemiological studies of human populations compensate for some of the deficiencies of animal studies and have the significant advantage that they involve the appropriate species and generally appropriate exposure levels. There are, however, certain disadvantages. There is usually much uncertainty about the actual levels of exposure and it is not possible to study effects on humans in the same detail that is possible with laboratory animals. Also, if there is no exposed human population, as would be the case with a new chemical, an epidemiological study cannot be carried out. Even when there is an exposed human population, they may not have been exposed sufficiently long for effects, such as cancer, to have become apparent. In that situation it is necessary to use animal toxicology studies, in which cancer effects can be detected in a much shorter timeframe. Human studies of chemical exposures often take place in occupational settings and include only adult males. The results of such studies may not necessarily reflect how other members of the general population would respond if exposed. Potentially sensitive individuals include the young, elderly, or infirm or unwell. Furthermore, epidemiological studies are subject to a number of biases and potential confounders that may make their interpretation complex and controversial.

Despite the limitations of toxicological and epidemiological studies, scientists have devised a wide variety of methods for utilizing the results of such studies to derive best estimates of 'safe' exposures for people and the environment. Generally speaking, the application of these

methodologies comprises the multidisciplinary area of risk assessment. The following sections outline some of the key approaches to deriving 'safe' levels of exposure.

5.1 Application of 'safety' factors

The application of 'safety' or 'uncertainty' factors has been the traditional approach to risk assessment, particularly for health effects that are assumed to have a threshold of exposure below which toxic effects are unlikely to occur (e.g. non-cancer health effects). The methodology involves the identification of those studies that investigate the most 'sensitive' endpoint or health effect and the application of 'safety' or 'uncertainty' factors to those results (Table 5.1). The study or studies that demonstrate the dose level at which no adverse health effects were observed or the lowest dose at which adverse health effects were observed for the most sensitive endpoints is determined. The no observable adverse effect level (NOAEL) or the lowest observable adverse effect level (LOAEL) is then divided by 'safety' or 'uncertainty' factors (usually multiples of 10), which may range from 10 to several thousand. These factors are meant to account for:

- the fact that some members of the general population will be more susceptible to the health effects of certain agents, whether because of other exposures, a genetic predisposition or the presence of an existing disease (e.g. respiratory or heart disease)
- extrapolation from effects seen in animals to humans (interspecies variability)
- the adequacy of the overall database or nature of the chosen study or studies (WHO, 1994).

Barnes and Dourson (1988) have presented guidelines followed by the US EPA for the use and application of 'uncertainty' and 'modifying' factors.

Table 5.1 NOAEL/LOAEL plus safety factor approach

• Take the NOAEL (no observable adverse effect level) or LOAEL (lowest observable adverse effect level) and divide by safety factor(s).
• Safety factors (usually multiples of 10) take into account inter-individual sensitivity, interspecies extrapolation, and other uncertainties.
• The calculated exposure criterion (e.g. TDI) is dependent on the dose levels and sample sizes of the study on which the NOAEL or LOAEL is based.

The method of selecting a NOAEL or LOAEL has been criticized for not using all of the data from the selected study or studies (Murrell *et al.*, 1998). Information on the dose-response curve, if available, is ignored. Furthermore, the NOAEL or LOAEL obtained depends on the dose levels and the sample size, which affects the statistical precision of the study. Guidelines have not been established to take into consideration the fact that some studies have used larger (or smaller) numbers of animals and, therefore, are generally more (or less) reliable than other studies (Barnes and Dourson, 1988). The original selection (i.e. multiples of 10) and application of 'safety' factors to the NOAEL or LOAEL have also been considered arbitrary (Lehman and Fitzhugh, 1954).

The WHO, in its recent revision of its TDI for PCDD/Fs, and the Agency for Toxic Substances and Disease Registry's (ATSDR) calculation of a minimal risk level (MRL) both used the 'safety' factor approach, and these are described below.

5.1.1 WHO development of a tolerable daily intake for TCDD

The WHO has identified the most sensitive adverse effects resulting from exposure to TCDD (van Leeuwen *et al*., 2000; Van Leeuwen and Younes, 2000). These effects include the induction of endometriosis (Rier *et al*., 1993) and developmental neurobehavioral deficits in monkeys (Schantz and Bowman, 1989), and immune suppression (Gehrs and Smialowicz, 1998) and developmental reproductive toxicity in rats (Gray *et al.*, 1997ab). The developmental reproductive effects are manifested as decreased sperm counts and an increased incidence of female urogenital malformations. These studies are discussed in more detail in Section 4.1.4. The LOAELs ranged from body burdens in animals of 28–73 ng/kg bw (Table 4.2). Assuming steady-state conditions, the corresponding estimated human daily intakes were calculated from:

Intake (ng/kg bw/day) = body burden (ng/kg bw) x (ln(2)/half-life)/f

where f is the fraction of dose absorbed (assumed to be 50% for humans), and with an estimated human half-life of 7.5 years. The estimated intakes ranged from 14 to 37 pg/kg bw/day. It was noted that the lower and highest concentrations were based on acute gavage (bolus) exposure to rats. Effects seen at a human daily intake of 21 pg/kg bw/day were based on chronic (daily for four years) dietary exposure of monkeys. The latter exposure regimen more closely resembles human intake of TCDD.

To arrive at the TDI, which was set as a range of 1–4 pg/kg bw/day, a 'safety' factor of 10 was applied because the estimated human intakes were based on LOAELs and not on NOAELs. In addition, it was noted that although for many parameters humans might be less sensitive than animals, uncertainty still remains regarding animal-to-human susceptibilities. Differences also exist in the half-lives of elimination for the different components of a TEQ mixture. The safety factor of 10 was considered a composite factor to account for all these uncertainties. It was concluded that since body burdens had been used to scale across species, the use of an uncertainty factor to account for interspecies differences in toxicokinetics was not required (van Leeuwen *et al*., 2000; Van Leeuwen and Younes, 2000).

5.1.2 ATSDR's minimal risk level for TCDD

The ATSDR (1998) has estimated an MRL of 1 pg TEQ/kg bw/day for chronic oral exposure to TCDD based on developmental toxicity in monkeys (Schantz *et al.*, 1992). The basis of this study is presented in more detail in Section 4.1.4.3. Significant alterations in play behavior, displacement, and self-directed behavior were observed in offspring exposed perinatally to 5 ng kg^{-1} TCDD, relative to controls. This LOAEL was said to correspond to a daily intake in monkeys of 120 pg/kg bw/day. An uncertainty factor of 90 was applied to this dose (3 for the use of a LOAEL, 3 for extrapolation from animals to humans, and 10 for human variability) to derive the MRL. Note that the investigators did not use body burden to scale across species in the derivation of the MRL as compared to the WHO derivation of the TDI.

5.2 Low-dose extrapolation

As mentioned in the previous section, the 'safety' or 'uncertainty' factor approach generally assumes the existence of a threshold of effect. However, for some types of effects, particularly cancer, there is uncertainty about whether such thresholds exist. This has led to the development and use of low-dose extrapolation. If there is no verifiable exposure threshold for the cancer-

causing effect of a chemical, then the possibility exists that any exposure may carry some level of risk. The question is then how to estimate those risks at very low levels of exposure, well below those doses that can practically be investigated in animal toxicology studies or measured in epidemiological studies. A number of methods have been developed to extrapolate from established levels of toxic response in toxicological or epidemiological studies to estimating the risks associated with very low levels of exposure, such as those associated with environmental contaminants. These methods involve the use of various mathematical models, some simple, some very complex. The limitation of this approach is that no one knows the actual shape of the dose-response relationship at low levels of exposure, and different models may predict widely varying degrees of risk at low exposures.

In cancer risk assessment, which has traditionally been based on low-dose extrapolation methods, a dose-response assessment is conducted to characterize the relationship between the exposure to an agent and the incidence of an adverse health effect in the exposed populations. The dose-response relationship is often expressed in terms of a linear slope (called a potency slope). The results of the dose-response assessment are then used to characterize the probability or risk of cancer associated with a given exposure level for a specific exposed population.

5.2.1 Dose-response assessment using animal data

In the absence of appropriate human studies, data from an animal species that responds most like humans can be used in the dose-response assessment. The US EPA (1989) has established guidelines for selecting the appropriate set of data for the assessment, assuming several studies are available to choose from. First, the tumor incidence data are separated according to organ site and tumor type. Second, all biologically and statistically acceptable data sets are presented. Third, the range of the risk estimates is presented, with consideration of the biological relevance and appropriateness of route of exposure. Finally, because it is possible that human sensitivity is as high as the most sensitive responding animal species, the biologically acceptable data set from long-term animal studies showing the greatest sensitivity (i.e. the highest potency) is generally given the greatest emphasis.

Low-dose estimates derived from experimental animal data extrapolated to humans are complicated by a variety of factors that differ among species and potentially affect the response to carcinogens. These include differences between humans and experimental test animals with respect to life span, body size, genetic variability, population homogeneity, existence of concurrent disease, pharmacokinetic effects such as metabolism and excretion patterns, and the exposure regimen. Extrapolations may also be necessary for route of exposure when the exposure route in the animal study selected for the dose-response assessment differs from the route of exposure expected in humans (US EPA, 1989).

Equivalent doses between species (animal-to-human dose conversions) may be expressed in a variety of ways, including intake per day (e.g. mg/kg bw/day) or intake per lifetime (e.g. mg/kg/bw/lifetime), concentration in the diet (e.g. mg kg^{-1}) or other media such as water, or surface exposures (e.g. mg/m^2 surface area per day). For ingestion doses, the approach used by the US EPA is to scale the daily applied doses experienced for a lifetime in proportion to body weight raised to the 0.75 power (US EPA, 1996). This is a change from the 1986 US EPA cancer risk assessment guidelines, which proposed a single scaling factor of body weight raised to the 0.66 power (US EPA, 1986).

Since risks at low exposure levels cannot be directly measured by high-dose animal experiments, mathematical models are used to specify the form of the dose-response relationship at low doses. The choice of model can have a large impact on the final risk estimate, particularly if the human exposures of interest are as much as 100 or 1000 times lower than the doses used in the animal experiments. The discrepancies resulting from the use of different models can be 1000-fold or greater.

Biologically based models, particularly models based on the Armitage-Doll multistage theory of carcinogenesis (Armitage and Doll, 1954), have generally been used for producing low-dose risk estimates from animal bioassay data. The multistage theory asserts that in order for a cell to become cancerous it must progress through a series of ordered, independent and irreversible stages. This model is approximately linear in the low-dose regions of the dose-response curve and is thought to be conservative (US EPA, 1993). The version of the linearized multistage (LMS) model traditionally employed by the US EPA was developed by Crump *et al.* (1977) and is expressed as follows:

For $k \geq 1$, $P(d) = 1 - exp[-(q_0 + q_1 d + q_2 d^2 + ... + q_k d^k)]$

where:

- $P(d)$ = the probability of cancer at dose d
- k = the number of stages (k may also be assumed to be equal to the number of dose levels minus one)
- q_k = coefficients fitted to the data
- d^k = the applied dose raised to the k^{th} power.

The upper 95% confidence interval estimate for q_1 (q_1*) is then used in calculating comparable human risk. Other biologically based models, which take into account effects on cell proliferation, such as the two-stage clonal expansion model, have been used (Chen and Farland, 1991; Moolgavkar and Knudson, 1981). These and other dose-response models have been described in more detail by the US EPA (1993). The US EPA, in its 1996 draft *Proposed Guidelines for Carcinogen Risk Assessment*, has proposed the use of straight-line extrapolation for a linear default, rather than the LMS (US EPA, 1996). The LMS model is no longer believed to accurately reflect cancer processes, and, as such, is no longer warranted as a default model. Krewski *et al.* (1984) have demonstrated that the straight-line and LMS approaches produce comparable risk estimates.

5.2.2 Dose-response assessment based on epidemiological studies

Dose-response estimates based on adequate positive epidemiological data are preferred over estimates based on animal data (Smith and Wright, 1997). The criteria for selecting an epidemiological study for dose-response assessment include:

- consistency of findings with other studies
- quality of exposure data for the relevant period
- statistical precision of the risk estimates
- dose-response data
- data concerning major confounding factors
- adequacy of follow-up in cohort studies.

The use of epidemiological data in risk assessment should not be based solely on comparison of the quality of available human exposure data to that in animal studies (Smith, 1988). Even if the human exposure data are poor, the fact than no species extrapolation is necessary often makes the use of human data preferable to the use of animal data. There are, in fact, surrogate measures for exposure, such as duration of exposure, that can be used where data on mean human exposure levels are available (Enterline, 1987; Shore *et al.*, 1992).

Epidemiological studies used in risk assessment generally involve high exposures to the agents of concern, thus requiring extrapolation to risks at low exposure levels. Linear dose-response assumptions for low doses have been used extensively for cancer risk assessment from epidemiological data (Smith and Wright, 1997). One simple method for modeling exposure-response is to plot exposure versus a relative risk estimate, such as the standardized mortality ratio (SMR), by assigning a single average exposure level for the entire cohort and extrapolating linearly from the observed SMR to the origin (SMR = 1) (Smith, 1988). This approach is essentially equal to fitting the model SMR = $1 + x\beta$, where x = exposure and β = the change in the SMR per unit of exposure (i.e. the slope). When dose-specific data are available, such as when SMRs are presented for different levels of cumulative exposure, a simple model is to fit the data using weighted least squares regression, forcing the line through an SMR of 1 for zero exposure. This model may also be represented as SMR = $1 + x\beta$, where β is obtained from weighted least squares regression (Smith and Wright, 1997).

It is possible to apply large numbers of different statistical models, each with different assumptions. Normally, however, very few data points are available, and since extrapolations have to be made far below the observed data points, different models can obviously produce markedly different results. Some investigators propose using a variety of different models and giving a range of results (Stayner *et al.*, 1994). However, this approach creates serious problems with the use of human data for health risk assessment (as it does in animal studies).

There are a number of reasons for proposing the relative risk model. First, relative risk estimates are usually given in published studies. This means that risk assessments can be conducted without obtaining the original study data. Second, relative risk estimates in the published literature have usually already been adjusted for age. Since all diseases are strongly related to age, modeling risk estimates by other approaches, such as additive risk models ($\lambda_x = \lambda_0 + x\beta$, where λ_x = incidence rate at exposure x, and λ_0 = incidence rate in unexposed) need to incorporate complex functions of age. Another reason is that when relative risk estimates are plotted against cumulative exposures, the relationship is usually linear or close to it. There are seldom sufficient data points to justify rejecting linearity on statistical grounds. It should be noted that apparent non-linearity at low exposure points in cohort studies can be fitted with statistical models that have a profound impact on risk extrapolations to lower doses. However, the empirical evidence for non-linearity may be extremely weak. Finally, other than the possible existence of a threshold of effect, there are often no good biological reasons for rejecting linearity. Since the simplest model that fits the data is usually the most appropriate, it would seem preferable to use the linear relative risk model for low-dose extrapolation using epidemiological data, unless there are good reasons to reject it (i.e. clear evidence of non-linearity) (Smith and Wright, 1997). This does not mean that the investigation of other models is not important for research purposes. However, for regulatory purposes we believe that the linear model should be the first choice, unless it does not adequately fit the data.

There is one situation in which the relative risk model cannot be used (Smith and Wright, 1997). This occurs when the background rate of the disease in question is extremely low. In these cases, relative risk estimates are very unstable. For example, asbestos is by far the main cause of mesothelioma. The background rates without asbestos exposure are extremely low. SMR estimates are therefore very large and unstable because the expected number of cases for a cohort are very small (usually a small fraction of 1). In these situations, additive risk models may need to be used, but they will not be discussed here.

5.2.3 Uncertainties in low-dose extrapolation

The major single source of uncertainty is the shape of the dose-response curve with linear extrapolation of cancer risk to low doses. The possibility of a threshold at lower doses cannot be excluded and the assumption that the exposure response is linear at low doses may not be valid. We cannot be certain what risks are associated with very low exposures to chemicals. We can postulate a variety of shapes for dose-response curves in the low-dose region, but we cannot provide empirical evidence for them, nor is it likely that we will be able to do so in the future. Thresholds of effect may exist for some exposures, but they are very difficult to demonstrate with confidence. We may argue that the dose-response curve will be linear at low doses, or we may say at least that it is unlikely that it is supralinear, but we do not know. With epidemiological studies, although linear extrapolation down to low exposure regions is used, the range of extrapolation is usually much less than for animal studies. This means that the uncertainties of risk extrapolation are also much less than for animal studies. The assumption of linearity should be seen as a convenient one for simplifying risk management decisions. The assumption is conservative and more complex models have little or no empirical evidence to support them. Low-dose extrapolation is contentious enough without adding the complexity of unsubstantiated mathematical models and imprecise pharmacokinetic data. Indeed, it might be better to think of linear risk extrapolation in safety factor terms (Smith and Sharp, 1985).

Much of the controversy surrounding the estimation of dioxin cancer potency relates to the argument that it may be a threshold carcinogen. It has been argued that TCDD is a promoter rather than an initiator of carcinogenesis, and as such a NOAEL/safety factor approach would be more appropriate for risk assessment (Webster and Commoner, 1994). On the other hand, Portier (1987) found that even a promoter can act linearly at low doses if its effect is additive to background processes. It is not clear that TCDD is only a cancer promoter, however. Huff (1994) has summarized evidence that TCDD is a complete carcinogen based on experiments in laboratory animals, and reported that all species, strains and sexes so far tested developed tumors; uncommonly occurring and typically non-promotable organ site cancers have been induced; and dose-related and multi-site carcinogenesis has been observed. He further stated that adequate evidence of a threshold for cancer development has not been demonstrated.

Houk (1992) has argued that if the mode of action of TCDD-induced carcinogenesis is either receptor-mediated or the result of toxicity-induced cell proliferation, then the occurrence of cancer produced by these mechanisms would probably occur only above a threshold of exposure. Conversely, Tritscher *et al*. (1994) has stated that the possibility of linearity in the low-dose range (non-threshold behavior) cannot be rejected based on the assumption that the carcinogenicity of TCDD is receptor mediated.

A key source of uncertainty when using human data from occupationally exposed cohorts involves the actual exposures in the work place. While it is possible that the exposures to TCDD were higher or lower than estimated, it is unlikely that actual exposure would be more than five times higher or five times lower than estimated. In the context of cancer risk assessment, the degree of uncertainty associated with the exposures is quite low (Smith, 1988). In the case of TCDD, the long half-life in humans means that recent biological measurements allow assessment of past human exposure. The use of back-extrapolated serum TCDD as a measure of dose essentially estimates serum level at the time last exposed (Institute of Medicine, 1996). For short-term exposures, this back-extrapolated dose will be highly correlated with the actual cumulative dose. For long-term exposures, back-extrapolated serum TCDD will underestimate the cumulative dose because some (possibly a significant amount) of the TCDD has left the body by the time of last exposure (Institute of Medicine, 1996).

In contrast to epidemiological studies, exposure data in animal bioassays are very accurate. However, the main source of error in using animal data for human health risk assessment is the animal-to-human extrapolation of risk. Extrapolation between species, such as rodents to humans, could involve at least an order of magnitude error. Carcinogenic potency comparisons, even between rodent species, frequently show differences that exceed one order of magnitude (Gaylor and Chen, 1986). It is noteworthy that the controversial adjustment for body surface area differences, when extrapolating from animal bioassays to humans, can cause another order of magnitude difference in comparative dose estimates, as compared to using a simple dose per body weight extrapolation (Smith, 1988). Generally, the uncertainty of animal-to-human extrapolation probably lies within one or two orders of magnitude, except in the case where there may be no effect in an animal model but an effect would occur in exposed humans (or vice versa).

5.2.4 Derivation of cancer potency factors

5.2.4.1 Cancer potency factors based on animal data

The US EPA has used the LMS model for risk extrapolation of animal data for TCDD (US EPA, 1988; 1994b). The results for liver tumors for the female rat in the two-year feeding study conducted by Kociba *et al.* (1978) were the dose-response data used in the analysis. The choice of study was based on the high quality of the study, tumor response at multiple sites, appropriate route of exposure as compared to humans, and less controversial tumor sites than the mouse liver (US EPA, 1988). This study had the largest slope factor, q_1*, of all the available studies. The upper 95% confidence limit of 1.6×10^{-4} $(pg/kg\ bw/day)^{-1}$ was the cancer potency estimate that was used for risk extrapolation.

Most recently, the US EPA has proposed an upper bound estimate of human cancer risk based on animal data of 1.4×10^{-3} $(pg/kg\ bw/day)^{-1}$ (US EPA, 2000). This risk factor, which is again derived using the LMS model, is based on the use of body burden as the dose metric and a re-evaluation of the female rat liver tumors in the Kociba study using revised pathology criteria for such lesions.

5.2.4.2 Cancer potency factors based on human epidemiological data

The US EPA has performed low-dose extrapolations using the dose-response data from the occupational cohorts of Fingerhut *et al.* (1991ab), Manz *et al.* (1991), and Zober *et al.* (1990) (US EPA, 1994b). The maximum likelihood and 95% lower confidence limits of incremental cancer risk were calculated for lung and all-cancers combined using both the additive and relative

risk models. The US EPA's practice for calculating risk estimates derived from epidemiological data is to use point estimates or maximum likelihood estimates (MLE) rather than upper-limit risk estimates (US EPA, 1994b). For lung cancer, the unit risk estimates for the individual studies ranged from 3×10^{-4} to 2×10^{-2} $(pg/kg\ bw/day)^{-1}$, with the estimates for all studies combined between 3×10^{-4} and 5×10^{-4} $(pg/kg\ bw/day)^{-1}$. It was noted that the data from Fingerhut *et al.* (1991ab), the largest of the three cohorts, drove much of the estimate. For all-cancers combined, the range of MLEs for the individual studies was 1×10^{-3} to 8×10^{-2} $(pg/kg\ bw/day)^{-1}$. The estimates for all studies combined ranged between 2×10^{-3} and 3×10^{-3} $(pg/kg\ bw/day)^{-1}$. The US EPA concluded that the lung in the male human is a more sensitive target organ for TCDD than the liver of the female rat, although smoking may affect the lung cancer response (US EPA, 1994b). It was further stated that the risk estimates based on rat tumors are within the range of uncertainty of those based on human data, and that both animal and human responses to the carcinogenic effects of TCDD are consistent with low-dose linearity.

Becher *et al.* (1996) conducted a quantitative risk assessment for TCDD using the results from the cohort of 1189 workers from the Boehringer-Ingelheim chemical plant in Germany (Flesch-Janys *et al*., 1995; 1996). The integrated TCDD concentration over time (area under the curve) was used in the analysis (Poisson and Cox regression) as the exposure variable. The area under the curve was calculated using the results from the TCDD half-life estimated for TCDD and workplace history data. The endpoints utilized were total cancer and lung cancer mortality. The mean German population background level for TCDD was taken into account, as well as the German background total cancer and total mortality rates. For a unit intake of 1 pg/kg bw/day the risk estimates ranged from 1.2×10^{-3} to 7.7×10^{-3} cancers. These results are in close agreement with the aforementioned US EPA analysis.

5.3 Benchmark dose or point of departure

Because of the widely accepted limitations of both the 'safety' factor and the low-dose extrapolation approaches, alternative methods of deriving 'safe' levels of exposure have been proposed. The benchmark dose approach (BMD) has been considered as an addition to, or replacement for, the traditional methods of non-cancer risk assessment (Barnes *et al*., 1995). The BMD is defined as the lower 95% confidence limit of the dose estimated to produce an effect in 5 or 10% of the test population (animal or human), and is often referred to as the LED_5 or LED_{10}. The lower 95% confidence limit is public health conservative and takes into account uncertainty associated with the size of the experimental groups that produced the data on which the BMD is based. Arbitrary safety factors are then applied to the results of the benchmark dose analysis to arrive at a permissible exposure level for a given chemical.

The BMD has generally been applied to the assessment of non-cancer health risks, but is now gaining popularity for use in cancer risk assessment (Portier, 2000; US EPA, 1996). The US EPA has described the LED_{10} as a point of departure for extrapolation (US EPA, 1996). It is defined as a point that is either a data point or an estimated point that can be considered to be in the range of observation without significant extrapolation. The reasoning for the choice of an LED_{10} is that a 10% response is usually at or just below the experimental dose range in most long-term animal cancer bioassays. Therefore, it does not involve extensive extrapolation into the unknown area of the dose-response curve. For cancer risk assessment using epidemiological data, Smith and Sharp

(1985) have proposed a benchmark of that exposure that would cause 1% cancer excess (1 in 100 risk).

Advantages of the BMD approach are that it includes use of dose-response data, incorporation of data uncertainty, and greater consistency in assessing the level of effect across endpoints (Barnes *et al*., 1995). The method has the significant advantage in that the BMD is within or close to the dose or exposure range for which experimental or epidemiological data exist. The uncertainties associated with results from the various models of risk extrapolation to low doses far outside the observable range are therefore alleviated. Furthermore, it is simpler for risk managers and the public to grasp the meaning of a 1 in 10 or 1 in 100 risk or probability versus the meaning of a 1 in 100,000 or 1 in a million risk for disease.

5.3.1 ED_{01}s for TCDD based on human data

Portier (2000) used the benchmark dose approach to calculate the doses associated with a 1% increase (ED_{01}) in cancer risk using the results from the occupational studies of the NIOSH (Fingerhut *et al*., 1991ab), BASF (Zober *et al*., 1990) and Boehringer-Ingelheim (Manz *et al*., 1991) cohorts. All three of these studies provided direct measurements of exposure in the form of samples of blood levels of TCDD in their working cohort. These measures were taken long after exposure so that some back-extrapolation to earlier exposures was needed to provide a reasonable exposure measure for the lifetime of each member of the cohort. The average length of employment and years since last employment were calculated from the individuals used in the sample. These were linked to a first-order elimination and uptake pharmacokinetic model from which yearly increases in blood concentrations during employment were estimated. These were applied to the entire cohorts from each study and integrated over time to develop average daily lipid-adjusted blood concentrations. Assuming 50% uptake from the gastrointestinal tract, the daily exposure (ng/kg bw) that would result in a lifetime steady-state exposure resulting in the average daily blood concentration was calculated.

For the multiplicative relative risk model the doses associated with a 1% increase in lifetime risk are in the range of exposures from the occupational cohort for Fingerhut *et al.* (1991ab) and slightly below this range from the cohorts for Zober *et al.* (1990) and Manz *et al.* (1991). These values, for lung and all-cancers combined, are shown in Table 5.2.

The ED_{01} for all studies combined was 32.3 pg/kg bw/day for lung cancer and 5.9 pg/kg bw/day for all-cancers combined. For individual studies, the ED_{01}s ranged from 3.0 pg/kg bw/day (Zober *et al*., 1990) to 39.1 pg/kg bw/day (Fingerhut *et al*., 1991ab) for lung cancer and from 1.8 pg/kg bw/day (Zober *et al*., 1990) to 7.1 pg/kg bw/day (Fingerhut *et al*., 1991ab) for all-cancers combined.

The corresponding steady-state body burdens, again assuming 50% absorption of TCDD by the gastrointestinal tract, were also estimated and ranged from 5.6 ng kg^{-1} (Zober *et al*., 1990) to 73.1 ng kg^{-1} (Fingerhut *et al*., 1991ab) for lung cancer. The ED_{01} body burdens ranged from 3.4 ng kg^{-1} (Zober *et al*., 1990) to 13.3 ng kg^{-1} (Fingerhut *et al*., 1991ab) for all-cancers combined. The ED_{01} body burden for all studies combined was 60.4 ng kg^{-1} for lung cancer and 11.0 ng kg^{-1} for all-cancers combined.

Table 5.2 Doses yielding 1% additional risk (95% lower confidence bound) based on human data using a multiplicative relative risk model

Study (cohort)	Lung cancer		All-cancers combined	
	Exposure dose ED_{01} (pg/kg bw/day)	Body burden ED_{01} (ng/kg bw)	Exposure dose ED_{01} (pg/kg bw/day)	Body burden ED_{01} (ng/kg bw)
NIOSH, USA (Fingerhut *et al*., 1991ab)	39.1 (20.8)	73.1 (38.9)	7.1 (4.8)	13.3 (9.0)
BASF, Germany[1] (Zober *et al*., 1990)	3.0–14.5	5.6–27.1	1.8–6.2	3.4–11.0
Boehringer-Ingelheim, Germany (Manz *et al*., 1991)	22.7 (11.1)	42.5 (21.0)	3.0 (1.9)	5.6 (3.6)
All studies combined	32.3 (19.6)	60.4 (36.7)	5.9 (4.2)	11.0 (7.9)

1. Ranges for this study reflect the range of ED_{01} estimates from the published works on this cohort by Zober *et al.* (1990), Ott *et al.* (1993) and Ott and Zober (1996).

The US EPA (2000) has recently presented estimates of upper bound risk factors calculated from human ED_{01}s for the NIOSH, BASF and Boehringer-Ingelheim cohorts. Risk factors in the range 8.6×10^{-3} (pg/kg bw/day)$^{-1}$ for all-cancer deaths in the Boehringer-Ingelheim cohort to 2.5×10^{-4} (pg/kg bw/day)$^{-1}$ for lung cancer deaths in the smaller BASF cohort were derived. LED_{01}s for all-cancer deaths spanned approximately an order of magnitude and generated slope factors in the range 8.6×10^{-3} to 8×10^{-4} (pg/kg bw/day)$^{-1}$. Slightly smaller slope factors were obtained when LED_{01}s for lung cancer were used. Poisson regression on the combined NIOSH, BASF and Boehringer-Ingelheim cohorts yielded a slope factor estimate of approximately 1×10^{-3} (pg/kg bw/day)$^{-1}$. Consequently, the EPA has suggested the use of 1×10^{-3} (pg/kg bw/day)$^{-1}$ as the estimator of upper bound cancer risk for both background intakes and incremental intakes above background (US EPA, 2000).

5.4 Public health risk assessment

A limitation of all the previous methods outlined above is that they do not take into account the existing background level of exposure and consider only incremental risk estimates for maximally exposed individuals. Such estimates of risk do not address the true public health risks to which background exposures also contribute. Smith *et al.* (1996) have described an approach, referred to as a public health risk assessment, whereby chemical substances would be classified into a level of concern based on the potential health risks associated with typical national and regional background exposures. While various problems may arise with this approach, the main advantage is that resources would be allocated to reduce the most important sources of human exposure. With the previously described incremental risk assessment methods, by excluding background exposures large expenditures can be incurred in reducing exposure by, for example, undertaking remediation of a hazardous waste site, even when background population exposures from other sources may be greater than the potential exposure from the waste site.

Using a hypothetical point source (e.g. a waste incinerator or a contaminated site) as an example, Table 5.3 outlines a comparison of the proposed steps in public health risk assessment versus the steps utilized in incremental risk assessment. Step 1 of public health risk assessment includes ascertaining typical background exposures to the substances of concern as well as ascertaining

incremental exposures due to the source under consideration. Ascertaining background exposures would be on a national level, and would not be part of the local site investigation. In some instances, it may be necessary to conduct population exposure studies. To assess risks from dioxin-like compounds, the New Zealand background population exposure data for these contaminants available from the Organochlorines Programme (see Section 3.3) should provide sufficient information. Data concerning background levels in specific media, such as air and soil, have been presented in risk assessments concerning emissions from incinerators (Smith and Goeden, 1990), and are also available in the New Zealand situation (Section 3.2).

Step 2 of public health risk assessment would involve the characterization of health risks associated with background population exposures to the substances of concern, and again would be conducted at a national level. Incremental risk assessment, in contrast, characterizes the individual risk associated only with exposures originating from the source. Risk management (Step 3) decisions based on public health risk assessment would incorporate existing public health risks associated with the substances of concern, while an incremental risk assessment approach would consider only the acceptability of the added risks associated with the source.

Table 5.3 Comparison of steps in public health risk assessment versus incremental risk assessment

Public health risk assessment Step 1: • Ascertain potential average background exposures to substance of concern at national or regional level. • Ascertain potential added individual exposure due to source under consideration. Step 2: • Characterize health risks associated with typical background exposures. Step 3 (Risk management step): • Place compound in a priority class based on risk estimates for background exposures (see Table 5.4) • Base risk management decisions on priority classes of the substances of concern and the potential added exposure from the source.
Incremental risk assessment Step 1: • Ascertain potential maximum individual exposure. Step 2: • Characterize the risks associated with the individual incremental exposures. Step 3 (Risk management step): • Base risk management decisions on the acceptability of the potential incremental risks. • If the risks are 'unacceptable', manage or remediate the source to an acceptable risk level.

In the public health risk assessment approach, risk management would involve individual substances being classified into three priority classes (Table 5.4) (Smith *et al*., 1996):

Class 1 substances: These would include those substances for which existing background population risks are deemed unacceptable. For these chemicals, any added exposures from a source might be considered unacceptable by risk managers. Potentially, lead is an example of a Class 1 substance, since consideration of potential public health risk has led to national strategies for population exposure reduction.

Class 2 substances: These would include those substances for which potential risks associated with background population exposures are not considered significant, but for which there are some concerns about the margin of safety. An example of a possible Class 2 substance might be the dioxin-like compounds. Increased cancer risks have not been shown for background population exposure levels. Nevertheless, the highest general population exposure may occur for infants who are breast-fed for a relatively long time (Smith, 1987). Hence, it is reasonable to have some concern about the margin of safety. When considering an added exposure to dioxin-like compounds originating from a source, management steps might be required so that the source would not add to the background exposure by more than, say, 10%, for the maximally exposed individual. Consideration of dioxin-like compounds as a possible Class 2 substance is discussed further in Section 7.1.5.

Class 3 substances: These would include those substances for which background levels of population exposures are not a concern. Thus, a source might require increased control or management interventions only if the maximally exposed individual might receive a 100% increase in exposure above backgrounds.

Table 5.4 Priority classes for public health risk management of toxic substances in the environment

Class 1:
Substances for which no added exposure is permitted from a source unless offsets are achieved which would reduce local population exposure to those substances. Potential risks associated with the background population exposure to these substances are of concern and a national programme for exposure reduction is being implemented.
Class 2:
Substances for which potential risks associated with the background population exposures are not thought to be significant, but for which there are some concerns about the margin of safety. Resources should be used to reduce emissions from the source (e.g. increased emission control of a waste incinerator or management of a contaminated site) if the source might contribute a significant addition to background exposure (say 10%).
Class 3:
Substances for which there is not a concern about human health risks from the background population exposure. A source would be cleaned up if the maximally exposed person might receive a major increase in exposure above background (say 100%).

The above examples are given to illustrate the approach, but the actual classification of a chemical would require much more detailed consideration. The process of classifying chemicals in terms of public health risk would greatly aid in the assessment of emission sources or contaminated sites. Risk management decisions could be based on estimated or measured exposure without the need for extrapolation to scientifically meaningless levels of risk of the order of one in a million. Even more importantly, resources would be allocated in a manner that would have a meaningful impact on human exposure and associated public health risks.

One limitation of the proposed public health risk assessment approach is that it only deals with chemicals for which there are known background exposures. There will be a need for more population studies to investigate background exposures to some substances. Nevertheless, background population exposures exist for large numbers of chemical pollutants, including PCDD/Fs and other organochlorine compounds in New Zealand (Bates *et al*., 1999; Buckland *et al*., 2001). Furthermore, allocating resources to assess general population exposures to chemical substances is of clear potential value to public health. Thus, the advantages of a public health risk

assessment strategy can greatly outweigh the disadvantages when considered alongside incremental risk assessment methods.

5.5 Summary of the risk assessment and risk management approaches

1. NOAEL/LOAEL plus safety factors

(a) Identification of LOAELs or NOAELs.

(b) Exposure regulations that incorporate safety factors from the LOAELs or NOAELs. An example is the WHO derivation of the TDI of 1–4 pg/kg bw/day for TCDD from LOAELs (van Leeuwen *et al*., 2000; Van Leeuwen and Younes, 2000).

2. Incremental cancer risk assessment

(a) Examples include low-dose extrapolation using the results of Kociba *et al.* (1978) animal (rat) cancer bioassay. The upper 95% confidence limit of 1.6×10^{-4} $(pg/kg\ bw/day)^{-1}$ was the estimated potency based on liver cancer in female rats. Here an intake of 0.006 pg TCDD/kg bw/day is associated with a one in a million risk (US EPA, 1985). More recently, the US EPA (2000) has proposed an upper bound risk estimate of 1.4×10^{-3} $(pg/kg\ bw/day)^{-1}$ from re-evaluation of the Kociba rat data. This represents the US EPA's most current upper bound slope factor for estimating cancer risk based on animal data.

Cancer potency unit risk estimates calculated by the US EPA based on human epidemiological data ranged from 1×10^{-3} to 8×10^{-2} $(pg/kg\ bw/day)^{-1}$ for lung cancer, and 2×10^{-3} to 3×10^{-3} $(pg/kg\ bw/day)^{-1}$ for all-cancers combined (US EPA, 1994b).

(b) Subsequent risk management decisions are based on a criterion for acceptable incremental cancer risks.

3. Benchmark dose

(a) Estimation of exposure related to a benchmark risk, e.g. ED_{01}, derived from human epidemiological data. For example, the ED_{01}s described by Portier (2000) ranged from 3.0 to 39.1 pg/kg bw/day for lung cancer and 1.8 to 7.1 pg/kg bw/day for all-cancers combined. The cancer potency factor most recently calculated by the US EPA (2000) from a meta-analysis of human ED_{01}s from three occupational cohorts was approximately 1×10^{-3} $(pg/kg\ bw/day)^{-1}$. This represents the US EPA's most current upper bound slope factor for estimating human cancer risk based on human data.

(b) Exposure regulation can incorporate safety factors applied to the exposure associated with the benchmark risk.

4. Public health risk assessment

(a) Public health risk assessment concerning background population exposures, as described by Smith *et al.* (1996).

(b) Exposure regulations involve:

(i) policies related to the existing background exposures

(ii) permissible incremental exposures from point sources according to their impact on background population exposures.

The advantages and disadvantages of each of these approaches are summarized in Table 5.5.

Table 5.5 Alternative approaches to risk assessment and risk management: advantages and disadvantages

Approach	Advantages	Disadvantages
1. NOAEL/LOAEL plus safety factors	Determination of NOAELs or LOAELs is conceptually simple.	LOAELs and NOAELs are moving targets, depending more on the number and size of the studies than on actual risks. The more studies there are, the lower it is likely the LOAELs or NOAELs will be. With few studies or small numbers of animals, LOAELs and NOAELs may be high with apparent low risks in spite of inadequate data. The smaller the number of animals per dose group, the more difficult it is to distinguish a difference from a control group, and the bigger the NOAEL/LOAEL becomes. LOAELs and NOAELs are greatly affected by the investigator choice of exposure levels, i.e. the dose rates used in the animal studies. The choice of safety factors is arbitrary.
2. Incremental cancer risk assessment	Transparent with few apparent subjective judgement decisions. The method generates the regulation directly. Takes into account the study size and resulting data uncertainty by using the upper confidence limit.	Ignores background population exposures. Includes major scientific uncertainties, in particular with regard to the shape of the dose-response relationships at low exposure levels.
3. Benchmark dose	Incorporates use of dose-response data, and takes into account data uncertainty. Greater consistency in assessing level of effect across studies. Does not involve extrapolation far outside the dose or exposure range for which data exist.	Results are still, to some extent, dependent on investigator choice of exposure levels. The choice of safety factors is arbitrary.
4. Public health risk assessment	Takes into account existing background exposures. Risk management decisions could be based on estimated or measured exposure without the need for extrapolation to scientifically meaningless risks of the order of one in a million. Resources could be allocated to have a more meaningful impact on human exposure and associated public health risks.	Only useful for chemicals for which there are known background exposures, and for which background exposure data are available or can be collected. Involves arbitrary decisions regarding tolerable added exposures.

6 Daily intake guidelines for dioxin-like compounds

Daily intake guidelines, such as TDIs and MRLs, are an important non-regulatory tool for protecting human health from environmental contaminants. A number of jurisdictions have established TDIs and similar measures for exposure from dioxin-like compounds, as summarized in Table 6.1. The criteria for the WHO, United States, United Kingdom, the Netherlands, Germany and Japan, which generally represent the most recent consideration of the available toxicological data, are discussed in more detail in the following sections.

Table 6.1 Daily intake guidelines for dioxin-like compounds

Country/organization	Limit values	Remarks	Reference
Canada	10 pg I-TEQ/kg bw/day	TDI	Health and Welfare Canada (1990); Feeley and Grant (1993)
Germany	1–10 pg I-TEQ/kg bw/day	TDI	Appel *et al.* (1994)
	1 pg I-TEQ/kg bw/day	Long-term objective	Toxicology Forum (1992)
Japan	4 pg TEQ/kg bw/day	TDI	Environment Agency and Ministry of Health and Welfare (1999)
Netherlands	1–4 pg TEQ/kg bw/day	TDI used for risk assessment, which includes the PCDD/Fs and dioxin-like PCBs.	de Stoppelaar (2000)
	1 pg/kg bw/day	Recommended limit of human exposure for 2,3,7,8-TCDD, and applicable to the intake of dioxin-like compounds expressed as TEQs.	Health Council of the Netherlands (1996)
Sweden	5 pg TEQ/kg bw/day	TDI; uses Nordic TEQ.	Ahlborg *et al.* (1988) [cited in Liem and van Zorge, 1995]
United Kingdom	10 pg I-TEQ/kg bw/day	TDI; the COT recommended it include PCDD/Fs and dioxin-like PCBs.	MAFF (1992), COT (1997)
United States	0.006 pg 2,3,7,8-TCDD/kg bw/day	Risk-specific dose based on lifetime cancer risk. Interpreted as TEQ.	US EPA (1985); US EPA (1994b)
	1 pg TEQ/kg bw/day	Minimal risk level: chronic (365-day) oral exposure to 2,3,7,8-TCDD, and applicable for other dioxin-like compounds expressed in total TEQs.	ATSDR (1998)
WHO	10 pg/kg bw/day	TDI for 2,3,7,8-TCDD; revised in 1998.	WHO (1991)
	1–4 pg TEQ/kg bw/day	Revised TDI range that includes the PCDD/Fs and dioxin-like PCBs using the most recent WHO TEF values (Van den Berg *et al*., 1998).	van Leeuwen *et al.* (2000); Van Leeuwen and Younes (2000)

6.1 World Health Organization

In 1990 a WHO Regional Office for Europe Expert Group, at a consultation in Bilthoven, recommended a TDI of 10 pg/kg bw/day for 2,3,7,8-TCDD (WHO, 1991). The Expert Group identified carcinogenicity and effects on reproduction and development as critical effects in laboratory animals, and used the NOAELs for these effects as the basis of the TDI. The critical study used for the identification of a NOAEL for carcinogenicity was Kociba *et al.* (1978; see Section 4.2.2) in which effects, including liver damage, were observed when low doses of 2,3,7,8-TCDD were administered to rats over two years. For pre-carcinogenic liver toxicity, reproductive

effects and immunotoxicity tested in the various animal species, a NOAEL of 1 ng/kg bw/day was identified. The consultation considered that, in view of the long half-life of TCDD, the critical toxicological parameter was the steady-state liver concentration of TCDD at the ingested dose corresponding to the NOAEL. By using steady-state conditions, this NOAEL was shown to be equivalent to a dose of approximately 100 pg/kg bw/day. A safety factor of 10 applied to this figure, to allow for differences in susceptibility between rats and humans, gave a TDI of 10 pg TCDD/kg bw/day.

This TDI was re-evaluated at a WHO consultation in May 1998 (van Leeuwen *et al*., 2000; Van Leeuwen and Younes, 2000). This consultation recommended that the daily threshold be reduced to a range of 1–4 pg TEQ/kg bw/day, where the TEQ refers to the combined toxic equivalents concentration based on the WHO-derived factors for PCDD/Fs, and certain PCB congeners that were recommended in 1997 (Van den Berg *et al.*, 1998; refer to Table 2.3). As discussed in Section 5.1.1, this TDI range is derived from LOAELs for the induction of endometriosis and developmental neurobehavioral defects in monkeys, and immune system suppression and developmental reproductive toxicity in rats, and estimation of the corresponding human daily intakes. A safety factor of 10 was applied to account for the use of a LOAEL, because uncertainty remains regarding animal-to-human susceptibilities and because differences exist in the half-lives of elimination for the different components of a TEQ mixture.

The WHO consultation recognized that subtle effects might already be occurring in the general population in developed countries at current background levels of exposure to dioxin-like compounds. It went on to say (Van Leeuwen and Younes, 2000): '*The consultation therefore stressed that the upper range of the TDI of 4 pg TEQ/kg bw should be considered a maximal tolerable intake on a provisional basis and that the ultimate goal is to reduce human intake levels below 1 pg TEQ/kg bw/day*', and '*The consultation therefore recommended that every effort should be made to limit environmental releases of dioxin and related compounds to the extent feasible in order to reduce their presence in the food chains, thereby resulting in continued reductions in human body burdens*'.

6.2 United States

6.2.1 US EPA risk-specific dose and reference dose

In 1985 the US EPA determined a risk-specific dose (RsD) of 0.006 pg TCDD/kg bw/day for a one in a million lifetime cancer risk (US EPA, 1985; 1988). This figure was derived from an upper bound (95% confidence limit) unit risk estimate for TCDD of 1.6×10^{-4} $(pg/kg\ bw/day)^{-1}$ based on the total cancer response in the female Sprague-Dawley rats from the Kociba *et al.* (1978) study. Further analysis of the Kociba data yielded an oral intake RsD of 0.01 pg TEQ/kg bw/day for a one in a million cancer risk, corresponding to a unit risk estimate of 1×10^{-4} $(pg/kg\ bw/day)^{-1}$ (US EPA, 1994b). The US EPA commented that '*this risk-specific dose estimate represents a plausible upper limit on risk based on the evaluation of animal and human data. "True" risks are not likely to exceed this value, may be less, and may even be zero for some members of the population*'.

For non-cancer effects, because of the relatively high background exposures compared to effect levels, the EPA has previously not recommended the derivation of a reference dose (RfD) for

dioxin-like compounds (US EPA, 1994b). This approach is endorsed in their most recent draft reassessment report (US EPA, 2000). Although RfDs are useful because they represent a health risk goal below which there is likely to be no appreciable risk of non-cancer effects over a lifetime of exposure, their primary use is to evaluate increments of exposure from specific sources when background exposures are low and insignificant. The EPA comment that any RfD that the Agency would recommend under the traditional approach for setting an RfD is likely to be 2–3 orders of magnitude below current background intakes and body burdens (US EPA, 2000). Because exceeding the RfD is not a statement of risk, establishing an RfD for an incremental exposure when the RfD has already been exceeded by average background exposures is meaningless.

Instead, the EPA (US EPA, 2000) suggest an approach based on:

- characterization of average background exposures
- characterization of the percent increase over background of individuals or subpopulations of interest
- a policy statement about when increases over background become significant.

This approach is very similar to the public health risk assessment approach outlined in Section 5.4.

6.2.2 ATSDR minimal risk level

The ATSDR (1998) has set an MRL of 1 pg/kg bw/day for chronic oral exposure (365 days or more) to 2,3,7,8-TCDD. As noted in Section 5.1.2, this is based on a LOAEL of 120 pg/kg bw/day for developmental toxicity in Rhesus monkeys (Schantz *et al*., 1992). An uncertainty factor of 90 was applied to derive the MRL. As it is ATSDR's policy to use public health guidance values (such as MRLs) derived for 2,3,7,8-TCDD for other dioxin-like compounds, expressed in total TEQs, this MRL can be interpreted as 1 pg TEQ/kg bw/day.

6.3 United Kingdom

The TDI of 10 pg TCDD/kg bw/day recommended by the WHO Expert Group in 1990 was endorsed by the UK Department of Health's Committee on the Toxicity of Chemicals in Food, Consumer Products, and the Environment (COT) (MAFF, 1992) on the basis of carcinogenicity, and reproductive and development effects. Since then, the COT has recommended that the TDI can be regarded as 10 pg TEQ/kg bw/day based on the combined intakes of PCDD/Fs and dioxin-like PCBs (COT, 1997). The COT has indicated their intention to review the data used by the WHO in their 1998 reassessment of the TDI, but to date no such review has been published.

6.4 Netherlands

In 1991 the Dutch government adopted the WHO recommendation of a TDI of 10 pg TCDD/kg bw/day. Following a recommendation from the National Institute of Public Health and the Environment, this TDI was considered as a TEQ for all PCDD/Fs (Liem and van Zorge, 1995).

The Committee on the Risk Evaluation of Substances, Health Council of the Netherlands, has since established a health-based recommended exposure limit for humans of 1 pg 2,3,7,8-TCDD/kg bw/day (Health Council of the Netherlands, 1996). The Committee considered that

studies on Rhesus monkeys that reported objective recognition effects (Bowman *et al*., 1989a), endometriosis (Rier *et al*., 1993), and prenatal death (Bowman *et al*., 1989b), and the study on Marmoset monkeys that reported a change in lymphocytes (Neubert et al., 1992) were the most relevant for the derivation of a health-based criterion. From these studies, a LOAEL of 0.1 ng/kg bw/day was determined. This was considered to be equivalent to a NOAEL of 0.05 ng/kg bw/day. Safety factors of 5 (for interspecies variation between monkeys and humans) and 10 (for differences in sensitivities between humans) were applied to give the exposure limit. Given the similarity of their effects, the Committee considered that this recommended exposure limit should be applicable to the intake of mixtures of PCDD/Fs and dioxin-like PCBs expressed as total TEQ.

Currently the Dutch government uses the TDI derived by the WHO in 1998, namely 1–4 pg TEQ/kg bw/day for risk assessment, where the TEQ represents the TEQs from the PCDD/Fs and dioxin-like PCBs (de Stoppelaar, 2000). The lower end of this TDI range is the same as the exposure limit derived by the Health Council of the Netherlands (1996).

6.5 Germany

In 1985, the German Federal Environment Agency, in consultation with the Federal Health Agency, established a daily intake range of 1–10 pg TCDD/kg bw/day (UBA, 1985). This was derived on the basis of a NOAEL of 1 ng/kg bw/day from the Kociba *et al*. (1978) rat study and a three-generation reproduction study, also on rats, by Murray *et al*. (1979), with safety factors of 100–1000. Adoption of the I-TEF scheme by the Federal Health Agency means that this TDI is regarded as a range of 1–10 pg I-TEQ/kg bw/day, and furthermore, it is regarded as imperative to reduce the daily intake of PCDD/Fs below 1 pg I-TEQ/kg bw/day (Toxicology Forum, 1992).

6.6 Japan

In Japan the Environment Agency and the Ministry of Health and Welfare have established a Health Risk Assessment Index and a TDI for PCDD/Fs. The Dioxin Risk Assessment Study Group of the Ministry of Health and Welfare proposed, in 1996, a provisional TDI of 10 pg/kg bw/day for 2,3,7,8-TCDD. This figure was based on the two-year Kociba study (Kociba *et al*., 1978) and data from a three-generation reproduction study on rats (Murray *et al*., 1978). Evaluation of *in utero* deaths, litter size, and inhibition of postnatal body weight gain led to the conclusion of a non-toxic dose of 1 ng/kg bw/day, to which an uncertainty factor of 100 was applied to produce the TDI noted. In 1997 the Environment Agency's Dioxin Risk Evaluation Committee, whilst taking into account the Kociba rat data, also took into consideration more recent experimental data on Rhesus monkeys, and adopted 5 pg I-TEQ/kg bw/day as the Health Risk Assessment Index for PCDD/Fs (Environment Agency, 1997).

Following the 1998 re-evaluation of the WHO TDI, committees from the Environment Agency and the Ministry of Health and Welfare jointly re-evaluated the Japanese TDI and set a provisional TDI for PCDD/Fs and dioxin-like PCBs at 4 pg TEQ/kg bw/day (Environment Agency and Ministry of Health and Welfare, 1999). This re-evaluation by the Japanese committees followed the same principle as the WHO 1998 re-evaluation; namely, the derivation of equivalent human body burden levels from LOAELs in experimental animals, and the application of uncertainty factors. Further, the joint committee evaluated the same experimental data considered by the WHO. From the data of Gehrs *et al.* (1997) and Gray *et al.* (1997b), they concluded that a level of

approximately 86 ng/kg is the lowest maternal body burden value just below or above which effects are manifested, including the female genital anomalies that were considered to be significant as a toxic endpoint. The committee noted that in some toxicity experiments effects have been observed at lower body burden values, but when dose-dependency, reliability, reproducibility, and the toxicological significance of the tests were comprehensively taken into consideration, they were considered to be inadequate to use as indices for human health effects. This included the studies of endometriosis and reduced learning ability in offspring of monkeys reported by Rier *et al.* (1993) and Schantz and Bowman (1989) respectively, and the decreased sperm count in offspring of rats reported by Gray *et al.* (1997a). The latter study drove the lower limit of 1 pg TEQ/kg bw/day of the WHO TDI range of 1–4 pg TEQ/kg bw/day. For a LOAEL of 86 ng/kg bw for the maternal body burden, an estimated human daily intake of 43.6 ng TEQ/kg bw/day was derived, and, by using an uncertainty factor of 10, the joint committee derived a provisional TDI of 4 ng TEQ/kg bw/day. An uncertainty factor of 10 was used because:

- a LOAEL rather than a NOAEL was used as the basis of the TDI calculation
- body burdens were used when assessing toxic endpoints, and, therefore, differences between species that arise from pharmacokinetics did not need to be considered
- there are no clear data showing that humans are more sensitive to dioxin-like compounds than experimental animals
- data related to individual differences in toxic endpoints in humans are insufficient
- data on the half-life of the dioxin congeners are generally inadequate.

7 Appraisal of the health risks to New Zealanders from background exposures to dioxin-like compounds

Everyone is exposed to PCDD/Fs and related compounds, and the measured concentrations of them in humans are referred to as 'body burdens'. Like lead, there are concerns about typical or background population body burdens, and also concerns about point sources that may increase concentrations originating from some local source of exposure. In order to establish national policies and regulations concerning dioxin-like compounds, we must first consider the potential health risks to the general population from existing body burdens of these chemicals.

One of the more difficult issues in risk assessment is the determination of the dose metric to use for animal-to-human extrapolations. Because of the differences in sensitivity between species, an appropriate animal-to-human extrapolation of tissue dose is required. In addition, the dose metric needs to reflect the magnitude and frequency of exposure for the toxic endpoint of concern. This is often particularly difficult because human exposures are frequently different from highly controlled exposures in experimental animals.

For dioxin-like compounds, dose can be expressed in a variety of ways, including daily intake (pg/kg bw/day), current body burden (ng/kg bw), average body burden over a period of time, and tissue (e.g. serum or plasma) concentrations. The US EPA has noted that body burden appears to be the most practical dose metric for appraising the risks from this group of compounds (US EPA, 2000). Furthermore, the average lifetime body burden under steady-state conditions is the most appropriate.

7.1 Health risks for the general population

In this section New Zealand exposure data for the general population are appraised using each of the risk methodologies previously described, including comparison against the WHO target level TDI and the ATSDR MRL derived from LOAELs and safety factors, the incremental cancer risk approach, and the benchmark dose approach. Although body burden rather than daily intake is the preferred dose metric for dioxin-like compounds (US EPA, 2000), this report appraises risk by both these dose metric expressions, thereby allowing for a comparison of responses for the endpoints being considered. The section concludes with the public health risk assessment methodology, which incorporates consideration of the background New Zealand population body burdens of dioxin-like compounds when assessing point sources of human exposure.

7.1.1 New Zealand exposure data

For both the dietary intake and the serum body burden data, concentrations are expressed as the total TEQ of the PCDD/Fs plus the dioxin-like PCBs, calculated using the 1997 WHO TEFs (Van den Berg *et al*., 1998).

7.1.1.1 Dietary intake

As discussed in Section 3.3.3.1, the dietary intake of dioxin-like compounds for New Zealanders has been estimated at 0.37 pg TEQ/kg bw/day for an adult male and 0.84 pg TEQ/kg bw/day for an adolescent male when calculated using the 1997 WHO TEFs (Tables A2 and A3, Appendix). Because it is necessary to consider a person's lifetime intake of dioxin-like compounds, dietary

intake apportioned on a time-weighted basis has been estimated. Here it is assumed that from the age of 15 through to 24 years, the intake is at the rate estimated for an adolescent male (i.e. 58.9 pg TEQ/day) (Table A3, Appendix). The intake is adjusted annually for changing body weight (which is assumed to increase from 56.5 kg for a 15 year old to 70 kg for a 24 year old) to provide intake as pg TEQ/kg bw/day. From the age of 25 through to death, it is assumed that the intake is at the rate for the adult male (i.e. 29.3 pg TEQ/day) (Table A2, Appendix), with an 80 kg body weight. For a young child through to the age of 14, the intake has been estimated by proportioning the adult intake (as pg TEQ/day) based on energy requirements of a six-year-old of 6.6 MJ/day (Brinsdon *et al*., 1999) and of an adult male of 10.8 MJ/day (Buckland *et al*., 1998c). This intake is also adjusted annually for a child's increasing body weight (which is assumed to increase from 18.5 kg for a 5 year old to 51 kg for a 14 year old), to provide intake as pg TEQ/kg bw/day. The average dietary intake is estimated for a period of 70 years. On this basis, the time-weighted intake for New Zealand males is estimated to be 0.50 pg TEQ/kg bw/day. It should be noted that this estimate does not include any intake from birth through to age five, including intake from breast feeding.

7.1.1.2 Body burden and average lifetime daily exposure

Dioxin-like compounds are stored in the body in fat. Measurements of them are made in fat – sometimes fat samples themselves, but more usually in fat in blood samples or fat in breast milk samples. Estimation of the total body burden takes advantage of the fact that the concentration in fat is constant throughout the body. Thus, whatever sample is used gives an estimate of concentration in fat. For example, if dioxin-like compounds are measured in the fat in blood samples, it is assumed that that concentration is representative of the concentration in all fat in the body, and we can then use data concerning the percentage of total body weight which is fat to estimate total body burdens.

Using the concentration of dioxin-like compounds in serum from the New Zealand population, human body burdens of these contaminants have been calculated (Section 3.3.3.2). An appraisal of the cancer and non-cancer health risks can be made either using the body burden data directly, or by considering the data in terms of equivalent daily intakes.

As discussed in Section 5.1.1, under steady-state conditions, the following expression can be used to equate body burden to an equivalent human daily intake:

$$\text{Intake (ng/kg bw/day)} = \text{body burden (ng/kg bw)} \times (\ln(2)/\text{half-life})/f$$

where f is the fraction of intake dose that is absorbed, and ln(2) is the natural logarithm of 2, which equals 0.693.

This same expression can be used to equate body burdens estimated for serum fat concentrations for the population to an equivalent daily intake. Thus, from the New Zealand serum study data (see Section 3.3.3.2, Buckland *et al*., 2001), and assuming a half-life of 7.5 years and that the fraction of the dose adsorbed is 90%, estimates of the equivalent daily intake of dioxin-like compounds for New Zealanders are reported in Table 7.1. These data are considered to reflect the average lifetime daily exposure for any individual in the population. Although the WHO, in their estimation of daily intakes for their TDI re-evaluation, assumed dose absorption of 50% (i.e. f = 0.5), we have assumed 90% absorption (f = 0.9) which is more in keeping with the available data for gastrointestinal absorption (see Section 2.7). It should also be noted that there is uncertainty in

the half-life for TCDD, and even greater uncertainty for other PCDD/F and PCB congeners. The range of half-lives that has been measured in human studies for TCDD and other congeners (see Section 2.7) may imply considerable variability in half-lives across the whole population.

Table 7.1 Average lifetime daily exposure to dioxin-like compounds for the New Zealand population

Age (years)	Body burden (ng TEQ/kg bw)			Average lifetime daily exposure (pg TEQ/kg bw/day)		
	Minimum	Maximum	Average	Minimum	Maximum	Average
15–24	1.25	3.34	2.38	0.35	0.94	0.67
25–34	1.93	5.11	3.28	0.54	1.4	0.92
35–49	3.29	7.11	4.86	0.93	2.0	1.4
50–64	4.19	11.3	6.30	1.2	3.2	1.8
65+	4.25	12.0	7.67	1.2	3.4	2.1
All data (15–65+)	1.25	12.0	4.90	0.35	3.4	1.4

As can be seen in Table 7.1, concentrations of TEQs in New Zealanders increase markedly with age. This can be explained for two reasons. The first is that dioxins are only slowly broken down and excreted and have a very long half-life. For example, if the half-life were 10 years then half of one day's intake will still be in the body 10 years later, a quarter 20 years later, and an eighth 30 years later. Concentrations thus build up and increase as we get older. However, because of the long half-life, it takes many years to reach 'steady-state' concentrations.

The second reason for a continuing increase in body burdens and ALDE estimates, even above the age range 35–49 when one would expect steady-state concentrations to have been achieved, is that older people in New Zealand could have experienced higher exposures in their earlier years. As noted in Section 3, PCDD/F sources and emissions have been decreasing. It is possible that someone currently aged 60 experienced a significantly higher intake of dioxin-like compounds when they were young than someone currently aged 40. Nevertheless, the increase with age appears greater than would be expected from this reason alone, and raises the possibility that the half-life of dioxin might increase with age, so that concentrations build up in the elderly.

It should be pointed out that the estimated daily intakes presented in Table 7.1 are too low for the younger age groups since their body concentrations are still building up. The best estimates of daily intake probably therefore come from the age range 35–49. By this age, with a half-life of 7.5 years, steady-state should have been reached. The higher daily intake estimates for the older age groups might be an over-estimate if elderly people actually have a comparatively longer half-life than younger people. Based in particular on the 35–49 age range, we can estimate that the average daily intake of dioxin-like compounds among New Zealanders in recent years has been about 1.4 pg/kg bw/day (see Table 7.1, rightmost column, age 35–49). This estimate of average daily intake is used to appraise risk from dioxin-like compounds in the following sections. By coincidence, this ALDE estimate of 1.4 pg/kg bw/day is also the estimated average daily intake for all data across all age groups.

It is important to understand the difference between the dietary intake and ALDE estimates because, as will be shown, these different dose metrics give rise to different margins of safety and

cancer risk estimates. The dietary intake estimate reflects a person's intake based on a modeled diet and concentrations in food produce at the time measurements were undertaken. In the current study, this represents intake based on concentrations in foods at 1997 when samples were collected. Consequently, the dietary intake estimate represents exposure at a single point in time. In contrast ALDE estimates includes intakes from dietary and non-dietary pathways, and contributions from historical and current exposures. Under steady-state conditions, these estimates represent a time-integrated lifetime exposure. Because it is believed that intakes of dioxin-like compounds were higher in the past than they are at present, ALDE estimates are expected to be higher than dietary intake estimates. Risk estimates derived using the ALDE data will therefore also be higher compared to estimates calculated from the dietary intake data, and similarly, margins of safety will be smaller.

7.1.2 Lowest or no observable adverse effect levels and incorporation of 'safety' factor approach

As reviewed earlier in Section 6, a number of jurisdictions have established daily intake guidelines for dioxin-like compounds on the basis of LOAELs in laboratory animal studies and the application of 'safety' or 'uncertainty' factors. Thus, the WHO has utilized LOAELs in its derivation of a TDI of dioxin equivalents. The TDI is estimated as a range of 1–4 pg TEQ/kg bw/day based on various health effects demonstrated in several animal species and application of a factor of 10 to account for interspecies extrapolation. It is unusual to apply uncertainty factors as low as 10 when extrapolating from animal toxicological data to derive acceptable human exposure limits. Similarly, the ATSDR has established an MRL of 1 pg TEQ/kg bw/day for chronic oral exposure to TCDD based on a LOAEL for developmental toxicity in monkeys and a safety factor of 90. It might appear that the ATSDR used a larger safety factor, but this is not the case since they did not include an adjustment for the much longer half-life of TCDD in humans (about 7.5 years) than in monkeys (about one year). Thus, if you take into account body concentrations of TCDD in monkeys, then the ATSDR safety margin was not much more than 10.

As noted earlier, the time-weighted average daily dietary intake has been estimated to be 0.50 pg TEQ/kg bw/day for a male New Zealander, and the ALDE for 35–49-year-old New Zealanders to be 1.4 pg TEQ/kg bw/day (range of 0.93–2.0 pg TEQ/kg bw/day). A comparison of these exposures with the WHO TDI and the ATSDR MRL shows that the daily intake in New Zealand has averaged at about the WHO and the ATSDR criteria of 1 pg TEQ/kg bw/day (Table 7.2). Of course, if the average has been at these values, then approximately half the population will have been exceeding these recommendations. In addition, it should be noted that the WHO and ATSDR recommendations were promulgated with unusually small margins of safety.

Table 7.2 Margin of safety of the estimated New Zealand exposures to dioxin-like compounds relative to the WHO and ATSDR criteria of 1 pg TEQ/kg bw/day

	NZ average exposure (pg TEQ/kg bw/day)	Margin of safety below 1 pg TEQ/kg bw/day
Daily dietary intake	0.50	2
ALDE	1.4	none

A comparison of the New Zealand body burden data (Table 7.1) with body burdens in animals shown to cause reproductive, neurobehavioral and immunotoxicity effects (Table 4.2) shows that

these body burdens are within an order of magnitude of each other, and confirms the slim margin of safety that exists for the population from exposure to dioxin-like compounds.

This assessment does not consider the exposure of breast feeding infants to dioxin-like compounds, which will result for a comparatively short period of time in intakes considerably exceeding the WHO and ATSDR exposure criteria. This situation is discussed more fully in Section 7.2.

7.1.3 Incremental cancer risk assessment and low-dose extrapolation approach

The 'safety' or 'uncertainty' factor approach implicitly assumes the existence of a threshold of effect. However, for health effects such as cancer, it is unclear whether such a threshold exists. Consequently, low-dose extrapolation methods are most frequently used to estimate the added lifetime risk of cancer resulting from exposure to a suspected carcinogen. As noted in Sections 5.2.4.1 and 6.2.1, the US EPA has derived a cancer potency factor for TCDD (95% confidence limit) of 1.6×10^{-4} $(pg/kg\ bw/day)^{-1}$ based on the results from a rodent bioassay (US EPA, 1985; 1988). An estimate of lifetime added cancer risk resulting from exposure to TCDD can be calculated from:

Lifetime added cancer risk = average daily intake x cancer potency factor

Using this expression, the estimated lifetime added cancer risk for a New Zealand male would be approximately 8.0×10^{-5}, where 0.50 pg/kg bw/day is the time-weighted average daily intake and 1.6×10^{-4} $(pg/kg\ bw/day)^{-1}$ is the cancer potency factor based on animal data. This number (8.0×10^{-5}) means that the estimate of lifetime added cancer risk resulting from a time-weighted average daily intake of 0.50 pg/kg bw/day over a lifetime is approximately eight additional cancers per 100,000 persons exposed. Similarly, based on the ALDE for the New Zealand population of 1.4 pg TEQ/kg bw/day, the lifetime added cancer risk can be calculated as 2.2×10^{-4}, or 22 additional cancers in 100,000 persons exposed.

A problem with the aforementioned cancer potency factor, and any estimate of cancer risk based on it, is that the rat-to-human extrapolation utilized in its derivation was based on a body surface correction factor, rather than TCDD half-life and body burden considerations (US EPA, 1988). When extrapolating from animals to man, the dose equivalent is often calculated by application of a dose/surface area conversion factor of 5.4 for the rat (US EPA, 1988). The derivation of this number is based on observations that many physiological rates tend to scale in proportion to a fractional power of body weight (US EPA, 1988). However, this method of species extrapolation is not appropriate in the case of TCDD because of the long half-life in humans as compared to the rat. The US EPA has examined the effect of this difference on the quantification of cancer risk and estimated that, for a human, TCDD half-life of six to 10 years and a rat TCDD half-life of approximately 25 days, the corresponding correction factors between humans to the rat become 88 to 1 (based on six years) and 146 to 1 (based on 10 years) versus a ratio of 5.4 to 1 applied in the original risk assessment (US EPA, 1988). This analysis shows that if total body burden only were considered, the very long half-life of TCDD in humans would result in cancer risk estimates between 16 (based on six years) and 27 times (based on 10 years) higher than results based on the current cancer potency estimate (US EPA, 1988). If we apply the rat-to-human conversion factors based on total body burden to the estimates of lifetime added cancer risk for New Zealanders and

assume a human half-life of 7.5 years and a rat half-life of 25 days, the lifetime added risk increases by a factor of 20.

Consequently, for New Zealand males, the cancer risk estimate is approximately 16 per 10,000 exposed (from 20 x 8 in 100,000) based on a time-weighted average daily dietary intake, and, for the New Zealand population, the estimate, based on the ALDE, is approximately 44 per 10,000 exposed (from 20 x 22 in 100,000). This is summarized in Table 7.3. Of course, it should be noted that if there were indeed a threshold above current exposures the actual risks would be zero. Alternatively, they could lie in a range from zero to the estimates actually given, but are unlikely to be higher than those given.

Table 7.3 Estimate of lifetime added cancer risk based on an animal-derived cancer potency factor

	New Zealand average exposure (pg TEQ/kg bw/day)	Lifetime added cancer risk
Daily dietary intake	0.50	1.6×10^{-3} [or 16 in 10,000]
ALDE	1.4	4.4×10^{-3} [or 44 in 100,000]

The US EPA has also performed low-dose extrapolation using the dose-response data from the occupational cohorts of Fingerhut *et al.* (1991ab), Manz *et al.* (1991), and Zober *et al.* (1990) (US EPA, 1994b), as previously discussed in Section 5.2.4.2. The MLE all-cancer unit risks from all studies combined ranged between 2×10^{-3} and 3×10^{-3} $(pg/kg\ bw/day)^{-1}$. As in the previous example, the estimates of lifetime added cancer risk for New Zealanders can be calculated by multiplying the aforementioned unit risks by the estimated average daily intake (either as dietary intake or ALDE). The results are shown in Table 7.4.

Table 7.4 Estimate of lifetime added cancer risk based on dose-response data from occupational cohorts

	New Zealand average exposure (pg TEQ/kg bw/day)	Lifetime added cancer risk[1]
Daily dietary intake	0.50	$1.0 \times 10^{-3} – 1.5 \times 10^{-3}$ [or about 10 – 15 in 10,000]
ALDE	1.4	$2.8 \times 10^{-3} – 4.2 \times 10^{-3}$ [or 28 – 42 in 10,000]

1. Range based on MLE unit risk of $2 \times 10^{-3} – 3 \times 10^{-3}$ $(pg/kg\ bw/day)^{-1}$.

The lifetime cancer risks vary from a range of about 10 in 10,000 to 15 in 10,000 based on the estimated time-weighted dietary intake for a male New Zealander, to a range of 28 in 10,000 to 42 in 10,000 based on the ALDE estimate for the New Zealand population.

Similar risk estimates are obtained by using the upper bound cancer potency factor of 1×10^{-3} $(pg/kg\ bw/day)^{-1}$ most recently proposed by the US EPA (2000). In this instance, lifetime added cancer risks of 5 in 10,000 to 14 in 10,000 are calculated.

It can be seen that the cancer risk estimates from the human studies are quite close to those from animal studies when the long human half-life is taken into account. The human studies included measurements of PCDD/Fs in blood samples from exposed male workers. They thus represent good estimates for adult male exposure. There are no cancer studies involving women, but since there is no good basis to expect cancer risks to be different for men and women, they can be regarded as good estimates for adults. When used for the total population, the implicit assumption is that children are neither more nor less susceptible to the cancer-causing effects of exposure to dioxin-like compounds than adults.

By contrast, when the animal studies are used for human risk estimation there are a large number of uncertainties. For example, there have been dramatic changes to the risk estimates derived from animal studies according to conversion factors used for animal-human extrapolation. Humans are also investigated extensively when cancer diagnoses are made, whereas there has been a lot of controversy in estimates of the number of cancers in the rats exposed to dioxin. In addition, the cancers in the animals are often at sites of little, if any, relevance to human cancer. Hence, emphasis should be placed on cancer risks derived from human data.

Overall, based on the human potency factors, the upper bound lifetime risk estimate for New Zealand background intakes of dioxin-like compounds may exceed one additional cancer per 1000 individuals. This cancer risk estimate is much higher than the value of 1 in 100,000 often used in New Zealand to regulate carcinogenic exposure form environmental sources.

7.1.4 Benchmark dose approach

The benchmark dose (BMD) is defined as the dose calculated to produce a given effect in a chosen percentage of the test population (animal or human). For cancer risk assessment the percentage is usually 1% (Smith and Sharp, 1985) and the BMD is often referred to as the ED_{01}. Customarily, the lower 95% confidence limit of the BMD is used as a conservative measure. Safety factors are then usually applied to the results of the benchmark dose analysis to arrive at a permissible exposure level for a given chemical. The rationale for using the BMD is that there is little extrapolation required below the observed dose range to estimate the dose of a chemical that might cause an increase of 1 in 100 exposed individuals in the study population to get cancer. Below that exposure, the uncertainties associated with the shape of the dose-response relationships are considerable. Of course, this is not to say that cancer risks of 1 in 100 are acceptable, but rather to note that this is about the limit of scientific extrapolation of data. Safety factors can be taken below the BMD dose. For example, a safety factor of 100 below an ED_{01} would result in a cancer risk of 1 in 10,000 exposed persons, if the dose-response relationship were linear. The advantage of this approach over incremental cancer risk assessment is that there is no pretence that we can actually estimate real cancer risks at such low doses.

Portier (2000) used the benchmark dose approach to calculate the doses associated with a 1% increase in cancer risk using the results from the occupational cohort studies of Fingerhut *et al.* (1991ab), Zober *et al.* (1990), and Manz *et al.* (1991). The ED_{01} for all studies combined was 5.9 pg/kg bw/day for all-cancers combined (see Section 5.3.1 and Table 5.2).

As previously mentioned, the time-weighted average daily dietary intake has been estimated to be 0.50 pg TEQ/kg bw/day for a male New Zealander, and the ALDE for 35–49-year-old New Zealanders to be 1.4 pg TEQ/kg bw/day. Thus the average daily intake of dioxin-like compounds

in New Zealand is at best only an order of magnitude lower than the estimated ED_{01}. Once again, the margin of safety can be seen to be very small (Table 7.5).

Table 7.5 Margin of safety of the estimated New Zealand exposures to dioxin-like compounds relative to a benchmark dose ED_{01} for cancer of 5.9 pg/kg bw/day

	New Zealand average exposure (pg TEQ/kg bw/day)	Margin of safety below ED_{01} of 5.9 pg/kg bw/day
Daily dietary intake	0.50	12
ALDE	1.4	4

Similarly, Portier (2000) reports an ED_{01} for all-cancers combined based on body burdens from the human occupational cohort studies of 11 ng/kg bw (Table 5.2). The New Zealand body burden average for the 35–49 age group is 4.86 ng TEQ/kg bw (Table 7.1), and again the margin of safety below the ED_{01} is very small (Table 7.6).

Table 7.6 Margin of safety for the New Zealand body burden of dioxin-like compounds relative to a body burden benchmark dose ED_{01} for cancer of 11 ng/kg bw

	New Zealand average exposure (ng TEQ/kg bw)	Margin of safety below ED_{01} of 11 ng/kg bw
Body burden	4.86	2

In summary, when assessing cancer risk using a benchmark dose derived from human data, the margin of safety between the average intake of dioxin-like compounds for the New Zealand population and the concentration estimated to result in a 1 in 100 cancer risk is found to be less than an order of magnitude.

7.1.5 Public health risk assessment

As discussed previously, traditional risk assessment methods ignore existing background levels of exposure and consider only incremental risk estimates for maximally exposed individuals. Note that the above methods have been used to estimate risks associated with the background human exposure. They could also be used to look at incremental exposures as if there were no background exposure, a head-in-the-sand approach to public health decision making which can hardly be called scientific. The public health risk assessment method takes into account current exposures as well as providing methods for considering single point sources of exposure adding to background.

The first step in public health risk assessment as applied to New Zealand involves ascertaining background levels of exposure to PCDD/Fs on a national level. New Zealand has a unique advantage in having data concerning the average daily TEQ intake and body burdens for New Zealanders, which have been estimated from concentrations in serum collected from a national random sample of the population (Bates *et al*., 1999; Buckland *et al*., 2001).

The second step in public health risk assessment involves characterizing the health risks associated with background population exposures, again conducted at a national level. Given the current average daily TEQ intakes for adult and adolescent males in New Zealand, and the most recent

data on the potential risk for non-cancer and cancer endpoints resulting from exposure to TCDD discussed in this document, the current background exposures are undesirably high, based on various considerations. Cancer risk estimates for background exposures have been noted to be high. The margin of safety between average population intake of dioxin-like compounds and the concentration estimated to result in a 1 in 100 cancer risk (benchmark dose method) is small. The margin of safety between various non-cancer effects in animal studies, in particular effects on the offspring of exposed mothers, is also small.

The third step in public health risk assessment involves a risk management decision on whether to place the dioxin-like group of compounds in priority Class 1 or 2. A Class 1 chemical was defined as a substance for which no added exposure is permitted from a source unless offsets to reduce local population exposures to this substance are achieved (Smith *et al*., 1996). Potential risks associated with the background population exposure to Class 1 substances are of concern and a national programme for exposure reduction is being implemented. A Class 2 chemical is a substance for which potential risks associated with the background population exposures are not thought to be significant, but for which there are some concerns about the margin of safety. As will be seen later in the Recommendations (Section 8), since population body burdens of dioxin-like compounds in New Zealand appear to have been falling over time, and can be expected to continue to fall with continuing implementation of sound policies and regulations relating to sources and emissions, we recommend that this group of compounds be classified in Class 2 rather than Class 1. This is in spite of the fact that potential risks associated with the background population exposures to dioxin-like compounds could be considered significant.

7.2 Health risk for breast-fed infants

Since dioxin-like compounds are lipophilic chemicals, they are associated with the fat component of maternal milk. A substantial research effort worldwide has been carried out to determine levels of contaminants in various population groups and to consider the significance of these contaminants to human breast-fed infants.

7.2.1 Dioxin concentrations in breast milk

Most data are available for samples of milk from first-time mothers, as standard international (WHO) protocols specify that milk from first-time mothers be analyzed for comparison purposes. Nevertheless, enough work has been done to show that PCDD/F levels increase with the age of the mother, but decrease with increasing number of periods of, and duration of, breast feeding (ATSDR, 1998).

In industrial areas of the Northern Hemisphere, human breast milk collected in the period 1990-1993 typically contained PCDD/F levels between 10 and 35 ng I-TEQ kg^{-1} on a fat weight basis. Where results are available over a period of time, it is clear that the levels are falling (Van Leeuwen and Younes, 2000). Thus, between 1988 and 1993 this decrease has been estimated to be in the range 10–60%, with the highest rates of decrease in areas with the highest initial concentrations (van Leeuwen *et al*., 2000). Levels of PCDD/F in breast milk from the USA, at 17 ng TEQ kg^{-1} fat basis (Schecter *et al*., 1989), have been estimated to contribute 35–53 pg TEQ/kg bw/day during the first year of a child's life (ATSDR, 1998)

As discussed in Section 3.3, human breast milk samples from New Zealand were collected during 1987/88 and the mean PCDD/F concentration from this historical data was 17 ng I-TEQ kg^{-1} fat basis, or 21 ng TEQ kg^{-1} fat basis when calculated using the 1997 WHO TEFs. A second breast milk study is currently underway, and the preliminary indication from this study is that over the 10-year period from 1987/88 to 1997/98, the New Zealand PCDD/F levels have fallen by about two-thirds (Institute of Environmental Science and Research, 2001).

7.2.2 Infant intakes of dioxin-like compounds

Infants may be exposed to dioxin-like compounds from various sources. Although results are sparse, the PCDD/F concentrations in the new-born baby reflect the level in their mother because of *in utero* exposure. Breast feeding is a significant source, while other food sources will contribute less and environmental intakes (from air, water, or soil) are generally insignificant.

The information available on *in utero* exposures to PCDD/Fs is limited. Concentrations in liver tissue of still-born infants ranged from 0.14–0.49 ng TEQ kg^{-1} (whole weight) or 6.4–12 ng TEQ kg^{-1} (lipid basis) (ATSDR, 1998). This body burden is very small in comparison to the lifetime body burden, although the concentration at birth on a lipid basis might approach that in the mother. Similarly, PCDD/Fs in placental material have been reported ranging from 8.4–17.6 ng TEQ kg^{-1} lipid basis (ATSDR, 1998).

Data on the concentrations of dioxin-like compounds in breast milk imply that infant exposures from breast feeding must be substantial, particularly as studies show that PCDD/Fs present in the milk (except for OCDD) are highly bioavailable to the infant, being at least 95% absorbed and retained (ATSDR, 1998).

Data have recently been published based on two studies that compared PCDD/F concentrations in breast-fed and formula-fed infants (US EPA, 2000). One was a comparison between two infants at 11 and 25 months, and the other measured adipose tissue from 17 infants (of whom nine were breast-fed and eight were formula fed) who died from sudden infant death syndrome. The combined data from the two studies gave the following results (TEQs calculated using the 1997 WHO TEFs):

Concentration in formula-fed infants:	< 5 ng TEQ kg^{-1} lipid basis
Concentration in breast-fed infants:	> 20 ng TEQ kg^{-1} lipid basis (max. of 35 ng TEQ kg^{-1}).

Other work relating to the influence of breast feeding on infant exposure to dioxin-like compounds has been based on models. As such, the outcomes are highly dependent on the assumptions on which the models are based. Perhaps the most significant prediction from these models is that over a period of breast feeding, and considering only post-natal exposures, a baby may be expected to reach the mother's PCDD/F concentration by the age of about six months. This conclusion is supported by analytical data (Abraham *et al*., 1996). An average infant intake from breast feeding of dioxin-like compounds (based on model calculations) of 92 pg TEQ/kg bw/day has been estimated (US EPA, 2000). In the New Zealand situation, an estimate of average infant intakes for a child who is breast-fed over the first 12 months of their life is between 37–52 pg TEQ/kg bw/day (Table 7.7).

A model previously developed by Smith (1987) has been used in the current appraisal to estimate the ratio of a breast-fed baby's body concentration of dioxin-like compounds to that of its mother.

Parameters were as previously reported by Smith (1987) except for the use of more accurate estimates of infant body weights (data as reported in Table 7.7), a 12 month average infant milk intake of 660 mL/day and, more significantly, the use of a half-life estimate of 7.5 years for both mother and infant. (It should be noted that the half-life of dioxin-like compounds in infants can be confusing. Infants grow very rapidly and this, concomitantly, dilutes body concentrations of these contaminants. Whilst the increasing body weight of the infant should be taken into account, the model used does this separately. We have taken half-life to refer solely to the duration of time dioxin-like compounds remain in the body. Therefore, we consider there is no good reason to assume a different half-life for infants than adults.).

Table 7.7 Estimated intake of dioxin-like compounds for an infant breast-fed for 12 months

Age of baby (months)	Milk intake (mLs/day)	Weight of baby (kg)	Concentration[1] (pg TEQ mL^{-1})	Baby's intake (pg TEQ/kg bw/day)
0–1	900	3.5	0.43	111
1–3	700–800	5.0–6.3	0.43	48–69
3–6	600–700	6.3–7.8	0.43	33–48
6–12	500–700	7.8–9.5	0.43	23–39
12 month average				37–52

1. TEQ for PCDD/Fs and dioxin-like PCBs. Data from the 1997/98 New Zealand breast milk study (Institute of Environmental Science and Research, 2001). Concentration is mean of 53 samples.

A graphical representation of the results from application of this model to the New Zealand situation is given in Figure 7.1. As noted earlier, the model suggests that the body concentration of dioxin-like compounds in a breast-fed infant reaches those of its mother after about six months of breast feeding.

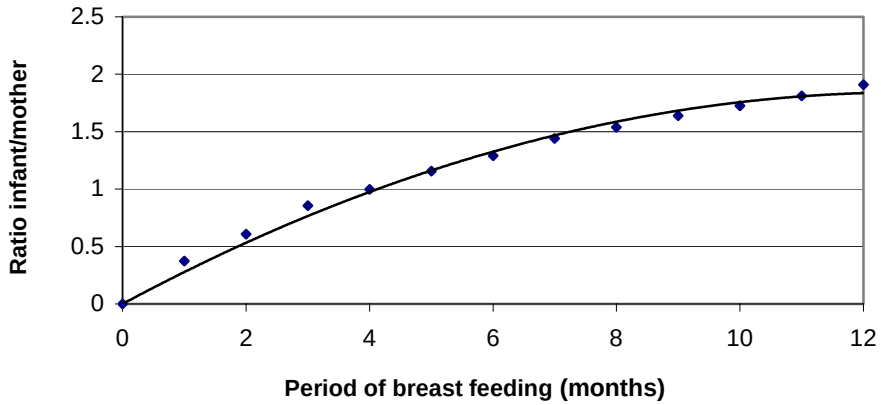

Figure 7.1 Concentration of dioxin-like compounds in a nursing infant relative to its mother during the period of breast feeding
[The model does not consider any pre-natal exposure of the infant, and therefore the Y-axis ratio of infant to mother is set at zero.]

Models also suggest that even if infants receive different exposures to dioxin-like compounds in early life (depending on whether or not they are breast-fed), they will have equivalent concentrations around the age of 10 years (US EPA, 2000). Thus breast feeding is not expected to

increase body burdens of dioxin-like compounds throughout life; rather it significantly increases the body burden of these contaminants in the early years of life.

7.2.3 Health significance of infant exposures

It is unclear whether the exposure to dioxin-like compounds received by infants *in utero* or from breast feeding is associated with any adverse effects. A few studies, reviewed by Feeley and Brouwer (2000), have found evidence, associated with *in utero* exposures to dioxin-like compounds, of developmental effects in infants, including low birth weight, thyroid hormone changes, delays in psychomotor and cognitive functions, and immune alterations. However, in most instances, these effects were subtle and generally within what can be described as normal population background variation (Feeley and Brouwer, 2000). In some of these studies, there was evidence of a benefit resulting from breast feeding on child development which was overlaid by the effects from the contaminants in the higher exposure cohorts only (National Research Council, 1999).

In the absence of direct evidence that adverse health effects will occur due to exposure in infancy, it is nevertheless prudent to include infant exposure when considering regulatory policies. As with other potential health effects of dioxin-like compounds it is reassuring that concentrations and body burdens are decreasing over time. At the same time, exposure of infants adds to the basis for recommending a precautionary approach concerning dioxin-like compounds in New Zealand.

7.3 Health risks for other 'special' populations

In addition to general population risks from background exposures to dioxin-like compounds, some individuals may also be further exposed from local elevated sources or by having unique diets, which would be in addition to the background exposure. Such additional exposures may occur in small segments of the population, such as people living near discrete local sources, recreational fishermen who consume fish from water bodies that receive PCDD/F contaminated discharges, or occupationally exposed workers. A consideration of exposure for high dietary intake consumers and timber workers who were historically exposed to PCP is given below.

7.3.1 High dietary intake consumers

It is reasonable to assume that, in general, dietary intake of dioxin-like compounds by New Zealanders will be similar to that estimated by the Organochlorines Programme dietary study (Buckland *et al*., 1998c) outlined in Section 3.3.3.1. However, some people may obtain food from sources more heavily contaminated with PCDD/Fs than most. When such situations have occurred overseas, they have often been associated with the consumption of fish that have grown in water bodies receiving PCDD/F-contaminated discharges; for example, discharges of pulp and paper mill effluent. In New Zealand three such water bodies have been identified: the Tarawera and Waikato Rivers and Lake Rotorua. This section examines the possible extra exposure to PCDD/Fs of hypothetical persons who obtained all their fish from any of these water bodies.

The Tarawera and Waikato Rivers both receive wastewater from a bleached kraft pulp and paper mill. Historically, both mills used elemental chlorine in their bleach plants, but now use a bleaching sequence based on oxygen delignification and chlorine dioxide. Biota from these rivers have been studied to assess the magnitude of uptake of PCDD/Fs discharged from the mill sites.

These data can be used to estimate potential dietary intakes from these sources. The Lake Rotorua catchment contains a number of timber treatment sites that once used PCP. One particularly large site is known to be severely contaminated with PCDD/Fs (Ministry for the Environment and Department of Health, 1992). Biota were collected from Lake Rotorua in 1993 to assess the impacts of discharges containing PCDD/Fs from these timber treatment sites.

The current assessment of possible additional PCDD/F intake of people consuming fish caught in these water bodies is based on the methodology of the Organochlorines Programme dietary study, which involved the assessment of model diets. The approach adopted was to replace the contribution made by New Zealand fish to PCDD/F intake of these model diets with the estimated corresponding intake if the fish were obtained entirely from the Tarawera or Waikato Rivers, or Lake Rotorua.

As discussed in Section 3.3.3.1, model diets for an adult male and for an adolescent male New Zealander were prepared. In constructing these diets it was estimated that the adult male would consume 32.4 g of New Zealand fish daily, and the adolescent male 64.5 g of New Zealand fish daily (see Tables A2 and A3, Appendix). Chemical analysis of foods contributing to the model diets showed that the adult male and the adolescent male would consume, respectively, a total of 0.37 and 0.84 pg TEQ/kg bw/day of PCDD/F/PCBs based on the 1997 WHO TEFs (Table 3.5).

In the Organochlorines Programme dietary intake assessment, the contribution by New Zealand fish (not including shellfish) to the PCDD/F TEQ intake of adult males (assuming daily average consumption of 32.4 g) was 0.014 pg TEQ/kg bw/day (approximately 4% of the total intake from dioxin-like compounds; see Table A2, Appendix) and for adolescent males (assuming daily average consumption of 64.5 g) was 0.031 pg TEQ/kg bw/day (approximately 4% of total; Table A3, Appendix). Dioxin-like PCBs also contributed to the total dietary intake, but, for the purposes of this assessment, it is only the PCDD/Fs that are believed to be increased in the three water bodies being considered. Therefore, any TEQs contributed by the dioxin-like PCBs are assumed to remain the same, whatever the source of New Zealand fish in the diet.

PCDD/F concentrations in eel and whitebait caught in 1998 from the Tarawera River (Fletcher Challenge Paper, 1999), in trout caught in 1995 from the Waikato River (Kingett Mitchell, 1996) (in both cases at sites downstream of the mill discharge) and in trout from Lake Rotorua caught in 1993 (Gifford *et al*., 1996) are summarized in Table 7.8. The concentrations given have been recalculated from the original data in the source publications, using the 1997 WHO TEFs.

Table 7.8 Concentrations of PCDD/Fs in fish from the Tarawera and Waikato Rivers and Lake Rotorua

Source	Species	Concentration (ng TEQ kg^{-1} wet wt)		
		Minimum	Maximum	Mean
Tarawera River[1]	Eel (flesh)	0.21	0.35	0.28
Tarawera River[1]	Whitebait	0.14	0.14	0.14
Waikato River[1]	Trout (fillet)	0.24	0.81	0.56
Lake Rotorua	Trout (fillet)	0.62	1.34	1.08

1. Downstream sites of pulp and paper mill discharge.

By substituting the concentrations of PCDD/Fs in New Zealand fresh fish used in the Organochlorines Programme dietary study (which consisted entirely of fish purchased at retail outlets), with the fish concentrations in Table 7.8, the impact on a person's intake of dioxin-like compounds can be estimated for the hypothetical circumstance in which all their New Zealand fish consumed were from the Tarawera or Waikato Rivers, or Lake Rotorua. Using the mean fish tissue concentrations, Table 7.9 shows the estimated intakes separately for adolescent and adult New Zealand males, and for a male New Zealander if intake is apportioned on a time-weighted basis (assuming 10 years on the adolescent diet, as discussed in Section 7.1.1.1).

Table 7.9 Estimated intake of dioxin-like compounds from model diets with various sources of New Zealand fish

Source of fish	Species	Dietary intake[1] (pg TEQ/kg bw/day)			Increase[2] (%)
		Adult	Adolescent	Time-weighted	
Retail outlets[3]	Mixed	0.37	0.84	0.50	–
Tarawera River	Eel	0.47	1.07	0.62	25
Tarawera River	Whitebait	0.41	0.94	0.55	10
Waikato River	Trout	0.58	1.32	0.77	55
Lake Rotorua	Trout	0.79	1.80	1.03	110

1. Dietary intake from all foods consumed based on model diets.
2. Increase in intakes of dioxin-like compounds over the intakes from the dietary survey. The increase reported is the average increase of the adult and adolescent male and the time-weighted intakes.
3. Intakes from the Organochlorines Programme dietary study (Buckland *et al*., 1998c).

The results show that in situations where a person is consuming fish with a higher PCDD/F concentration compared to fish available at retail outlets in New Zealand, an increase in dietary intake can occur. By association, an increase in dietary intake will result in an equivalent increase in cancer risk. Thus using the time-weighted intakes (Table 7.9) and the cancer potency factors derived from human data given in Section 7.1.3, the cancer risk to people consuming fish from the Tarawera or Waikato Rivers or Lake Rotorua as part of their normal diets is estimated in the range 5–31 per 10,000 persons exposed. This compares with an estimated cancer risk range of 5–15 per 10,000 persons exposed for a time-weighted dietary intake of 0.50 pg TEQ/kg bw/day.

Intakes and cancer risk could be further exaggerated for recreational fishermen who consume significantly greater quantities of fish caught in these or other impacted waterbodies than the typical New Zealander considered in this model.

Table 7.9 also shows that, in some circumstances, the daily intake by adolescent males of dioxin-like compounds from their diet could exceed 1 pg TEQ/kg bw/day, which is the target TDI established by WHO and the MRL set by the ATSDR. However, as noted earlier in this report, the higher calorific intake represented by the adolescent diet is only representative of a fraction of a person's lifespan. Only the consumption of Lake Rotorua trout resulted in the estimated time-weighted intakes of New Zealand males exceeding 1 pg TEQ/kg bw/day, and then only marginally.

As a comparison, fish caught from reference sites for the Tarawera and Waikato River studies had PCDD/F concentrations similar to the concentrations measured in the fish purchased from retail

outlets used in the dietary study (0.034 ng TEQ kg^{-1} wet weight). Thus, the PCDD/F concentrations measured in eel from the Rangitaiki River, a river close to the Tarawera but without kraft effluent discharge (Fletcher Challenge Paper, 1999), and from a site upstream of the mill discharge on the Waikato River (Kingett Mitchell, 1996) were 0.037 and 0.049 ng TEQ kg^{-1} wet weight respectively, based on the 1997 WHO TEFs.

There is one other situation that should be mentioned for completeness. That is when a person is in the habit of eating parts of the fish, such as the liver, roe, or stomach contents, as is understood to be a more common practice amongst the local Maori populations. Some of these fish parts may accumulate comparatively higher levels of PCDD/Fs than the flesh of the fish. For example, the liver from eels collected from the Tarawera River had a PCDD/F concentration of 0.83 ng TEQ kg^{-1} wet weight, compared to a mean concentration in the flesh (back muscle) of 0.28 ng TEQ kg^{-1} wet weight (Fletcher Challenge Paper, 1999). Thus, a person consuming quantities of these fish parts could, potentially, have a higher PCDD/F intake than those estimated in Table 7.9. However, no data were available on the extent to which these fish parts are consumed by local indigenous populations for a comparative assessment to be made.

7.3.2 Occupationally exposed timber workers

As mentioned in Section 3.3.2, some people may be exposed to dioxin-like compounds as a result of their work environment and work practices. Typically, occupational exposures have generally been associated with the manufacture or use of industrial chemicals contaminated with PCDD/Fs, including chlorophenols and the herbicide 2,4,5-T.

In New Zealand, the historical use of PCP in the timber industry has resulted in occupational exposure to PCDD/Fs for some timber workers. PCP was widely used both for antisapstain treatment for the interim protection of freshly sawn timber against fungal staining and as a permanent timber preservative. It was used from the mid to late 1950s until 1988, when it was voluntarily withdrawn from use by the timber industry after potential health and environmental effects were recognized (Buckland *et al*., 2000).

The issue of possible health effects to New Zealand workers arose in the early to mid 1990s when fitters who had been working with PCP holding tanks expressed concern about their health. Subsequently, further health concerns were raised by sawmill workers (Bandaranayake *et al*., 1999). In 1996 a report prepared by a PCP Expert Medical Panel, on behalf of New Zealand's major timber companies, determined that, based on a review of the toxicological and epidemiological literature, '*exposure to PCP in the timber industry will result in acute health effects, including eye irritation, upper and lower respiratory tract irritation and skin changes such as burning, irritation and dermatitis*' (Beasley *et al*., 1995). The report further noted that '*there have been no adequate studies of the long-term health effects of exposure. Thus, there is no firm evidence of significant long-term health effects, but this did not exclude the possibility of such effects could occur*'.

All major studies of human exposure to PCDDs so far focus on 2,3,7,8-TCDD, the most famous and most toxic of this group of chemicals. Human exposure to other forms of PCDD/F does occur, but usually in combination with exposure to 2,3,7,8-TCDD. Based on a small number of blood samples and measurements of PCDDs, the New Zealand sawmill workers appear to be a unique group in that their exposure manifest now in their blood analyses was to hexa- and hepta-

PCDDs, and not to 2,3,7,8-TCDD. The exposure data for these workers are reported in Table A1 (Appendix). Such exposures may occur elsewhere in the world with PCP contaminants, but we are not aware of any documentation of this so far. While it is not possible to draw conclusions about health effects from the small number of workers assessed so far, it is clear that human studies are needed of workers with these exposures. We would therefore recommend that a major cohort mortality study be designed of long-term health effects from sawmill work, focusing on PCP exposure. If the study is feasible and of sufficient statistical power to assess overall cancer mortality, then we would recommend that it be given high priority for funding.

With regard to those workers already known to be exposed, it should be noted that they have concentrations of toxic chemicals in their blood much increased beyond those in the general New Zealand population. Whether or not they would experience symptoms and health effects at these concentrations is not known. However, in contrast to often unwarranted fears of chemical exposure, these workers have biologically proven concentrations of PCDD/Fs in their bodies. Furthermore, there is no known treatment to remove these contaminants from them. Although the PCDD/Fs gradually break down and are eliminated from the body, because these chemicals have long half-lives, these workers continue to be exposed for many years after their workplace exposure ceased.

8 Recommendations

In the light of the ever-increasing scientific information concerning the toxicity of dioxin-like compounds, and the information concerning body burdens present in the New Zealand population, the following recommendations are made.

Recommendation 1: A precautionary approach should be adopted concerning dioxin-like compounds in New Zealand.

The reasons for recommending a precautionary approach are as follows.

(a) Although body burdens of dioxin-like compounds in New Zealand are a little lower than in Europe and North America, current population body burdens of these contaminants in New Zealand include people who are within a factor of 10 of body burdens that have been shown to cause deleterious effects in animal studies. The main effects in exposed animals involve their offspring, which have decreased sperm counts, immune system suppression, increased genital malformations and neurobehavioral effects. This margin of safety of less than 10 between the concentrations of TCDD in the animals with these effects in their offspring, and the concentration of dioxin-like compounds (as TEQs) in the average person in the general New Zealand population, is much lower than usually sought for general population exposures to toxic chemicals.

(b) Cancer risk estimates derived for the general New Zealand population based on either animal or human studies indicate high potential risks; these risks may exceed one additional cancer per 1000 individuals. In the past, the yardsticks for identifying 'acceptable' environmental exposure to carcinogenic chemicals have usually been 2–3 orders of magnitude lower, in a range of 1 in 100,000 to 1 in a million exposed persons getting cancer.

(c) Infants who are breast-fed have, for the period of breast feeding, a much higher intake of dioxin-like compounds per body weight than adults and non-breast-fed infants. Modeling of intake of breast-fed babies suggests that breast-fed babies body concentrations of dioxin-like compounds exceed those of adults after about four to six months of breast feeding, and continue to increase above the concentration in the mother if breast feeding continues. While no direct health consequences have yet been established in babies receiving dioxin-like compounds in breast milk at concentrations generally found, the concern about breast milk adds to the reasons for recommending a precautionary approach.

Recommendation 2: A goal of ongoing reduction in population body burdens of dioxin-like compounds should be stated.

International evidence suggests that population exposures in Europe and North America have been decreasing over time as a result of dioxin source and emission reduction programs. Limited evidence suggests that population body burdens have also reduced in New Zealand. In fact, population body burdens of dioxin-like compounds in New Zealand are currently somewhat lower than reported for Europe and North America. Nevertheless, the precautionary approach should include goals of further population exposure reduction for the reasons stated in Recommendation 1 above. The goal might be a reduction somewhere in the range of 3–7.5% per year. Over a 10-year period, body burdens would then fall to about 50–75% of current values. Population exposure reductions require reductions in sources and emissions based on the New Zealand source inventory.

Recommendation 3: Identifying a tolerable daily intake is not recommended.

The WHO recently lowered its TDI to a target of 1 pg TEQ/kg bw/day. Unfortunately, a large proportion of the general population in North America and Europe, and a large number of New Zealanders, exceed this daily intake. In addition, the TDI was set by the WHO with a very small margin of safety. An intake of around 1 pg TEQ/kg bw/day would result in many people achieving body concentrations within a factor of 10 of the concentrations producing effects in animals. It is important to note that if small animal studies produce 'statistically significant' effects at certain dose levels which are real effects, then larger studies in future with a wider range of dose points will find effects at even lower concentrations. And humans could be more susceptible than the animals used in these studies.

Since exposures in recent years in New Zealand have resulted in body concentrations associated with high cancer risks, and with small margins of safety from effect levels in animals, it can be said that recent intakes of dioxin-like compounds in the New Zealand population have not been 'tolerable'. Furthermore, based on cancer risk estimates and margin-of-safety concepts, an intake appropriately labeled 'tolerable' would be very much lower than current intakes, perhaps of the order of 10 or more times lower. Since we do not believe it to be helpful to set a TDI which would be currently exceeded by the large majority of the population, we recommend that no TDI be set, but that a plan for ongoing reduction in body burdens should be stated (Recommendation 2).

Recommendation 4: A health exposure criterion should be established to regulate point sources of exposure.

Regulatory decisions concerning point sources of exposure to dioxin-like compounds should be consistent with the long-term goal of population exposure reduction. As such, they should be based on the existing population burden of these contaminants. Therefore a health exposure criterion (HEC) within the context of the public health risk assessment approach should be established to regulate point sources of exposure. An HEC could be based on the following:

(a) **Class 1 Category**
Zero tolerance for additional population exposure, which could be achieved by having an offset programme. Permitting any new point source would include the permit applicant contributing to costs of reducing exposures from other sources of dioxin-like compounds present in the exposed community.

(b) **Class 2 Category**
Since offset programs are cumbersome to administer, and in view of the apparent reduction in population burdens of dioxin-like compounds that have been occurring in New Zealand in recent years, a modest increased dioxin burden could be allowed for point sources. Thus, an HEC could be set at 5%, 10% or 20% of the current average population burden of dioxin-like compounds among New Zealand adults for the plausible maximally exposed person from the point source. An HEC of one of these should not interfere with the long-term goal of population dioxin burden reduction. For example, if the overall population burden reduction is 5% per year, and if the HEC were set at 10% of the current average population burden, then an increment of 10% in exposure of some people due to the new activity would be counterbalanced in two years by the overall reductions in other sources of exposure.

Taking the above into account, we recommend that for the purpose of developing New Zealand policy on dioxin-like compounds, these chemicals be placed in the Class 2 category.

Recommendation 5: Application of the HEC should involve consideration of the plausible maximally exposed person from the point source activity.

The goal is reduction in population burdens of dioxin-like compounds in real people. Hence, risk assessments to establish potential human exposure from point sources should involve realistic assumptions of what is likely to occur in the real world, rather than being based on a series of improbable worst-case assumptions – as is sometimes done. The underlying goal should be to make estimates of maximum human exposure such that they would actually be confirmed in real people, if measurements could be made on them. (It should be noted that generally such measurements cannot be made, but it is the principle of realistic exposure estimation that is important.)

Recommendation 6: The New Zealand population burden of dioxin-like compounds should be monitored periodically, perhaps every 5–10 years.

New Zealand has led the world in having blood collected from a national random sample of the population for measurement of body burden of dioxin-like compounds in the general population. The pooling of blood samples from persons of similar age, sex and location is an innovative study design feature, which makes such surveys affordable. It is recommended that a similar survey be undertaken no more than 10 years from the recent one, which was conducted in 1997. The new survey could be used to monitor progress towards the overall goal of population exposure reduction to dioxin-like compounds. Further surveys should also be undertaken of concentrations of dioxin-like compounds in human breast milk.

Recommendation 7: Policies and the HEC should be reviewed after consideration of trends revealed by future population monitoring.

Population monitoring in 10 years would reveal if the overall goal of population burden reduction of dioxin-like compounds is being achieved. If it were not being achieved, then the major sources of population exposure would need to be investigated further to ascertain why. The long-term goal could be revised, based on results of scientific studies reported in the intervening years. In addition, the HEC should be reassessed based on then available health effects information, and based on the achievement or non-achievement of goals in population exposure reduction.

9 Units and abbreviations

g	gram
µg	microgram (10^{-6} grams)
µg kg^{-1}	micrograms per kilogram
µg/kg bw	micrograms per kilogram bodyweight
µg L^{-1}	micrograms per liter
ng	nanogram (10^{-9} grams)
ng kg^{-1}	nanograms per kilogram
ng/kg bw	nanograms per kilogram bodyweight
ng/kg bw/day	nanograms per kilogram bodyweight per day
ng L^{-1}	nanograms per liter
pg	picogram (10^{-12} grams)
pg/kg bw/day	picograms per kilogram bodyweight per day
fg	femtogram (10^{-15} grams)
fg m^{-3}	femtograms per cubic meter
2,3,7,8-TCDD	2,3,7,8-tetrachlorodibenzo-p-dioxin. Also abbreviated simply as TCDD.
2,4,5-T	2,4,5-trichlorophenoxyacetic acid
2,4-D	2,4-dichlorophenoxyacetic acid
Ah receptor	aryl hydrocarbon receptor
ALDE	average lifetime daily exposure
ATSDR (USA)	Agency for Toxic Substances and Disease Registry
BMD	benchmark dose
BMI	body mass index
bw	bodyweight
CI	confidence interval
COT (UK)	Committee on the Toxicity of Chemicals in Food, Consumer Products and the Environment
DNA	deoxyribonucleic acid
DSA	delayed spatial alternation
DTH	delayed-type hypersensitivity
ED	effective dose
HEC	health exposure criterion
IARC	International Agency for Research on Cancer
I-TEQ	international toxic equivalents
LED	lower limit on effective dose
LMS	linearized multistage
LOAEL	lowest observable adverse effect level

LOD	limit of detection
MAFF (UK)	Ministry of Agriculture, Fisheries and Food
MLE	maximum likelihood estimate
MRL	minimal risk level
NIOSH (USA)	National Institute for Occupational Safety and Health
NOAEL	no observable adverse effect level
OCDD	octachlorodibenzo-p-dioxin
PCBs	polychlorinated biphenyls
PCDDs	polychlorinated dibenzo-p-dioxins
PCDD/Fs	collectively the PCDDs and PCDFs
PCDFs	polychlorinated dibenzofurans
PCP	pentachlorophenol
RL	discrimination-reversal learning
RfD	reference dose
RsD	risk-specific dose
SMR	standardized mortality ratio
STS	soft-tissue sarcoma
TDI	tolerable daily intake
TEF	toxic equivalency factor
TEQ	toxic equivalents
UNEP	United National Environment Programme
US EPA	United States Environmental Protection Agency
WHO	World Health Organization

10 Glossary

Adverse effect	A biochemical change, functional impairment or pathologic lesion that affects the performance of a whole organism, or reduces an organism's ability to respond to an additional environmental challenge.
Agent Orange	A 1:1 mixture of the n-butyl esters of 2,4,5-T and 2,4-D used as a defoliant in Vietnam. The mixture contained varying amounts of 2,3,7,8-TCDD as a contaminant, at concentrations as high as approximately 100 mg kg^{-1}.
Ah receptor	A protein molecule expressed on the surface of many cells (both mammalian and non-mammalian). Its primary function in the body is uncertain, but it is structurally related to many other important cell proteins involved in, for instance, rhythmic functions and organ development. When TCDD or other dioxin-like compounds bind to this protein, it causes biochemical changes in the cell, including the stimulation of aryl hydrocarbons (the source of the term 'Ah').
ALDE	Average lifetime daily exposure: the measure of exposure estimated from serum PCDD/F concentrations that reflect historic and current exposures from all routes. Under steady-state conditions, ALDE estimates represent a time-integrated lifetime exposure.
Background exposure	The exposure a person might be expected to have if they are not exposed to any particular identifiable source, such as living near a point source or working in an occupational setting where exposures may occur.
Benchmark dose	The benchmark dose (BMD) is usually defined as the lower confidence limit on the dose that produces a specified magnitude of changes in a specified adverse response. For example, a BMD_{10} would be the dose at the 95% lower confidence limit on a 10% response, and the benchmark response would be 10%. The BMD is determined by modeling the dose-response curve in the region of the dose-response relationship where biologically observable data are feasible.
Body burden	The concentration of a contaminant in the body. Often expressed as an amount per mass of body weight (e.g. ng/kg bw).
Carcinogen	A chemical capable of inducing cancer.
Chloracne	A particular type of acne on the face, neck, chest, back and extremities, which is often prolonged (it may last for decades) and may recur after remission. It is associated with chlorinated chemicals, particularly the PCDDs, PCDFs and PCBs.

Cohort	A group or groups of people who have had a common exposure (e.g. exposure to a toxicant suspected of causing a disease) and are followed forward from exposure to outcome.
Dioxin	A generic term used to describe, collectively, the PCDDs and PCDFs. Sometimes also used for specific reference to 2,3,7,8-TCDD, which is considered to be the reference congener for the PCDD and PCDF family of compounds.
Dioxin-like compounds	A generic term used to describe the PCDDs, PCDFs and dioxin-like PCBs (i.e. it includes the 'dioxins').
Dioxin-like PCBs	The non-*ortho* and *mono*-ortho PCB congeners that elicit dioxin-specific biochemical and toxic responses by interaction with the Ah receptor.
Dose-response relationship	The quantitative relationship between the amount of exposure to a toxicant and the incidence of the adverse effects.
Effective dose (ED)	The dose that corresponds to an increase, expressed as a percent response, in relation to expected levels of an adverse effect and can be defined as a percent increase over background rates or a percent increase between background and maximal rates. ED_{01} is the dose corresponding to a 1% increase in an adverse effect.
Endpoint	In relation to a toxicity study, this means a particular toxic effect, such as cancer in a particular organ.
Environmental media	Media present in our environment. Includes abiotic media such as soil, water, sediment and air, and biotic media.
Epidemiology	The investigation of factors that determine the frequency, distribution and spread of disease or other health-related conditions within human populations.
Genotoxic	A specific adverse effect on the genome of living cells that, upon duplication of the affected cells, can be expressed as a mutagenic, clastogenic or carcinogenic event because of specific alteration of the molecular structure of the genome.
Half-life	A measure of the time required to eliminate one half of a quantity of a chemical from the body or from an environmental medium.
Health exposure criterion (HEC)	An estimated level of exposure to a hazardous substance that can be used for developing regulatory measures and public policy to manage ongoing population exposures to that substance. When used in the context of a public health risk assessment approach, the HEC is directly related to the existing background exposure of the population to the substance being considered.

Immune system toxicity (immunotoxicity)	The occurrence of adverse effects on the immune system that may result from exposure to environmental agents, such as chemicals.
In vitro	Isolated from the living organism and artificially maintained, as in a test tube (literally 'in glass').
In vivo	Occurring within the living organism.
Latency	The delay that is often seen between a period of exposure to an environmental agent or hazardous substance, and the onset of a toxic response, most commonly cancer. Development of tumors may occur decades after the exposure believed to be responsible has occurred.
LOAEL	Lowest observable adverse effect level: the lowest exposure of a chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed group and its appropriate control group.
Lower limit on effective $dose_{01}$ (LED_{01})	The 95% lower confidence limit of the dose of a chemical needed to produce a 1% increase of an adverse effect in those exposed to the chemical, or a 1% of the maximal response, relative to control.
Margin of safety	The ratio between a derived exposure level that is considered to be without an appreciable risk of an adverse health effect and the estimated exposure of a population.
Minimal risk level (MRL)	An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse non-cancer health effects over a specified route and duration of exposure. MRLs are derived using the NOAEL/LOAEL plus safety factor approach. Generally, MRLs established by the ATSDR are based on the most sensitive chemical-induced endpoint considered to be of relevance to humans.
Mortality	Death. The mortality rate is the number of deaths in a population during a specified interval of time.
Neurobehavioral toxicity	A toxic effect on the behavior or development of an organism, such as learning or socializing skills.
NOAEL	No observable adverse effect level: the dose of a chemical in a study, or a group of studies, at which there are no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed group and its appropriate control group. Effects may be produced at this dose, but they are not considered to be adverse.
Pharmacokinetics	The quantitative description of the fate of an exogenous substance in an organism. It involves the processes of absorption, distribution, metabolism and excretion (metabolism and excretion equal elimination) of the substance by the organism.

Ranch Hand	'Ranch Hand' refers to the US military servicemen who served as Air Force Operation Ranch Hand or Army Chemical Corps members in Vietnam, and were directly involved in the application of Agent Orange (and other herbicides).
Reference dose (RfD)	An estimate of a daily oral exposure to the human population that is likely to be without appreciable risk of deleterious effects during a lifetime. A RfD can be derived from a NOAEL, LOAEL or benchmark dose, with uncertainty factors applied to reflect limitations of the data used. RfDs are generally used by the US EPA in their non-cancer health assessments. In this context, a RfD is not itself an action level, nor does it establish an acceptable daily dose. Their primary use is to evaluate increments of exposure from specific sources above background when background exposures are low and insignificant.
Reproductive toxicity	A toxic effect related to reproductive performance. This broad term includes effects on fertility and reproductive outcomes such as birth deformities or behavioral/development effects which result following exposures of parents. Exposures may be prior to mating (to both males and females), and/or during gestation and lactation (to mothers of the offspring examined).
Risk-specific dose (RsD)	A chronic daily intake of a chemical that can be interpreted to result in a specific cancer risk, e.g. one in one million. In the derivation of a RsD, the US EPA use probabilistic estimates of cancer potency (such as the linearized multistage model), treating cancer as a non-threshold effect.
Tolerable daily intake (TDI)	An estimate of the amount of a contaminant in food or drinking water that can be ingested daily over a lifetime without a significant health risk. The term is used frequently in WHO health assessments. The term 'tolerable' is used as contaminants do not serve an intended function and as intake is unavoidably associated with the basic consumption of food and water. Tolerable does not generally indicate 'acceptable'. TDIs are usually derived using the NOAEL/LOAEL plus safety factor approach.
Toxic equivalency factor (TEF)	The relative toxicity of a dioxin-like compound compared to the toxicity of 2,3,7,8-TCDD.
Toxic equivalents (TEQ)	The toxic potency of a mixture of dioxin-like compounds in terms of 2,3,7,8-TCDD equivalents. The TEQ of a mixture is the sum of the products of the concentration of each congener present in the mixture with that congener's TEF.

Appendix: New Zealand population exposure data

Table A1 PCDD/F concentrations in the plasma of former New Zealand timber treatment workers with occupational exposure to PCP

	Concentration (ng kg^{-1}, lipid weight basis)			
	Sample 1 (Age: 34 years)	**Sample 2 (41 years)**	**Sample 3 (44 years)**	**Sample 4 (61 years)**
2,3,7,8-TCDD	1.86	4.69	2.30	< 3
1,2,3,7,8-PeCDD	5.11	19.5	11.0	9.88
1,2,3,4,7,8-HxCDD	3.05	13.3	21.0	22.4
1,2,3,6,7,8-HxCDD	28.3	154	252	274
1,2,3,7,8,9-HxCDD	4.22	31.0	26.6	15.6
1,2,3,4,6,7,8-HpCDD	27.9	258	447	223
OCDD	342	2370	2390	6990
2,3,7,8-TCDF	< 1	< 0.5	< 1	< 5
1,2,3,7,8-PeCDF	< 0.3	< 1	< 1	< 2
2,3,4,7,8-PeCDF	2.48	7.66	6.62	7.50
1,2,3,4,7,8-HxCDF	2.54	7.89	10.8	7.24
1,2,3,6,7,8-HxCDF	2.99	14.7	20.1	14.1
2,3,4,6,7,8-HxCDF	< 0.5	2.74	3.38	2.82
1,2,3,7,8,9-HxCDF	< 0.9	< 2	< 2	< 3
1,2,3,4,6,7,8-HpCDF	6.75	19.2	36.3	41.6
1,2,3,4,7,8,9-HpCDF	< 4	< 1	< 3	< 4
OCDF	< 10	< 3	< 7	< 10
I-TEQ (including ½ LODs)	10.6	45.9	51.9	53.9

Table A2 Estimated daily dietary intake of PCDD/Fs and PCBs for an adult male New Zealander with a 10.8 MJ/day median energy intake[1]

Composite food group	Amount eaten (g/day)	PCDD/F concentration[1] (ng TEQ kg^{-1})	PCDD/F intake (pg TEQ kg^{-1})	PCB concentration[1] (ng TEQ kg^{-1})	PCB intake (pg TEQ kg^{-1})	PCDD/F/PCB intake (pg TEQ kg^{-1})
Beef meat	109.6	0.0086	0.94	0.0065	0.71	1.65
Sheep meat	27.7	0.0092	0.25	0.0044	0.12	0.38
Pork meat	26.2	0.021	0.55	0.030	0.79	1.34
Beef fat	14.5	0.12	1.67	0.064	0.93	2.60
Sheep fat	4.3	0.042	0.18	0.016	0.069	0.25
Pork fat	6.5	0.027	0.18	0.036	0.23	0.41
Liver	13.2	0.070	0.92	0.033	0.44	1.36
Processed meat	80.7	0.016	1.29	0.014	1.13	2.42
Milk	278.1	0.0026	0.72	0.0019	0.53	1.25
Butter	10.5	0.090	0.95	0.12	1.26	2.21
Cheese	18.9	0.025	0.47	0.036	0.68	1.15
Ice cream/yoghurt	38.9	0.019	0.74	0.0055	0.21	0.95
New Zealand fish	32.4	0.034	1.10	0.050	1.62	2.72
Imported tinned fish	5.3	0.15	0.77	0.15	0.80	1.56
Shellfish	9.9	0.030	0.30	0.028	0.28	0.57
Poultry	45.5	0.0087	0.40	0.0035	0.16	0.56
Eggs	33.9	0.014	0.47	0.0093	0.32	0.79
Bread	151.3	0.0064	0.97	0.0036	0.54	1.51
Cereals	106.5	0.011	1.13	0.0023	0.24	1.37
Potatoes	119.3	0.022	2.62	0.0022	0.26	2.89
Snack foods	14.6	0.042	0.61	0.014	0.20	0.82
Vegetable fats/oils	10.3	0.041	0.42	0.013	0.13	0.56
Total intake (pg TEQ/day)			17.7		11.7	29.3
Total intake (pg TEQ/kg bw/day)[2]						0.37

1. Concentrations on a wet weight basis. Includes half LODs for non-detected congeners. TEQ based on the 1997 WHO TEFs (Van den Berg *et al.* , 1998).

2. For an 80 kg adult male.

Table A3 Estimated daily dietary intake of PCDD/Fs and PCBs for an adolescent male New Zealander with a 21.5 MJ/day (90th centile) energy intake[1]

Composite food group	Amount eaten (g/day)	PCDD/F concentration[1] (ng TEQ kg^{-1})	PCDD/F intake (pg TEQ kg^{-1})	PCB concentration[1] (ng TEQ kg^{-1})	PCB intake (pg TEQ kg^{-1})	PCDD/F/PCB intake (pg TEQ kg^{-1})
Beef meat	218.1	0.0086	1.88	0.0065	1.42	3.29
Sheep meat	27.6	0.0092	0.25	0.0044	0.12	0.38
Pork meat	17.4	0.021	0.37	0.030	0.52	0.89
Beef fat	14.5	0.12	1.67	0.064	0.93	2.60
Sheep fat	4.3	0.042	0.18	0.016	0.069	0.25
Pork fat	6.5	0.027	0.18	0.036	0.23	0.41
Liver	26.3	0.070	1.84	0.033	0.87	2.71
Processed meat	142.9	0.016	2.29	0.014	2.00	4.29
Milk	922.7	0.0026	2.40	0.0019	1.75	4.15
Butter	21.6	0.090	1.94	0.12	2.59	4.54
Cheese	37.7	0.025	0.94	0.036	1.36	2.30
Ice cream/yoghurt	77.5	0.019	1.47	0.0055	0.43	1.90
New Zealand fish	64.5	0.034	2.19	0.050	3.23	5.42
Imported tinned fish	10.5	0.15	1.52	0.15	1.58	3.10
Shellfish	19.8	0.030	0.59	0.028	0.55	1.15
Poultry	60.4	0.0087	0.53	0.0035	0.21	0.74
Eggs	33.7	0.014	0.47	0.0093	0.31	0.79
Bread	301.1	0.0064	1.93	0.0036	1.08	3.01
Cereals	309.9	0.011	3.28	0.0023	0.71	4.00
Potatoes	395.9	0.022	8.71	0.0022	0.87	9.58
Snack foods	48.6	0.042	2.04	0.014	0.68	2.72
Vegetable fats/oils	13.7	0.041	0.56	0.013	0.18	0.74
Total intake (pg TEQ/day)			37.2		21.7	58.9
Total intake (pg TEQ/kg bw/day)[2]						0.84

1. Concentrations on a wet weight basis. Includes half LODs for non-detected congeners. TEQ based on the 1997 WHO TEFs (Van den Berg *et al*., 1998).
2. For a 70 kg adolescent male.

Table A4 Mean concentrations of PCDD/Fs in the serum of New Zealanders, by age

Congener	Concentration (ng kg^{-1} lipid weight basis)[1]				
	15–24 yrs	25–34 yrs	35–49 yrs	50–64 yrs	65+ yrs
2,3,7,8-TCDD	1.0	1.4	2.0	3.1	4.6
1,2,3,7,8-PeCDD	2.6	3.4	4.7	5.8	7.2
1,2,3,4,7,8-HxCDD	1.3	1.9	3.0	3.5	4.4
1,2,3,6,7,8-HxCDD	8.3	15.2	21.7	26.3	33.6
1,2,3,7,8,9-HxCDD	2.6	3.4	4.1	4.9	6.1
1,2,3,4,6,7,8-HpCDD	21.7	32.3	38.6	47.3	53.3
OCDD	227	320	385	411	455
2,3,7,8-TCDF	nc	nc	nc	nc	0.3
1,2,3,7,8-PeCDF	nc	nc	nc	nc	nc
2,3,4,7,8-PeCDF	2.3	2.9	4.0	5.0	6.1
1,2,3,4,7,8-HxCDF	1.3	1.6	2.1	2.7	3.3
1,2,3,6,7,8-HxCDF	1.5	2.0	2.5	3.2	3.7
2,3,4,6,7,8-HxCDF	0.5	0.7	0.8	1.0	0.9
1,2,3,7,8,9-HxCDF	nc	nc	nc	nc	nc
1,2,3,4,6,7,8-HpCDF	nc	nc	5.9	4.8	nc
1,2,3,4,7,8,9-HpCDF	nc	nc	0.3	nc	nc
OCDF	nc	nc	nc	nc	nc
Sum of PCDD/Fs (including ½ LODs)	287	399	487	526	589
Sum of PCDD/Fs (LODs = 0)	270	387	474	518	582
Total PCDD/F TEQ (including ½ LODs)	6.69	9.27	12.6	16.1	20.7
Total PCDD/F TEQ (LODs = 0)	6.54	9.18	12.6	16.1	20.7

1. For any individual congener, calculation of the mean includes half LOD values. TEQ based on the 1997 WHO TEFs (Van den Berg *et al*., 1998).

nc Not calculated. Mean concentration not reported if a congener was never or only infrequently detected in the samples.

Source: Buckland *et al*., 2001

Table A5 Mean concentrations of PCBs in the serum of New Zealanders, by age

Congener	Concentration (µg kg^{-1} lipid weight basis)[1]				
	15–24 yrs	**25–34 yrs**	**35–49 yrs**	**50–64 yrs**	**65+ yrs**
PCB #126	0.014	0.019	0.023	0.035	0.045
PCB #169	0.010	0.015	0.023	0.027	0.030
PCB #74	nc	nc	nc	4.7	7.5
PCB #118	nc	nc	nc	4.9	7.0
PCB #153	9.1	16.1	25.2	32.6	36.6
PCB #138 + PCB #158	5.6	10.6	15.9	20.9	24.2
PCB #187	nc	nc	5.2	7.2	8.5
PCB #180	7.3	13.5	22.2	28.1	30.9
PCB #170	nc	nc	9.3	11.6	12.7
PCB #194	nc	nc	nc	5.1	5.9
Sum of PCBs (including ½ LODs)	170	172	210	219	237
Sum of PCBs (LODs = 0)	20.8	44.9	81.8	118	139
	Concentration (ng TEQ kg^{-1} lipid weight basis)[2]				
Total PCB TEQ (including ½ LODs)	5.90	5.80	6.50	7.60	9.20
Total PCB TEQ (LODs = 0)	1.50	2.00	2.70	4.80	6.50

1. For any individual congener, calculation of the mean includes half LOD values.
2. TEQ based on the 1997 WHO TEFs (Van den Berg *et al*., 1998).

nc Not calculated. Mean concentration not reported if a congener was never or only infrequently detected in the samples.

Source: Buckland *et al*., 2001

Table A6 Derivation of body burdens of PCDD/Fs and PCBs and estimation of average lifetime daily exposures for the New Zealand population

Sex	Age (years)	Serum concentration (ng TEQ kg^{-1} lipid weight basis)			Bodyweight[1] (kg)	Skinfolds[1,2] (mm)	Fat content[3] (%)	PCDD/F and PCB body burden (ng TEQ/kg bw)			PCDD/F and PCB ALDE[4] (pg TEQ/kg bw/day)		
		Min.	Max.	Mean				Min.	Max.	Mean	Min.	Max.	Mean
Male	15–24	9.71	15.7	12.9	74.6	26.3	12.9	1.25	2.02	1.66	0.35	0.57	0.47
	25–34	11.9	17.1	14.3	81.5	32.8	16.2	1.93	2.76	2.32	0.54	0.78	0.65
	35–49	16.8	22.8	18.7	83.1	34.3	19.6	3.29	4.47	3.66	0.93	1.3	1.0
	50–64	20.1	27.0	23.1	84.6	35.7	20.8	4.19	5.62	4.80	1.2	1.6	1.4
	65+	22.7	31.3	25.3	75.2	31.6	18.7	4.25	5.85	4.73	1.2	1.6	1.3
Female	15–24	10.9	13.4	12.4	64.6	41.8	25.0	2.73	3.34	3.10	0.77	0.94	0.87
	25–34	14.1	18.7	15.5	68.6	48.2	27.4	3.86	5.11	4.25	1.1	1.4	1.2
	35–49	17.8	22.9	19.5	70.7	51.8	31.0	5.51	7.11	6.06	1.6	2.0	1.7
	50–64	23.6	35.1	24.3	72.7	55.4	32.1	7.59	11.3	7.80	2.1	3.2	2.2
	65+	30.4	38.5	33.9	65.7	42.7	31.1	9.45	12.0	10.6	2.7	3.4	3.0
Average all data								1.25	12.0	4.90	0.35	3.4	1.4

1. Bodyweight and skinfold measurements taken from the New Zealand Ministry of Health's National Nutrition Survey data (Russell *et al*., 1999). The serum concentrations were determined on a subgroup of the Survey sample frame.
2. Total for two skinfold measurements (triceps and subscapular).
3. Fat content derived from data for the sum of four skinfold measurements as reported in Shils and Young (1988). Because the New Zealand data are for the sum of two skinfold measurements, this will underestimate the fat content and hence body burden estimates reported in this table.
4. Average lifetime daily exposure (ALDE) calculated from: *Intake (ng/kg bw/day) = body burden (ng/kg bw) x (ln(2)/half-life)/f* where ln(2) is the natural logarithm of 2 (which equals 0.693) the half-life is taken as 7.5 years (2737.5 days) and f, the fraction of intake dose that is absorbed, is assumed to be 0.9.

Table A7 Concentrations of PCDD/Fs in the plasma of New Zealand men

	Concentration range (ng kg^{-1}, lipid weight basis)[1]		
	20–29 years (n=4)	**30–39 years (n=5)**	**40–60 years (n=5)**
2,3,7,8-TCDD	< 1–< 4	1.4–< 3	< 1–3.2
1,2,3,7,8-PeCDD	< 2–4.4	3.1–< 10	2.6–6.5
1,2,3,4,7,8-HxCDD	1.2–< 4	2.1–< 10	1.6–4.5
1,2,3,6,7,8-HxCDD	13.0–30.5	17.9–49.7	16.5–87.1
1,2,3,7,8,9-HxCDD	2.0–7.7	3.0–7.1	2.6–7.8
1,2,3,4,6,7,8-HpCDD	33.9–123	48.0–109	42.0–175
OCDD	344–1680	383–1560	274–899
2,3,7,8-TCDF	0.70–< 3	< 0.3–< 0.2	< 0.3–< 0.2
1,2,3,7,8-PeCDF	< 0.3–< 0.2	< 0.4–< 2	< 0.4–< 0.7
2,3,4,7,8-PeCDF	1.4–< 4	2.5–< 6	1.6–3.3
1,2,3,4,7,8-HxCDF	1.0–< 5	1.9–< 10	< 2–3.0
1,2,3,6,7,8-HxCDF	1.5–< 5	2.1–< 10	< 1–< 4
2,3,4,6,7,8-HxCDF	< 0.8–< 4	< 1–< 20	0.81–< 2
1,2,3,7,8,9-HxCDF	< 0.8–< 5	< 1–< 4	< 0.6–< 2
1,2,3,4,6,7,8-HpCDF	3.6–14.5	6.1–12.1	3.8–9.7
1,2,3,4,7,8,9-HpCDF	< 0.5–< 2	< 0.8–< 10	< 0.5–< 2
OCDF	< 2–< 10	< 4–< 100	< 2–< 5
I-TEQ (including ½ LODs)	4.69–13.4 (mean = 8.32)	8.40–16.7 (mean = 12.7)	7.24–19.8 (mean = 11.9)
WHO TEQ (including ½ LODs)[2]	4.63–14.1 (mean = 9.02)	9.60–17.9 (mean = 14.3)	8.12–22.5 (mean = 13.4)

1. The range of congener concentrations and I-TEQ data for each age group taken from Hannah *et al.* (1994).
2. WHO TEQs recalculated using the 1997 WHO TEFs (Van den Berg *et al*., 1998) from unpublished data for the individual samples. TEQ levels include half LODs for non-detected congeners.

Table A8 Concentrations of PCDD/Fs in the plasma of New Zealand women

	Concentration range (ng kg^{-1}, lipid weight basis)[1]		
	20–29 years (n=4)	**30–39 years (n=5)**	**40–60 years (n=5)**
2,3,7,8-TCDD	< 1–2.3	1.4–< 3	1.7–5.8
1,2,3,7,8-PeCDD	2.4–5.0	2.3–10.3	< 3–< 7
1,2,3,4,7,8-HxCDD	< 1–4.0	1.9–5.6	1.7–5.1
1,2,3,6,7,8-HxCDD	10.7–26.3	16.4–47.1	21.9–37.5
1,2,3,7,8,9-HxCDD	2.4–6.6	3.0–8.3	4.2–8.3
1,2,3,4,6,7,8-HpCDD	34.4–84.5	63.0–122	62.2–123
OCDD	296–962	546–1390	524–829
2,3,7,8-TCDF	< 0.5–< 0.7	< 0.4–< 1	< 0.4–< 1
1,2,3,7,8-PeCDF	< 0.5–< 1	< 0.5–< 0.7	< 0.3–< 2
2,3,4,7,8-PeCDF	1.6–3.3	1.5–7.8	2.6–54.2
1,2,3,4,7,8-HxCDF	1.8–3.1	1.3–< 5	< 2–19.2
1,2,3,6,7,8-HxCDF	1.7–3.5	1.3–< 5	< 2–< 10
2,3,4,6,7,8-HxCDF	< 1–< 2	< 0.8–< 3	0.79–< 10
1,2,3,7,8,9-HxCDF	< 2	< 0.9–< 3	< 0.8–< 5
1,2,3,4,6,7,8-HpCDF	4.2–14.7	3.6–11.2	5.0–14.6
1,2,3,4,7,8,9-HpCDF	< 1–< 2	< 0.6–< 3	< 0.7–< 4
OCDF	< 3–< 7	< 2–< 10	< 2–< 20
I-TEQ (including ½ LODs)	4.86–13.0 (mean = 8.20)	7.33–19.1 (mean = 13.5)	8.41–42.8 (mean = 19.4)
WHO TEQ (including ½ LODs)[2]	5.27–14.6 (mean = 9.10)	7.72–23.5 (mean = 15.2)	8.65–44.6 (mean = 20.6)

1. The range of congener concentrations and I-TEQ data for each age group taken from Hannah *et al.* (1994).
2. WHO TEQs recalculated using the 1997 WHO TEFs (Van den Berg *et al*., 1998) from unpublished data for the individual samples. TEQ levels include half LODs for non-detected congeners.

Table A9 Concentrations of PCDD/Fs in the breast milk of New Zealand women from the 1987/88 breast milk study, by geographic region

	Individual sample concentration (ng TEQ kg^{-1} milk fat)[1,2]			
	Auckland (urban)	**Christchurch (urban)**	**Northland (rural)**	**North Canterbury (rural)**
	6.2	40	19	17
	16	29	18	17
	7.8	16	18	39
	19	11	32	26
	16	23	14	25
	14	15	30	17
	17	20	15	25
	34	12	11	23
	25	33	22	
	24			
	14			
Mean TEQ level	18	22	20	24

1. TEQ based on the 1997 WHO TEFs (Van den Berg *et al*., 1998). TEQ levels include half LODs for non-detected congeners.
2. Original PCDD/F congener data from which the TEQ levels have been calculated taken from Bates *et al*. (1990).

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About the authors

Allan Smith

Dr Allan Smith is Professor of Environmental Epidemiology in the School of Public Health at the University of California at Berkeley. Allan was born and raised in New Zealand, obtaining a bachelor's degree in mathematics and chemistry at Victoria University in Wellington, followed by an MB, ChB and a PhD in epidemiology at the University of Otago Medical School.

As a Senior Lecturer in the Department of Community Health at the Wellington School of Medicine in the early 1980s, Allan carried out a number of the early epidemiological studies concerning the herbicide 2,4,5-T, which contained dioxin.

In 1983 Allan was appointed Professor of Epidemiology at Berkeley, from where he continued to teach and conduct research into environmental epidemiology issues. This included a particular focus on quantitative risk assessment and continuing research into health issues associated with dioxins. Amongst other activities, Allan was a participant in the international working group, convened in 1997 by the International Agency for Research on Cancer, to evaluate the carcinogenic risks to humans of dioxins. He chaired the epidemiology component of that assessment. Allan was also an external peer reviewer for both the 1994 and the 2000 US EPA draft dioxin reassessment reports.

Allan is widely recognized as one of the world's leading researchers into the relationship between inorganic arsenic in water supplies and various health effects, particularly cancer. He is a consultant to the World Health Organization in regard to the arsenic issue, and is currently running studies in Chile, Argentina, Bangladesh, India, California and Nevada.

Professor Smith was recently President of the International Society for Environmental Epidemiology.

Peggy Lopipero

Peggy Lopipero has a Masters in Public Health from the University of California at Berkeley and over 10 years experience in the fields of toxicology and epidemiology. Her work has concentrated on critical qualitative and quantitative reviews of the medical and toxicological literature for a multitude of environmental and occupational carcinogens, including dioxins. She has conducted meta-analyses and dose-response assessments using both human and animal data and has reviewed over 250 health risk assessments produced as part of the California Air Toxics 'Hot Spots' Programme.

In addition to her work with UC Berkeley, Peggy has worked as an independent consultant in environmental health for the past eight years. Current and past clients consist of the legal profession, public health organizations, environmental and engineering consulting firms, the Swiss state and federal government, California Environmental Protection Agency, and the University of California.