Ministry for the Environment
Manatū Mō Te Taiao

Toxicological Intake Values for Priority Contaminants in Soil

New Zealand Government

This report may be cited as: Ministry for the Environment. 2011. *Toxicological Intake Values for Priority Contaminants in Soil*. Wellington: Ministry for the Environment.

Published in June 2011 by the
Ministry for the Environment
Manatū Mō Te Taiao
PO Box 10362, Wellington 6143, New Zealand

ISBN: 978-0-478-37238-0

Publication number: ME 1056

Other publications in this series include:
Methodology for Deriving Standards for Contaminants in Soil to Protect Human Health

This document is available on the Ministry for the Environment's website:
www.mfe.govt.nz

Acknowledgements

This work was prepared as Landcare Research Contract Reports LC0708/129 and LC0809/101. We would like to thank Dr Jo-Anne Cavanagh for her extensive toxicological literature review and thorough draft recommendations on toxicological intake values for priority contaminants, and Dr Sim Ooi (Chadwick T&T, Australia) and Dr Peter DiMarco (Golder, Australia) for reviewing the draft reports.

Thanks to the members of the Toxicological Advisory Group ("ToxAG"), who considered and discussed the content and agreed on the final recommendations. The following people worked with Ministry staff to form the "ToxAG": Natalia Foronda (Ministry of Health); Chris Geering and Jim Waters (Environmental Risk Management Authority); and John Reeve (New Zealand Food Safety Authority).

Thanks also to the following people, who participated in the "ToxAG" in a non-decision-making function: Graeme Proffitt (Pattle Delamore Partners); Nick Kim (Environment Waikato); and Gerald Rys (Ministry for Agriculture and Forestry).

Finally, thanks to Alistair Bingham (JCL Air and Environment) and Kerry Laing (Tonkin and Taylor) for providing data on dioxin concentrations in PCP formulations and soil in New Zealand.

Contents

Executive Summary viii

1 Introduction 1

1.1 Background to toxicological criteria used in the derivation of soil contaminant standards 1

2 Priority Contaminants 8

2.1 Arsenic (As) 8
2.2 Boron (B) 19
2.3 Cadmium (Cd) 23
2.4 Chromium (Cr) 33
2.5 Copper (Cu) 44
2.6 Lead (inorganic) (Pb) 51
2.7 Mercury (inorganic) (Hg) 62
2.8 Benzo(a)pyrene (BaP) 68
2.9 DDT 84
2.10 Dieldrin 92
2.11 Pentachlorophenol (PCP) 97
2.12 Dioxins and dioxin-like polychlorinated biphenyls (PCBs) 106

Appendix 119

Acronyms and Glossary 120

References 125

Tables

Table S1:	Summary of toxicological intake values for threshold priority contaminants	ix
Table S2:	Summary of toxicological intake values for non-threshold priority contaminants	ix
Table 1:	HSNO classification of arsenic metal	9
Table 2:	Summary of oral reference health standards for arsenic as a threshold contaminant, used by different international agencies	13
Table 3:	Summary of oral reference health standards for arsenic as a non-threshold contaminant, used by different international agencies	14
Table 4:	Summary of the health effects of arsenic	17
Table 5:	Recommended toxicological criteria for arsenic	19
Table 6:	HSNO classification of boric acid	20
Table 7:	Summary of oral reference health standards for boron as a threshold contaminant, used by different international agencies	21
Table 8:	Summary of the health effects of boron	22
Table 9:	Recommended toxicological criteria for boron	23
Table 10:	HSNO classification of cadmium (II), as cadmium nitrate	26
Table 11:	Summary of oral reference health standards for cadmium as a threshold contaminant, used by different international agencies	29
Table 12:	Summary of cadmium health effects in animals and humans (ATSDR, 1999)	32
Table 13:	Recommended toxicological criteria for cadmium	33
Table 14:	HSNO classification of chromium (III) chloride	36
Table 15:	HSNO classification of chromium (VI) as sodium dichromate dihydrate	36
Table 16:	Summary of oral reference health standards for total chromium as a threshold contaminant, used by different international agencies	38
Table 17:	Summary of oral reference health standards for chromium (III) as a threshold contaminant, used by different international agencies	38
Table 18:	Summary of oral reference health standards for chromium (VI) as a non-threshold contaminant, used by different international agencies	39
Table 19:	Summary of oral reference health standards for chromium (VI) as a threshold contaminant, used by different international agencies	40
Table 20:	Summary of the health effects of chromium (III) in animals and humans	42
Table 21:	Summary of the health effects of chromium (VI) in animals and humans	43
Table 22:	Recommended toxicological criteria for chromium	44
Table 23:	HSNO classification of copper as copper (II) sulphate	46
Table 24:	Summary of oral toxicological intake values for copper as a threshold contaminant, used by different international agencies	47
Table 25:	Summary of the health effects of copper in animals and humans	50
Table 26:	Recommended toxicological criteria for copper	51
Table 27:	HSNO classification of lead, as lead chloride	54
Table 28:	Summary of oral reference health standards for lead as a threshold contaminant, used by different international agencies	58
Table 29:	Summary of effects associated with lead, as measured by blood lead concentrations (modified from ATSDR, 2007)	60

Table 30:	Recommended toxicological criteria for inorganic lead	62
Table 31:	HSNO classification of metallic mercury and mercury as mercuric chloride	63
Table 32:	Summary of oral reference health standards for inorganic mercury, based on total mercury, as a threshold contaminant, used by different international agencies	65
Table 33:	Summary of oral reference health standards for inorganic mercury as a threshold contaminant, used by different international agencies	65
Table 34:	Summary of the health effects of inorganic mercury	67
Table 35:	Recommended toxicological criteria for inorganic mercury (excluding elemental mercury)	68
Table 36:	HSNO classification of benzo(a)pyrene	70
Table 37:	Summary of oral reference health standards for benzo(a)pyrene, used by different international agencies or developed in the scientific literature	72
Table 38:	Summary of oral reference health standards for benzo(a)pyrene in a PAH mixture, used by different international agencies or developed in the scientific literature	74
Table 39:	Risk estimates for BaP determined by different international agencies, developed in the scientific literature or derived in the current study, with and without allometric cross-species scaling	77
Table 40:	Carcinogenicity classifications of selected PAHs by different sources	81
Table 41:	Potency equivalence factors used by various agencies	81
Table 42:	Summary of the health effects of benzo(a)pyrene	83
Table 43:	Recommended toxicological criteria for benzo(a)pyrene	84
Table 44:	Recommended PEFs for use in assessing potential carcinogenicity of PAH mixtures	84
Table 45:	Summary of oral reference health standards for DDTs as a threshold contaminant, used by different international agencies	88
Table 46:	Summary of oral reference health standards for DDTs, as a non-threshold contaminant, used by the US EPA	89
Table 47:	Summary of the health effects of DDT, DDE, and DDD	91
Table 48:	Recommended toxicological criteria for ∑DDT	92
Table 49:	Summary of oral reference health standards for dieldrin as a threshold contaminant, used by different international agencies	95
Table 50:	Summary of oral reference health standards for dieldrin as a non-threshold contaminant, used by different international agencies	95
Table 51:	Summary of the health effects of dieldrin in animals and humans	96
Table 52:	Recommended toxicological criteria for dieldrin	97
Table 53:	HSNO classification of pentachlorophenol	99
Table 54:	Summary of oral reference health standards for pentachlorophenol as a threshold contaminant, used by different international agencies	102
Table 55:	Summary of oral reference health standards for pentachlorophenol as a non-threshold contaminant, used by different international agencies	103
Table 56:	Summary of the health effects of pentachlorophenol	104
Table 57:	Recommended toxicological criteria for pentachlorophenol	105
Table 58:	Comparison of TEFs for dioxins established at various times	109
Table 59:	Summary of oral reference health standards for dioxins and furans (as TEQ) as a threshold contaminant, used by different international agencies	112

Table 60:	Summary of oral reference health standards for dioxins and dioxin-like compounds as non-threshold contaminants, established by the US EPA	113
Table 61:	Summary of dietary intakes of dioxins and dioxin-like PCBs for an adult male and adolescent male	115
Table 62:	Summary of the health effects of TCDD	116
Table 63:	Recommended toxicological criteria for dioxins	117
Table 64:	Recommended TEFs for dioxins and dioxin-like PCBs	118
Table A1:	CAS numbers and additional details on chemical names for the contaminants considered in this report	119

Executive Summary

Fourteen contaminants were identified by the National Environmental Standards Technical Reference Group in 2005 as of high priority for developing human-health-based soil contaminant standards, $SCSs_{(health)}$, for New Zealand. These contaminants comprised seven metals and metalloids (arsenic, cadmium, copper, chromium, lead, mercury, boron), three hydrocarbons (total petroleum hydrocarbons, benzene, benzo(a)pyrene), three chlorinated pesticides (dieldrin, DDTs, pentachlorophenol) and polychlorinated dibenzo-*p*-dioxins, polychlorinated dibenzo-*p*-furans (collectively dioxins) and selected (dioxin-like) polychlorinated biphenyls (dioxin-like PCBs).

This document presents recommendations for toxicological intake values for 12 of these priority contaminants. Toxicological intake values describe a concentration at which substances might pose no appreciable risk or minimal risk to human health depending on the substance being considered. Specifically:

- *Threshold* substances are those for which it is possible to identify a level of exposure at or below which they do not produce an adverse effect; toxicological intake values typically prescribe a daily level of exposure over a lifetime where there is no appreciable risk to human health.
- *Non-threshold* substances, which include most carcinogens, pose an inherent risk at any level of exposure. For these values the toxicological intake values describe a level of exposure for which there is considered to be minimal risk. This may be determined from quantitative risk modelling for risk levels of 1 in 100,000 or application of a default factor of 10,000 to estimates of the lower 95% confidence limit ($BMDL_{10}$) of the benchmark dose that gives rise to a 10% response (BMD_{10}) and consideration of the use of allometric scaling to account for inter-species differences.

These recommendations are based on a literature review of the toxicity of contaminants, and reference health standards (RHS) developed by various international agencies. The term "reference health standards" is used in this report to refer to any value, set by a regulatory or advisory body, that provides an estimated daily (sometimes weekly or monthly) amount of a substance that can be taken into the body either without any, or with minimal additional, risk of detrimental health effects occurring (based on available scientific information).

Additionally, estimates of the background exposure (primarily from food and water) of New Zealanders for the priority threshold contaminants are made based on the most recent New Zealand Total Diet Survey[1] and information on the chemical quality of drinking water.[2] Exposure to non-threshold contaminants is based on an agreed acceptable increase in risk, and therefore exposure from all sources should be limited as much is reasonably practicable. It is considered that exposure to each source is managed by this principle, therefore it is irrelevant in the context of developing soil contaminant standards.

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[1] Vannoort RW, Thomson BM. 2005. *2003/2004 New Zealand Total Diet Survey*. New Zealand Food Safety Authority: Wellington.

[2] Davies H, Nokes C, Ritchie J. 2001. A report on the chemical quality of New Zealand's community drinking water supplies. *ESR Technical Report FW0120*. Ministry of Health: Wellington.

Toxicological intake values for the inhalation route are not considered as inhalation will be a negligible route of exposure for non-volatile or semi-volatile contaminants.

The recommended toxicological intake values and background exposures are shown in Tables S1 and S2, with a summary of the bases for the recommendations provided below.

Table S1: Summary of toxicological intake values for threshold priority contaminants

Contaminant	Oral (µg/kg bw/day) unless stated otherwise	Skin absorption factor	Background exposure (µg/kg bw/day) unless otherwise stated	
			Child	Adult
Cadmium – daily	0.8 25 µg/kg bw/month	0.001	0.41 12.5 µg/kg bw/month	0.26 7.9 µg/kg bw/wmonth
Copper	150	NA	56	20
Chromium III	1500	NA	1.2[a]	0.53[a]
Chromium VI	3	NA	No data	No data
Lead	1.9	NA	0.97	0.41
Mercury	2	NA	0.05	0.065
Boron	200	NA	80	17
Dieldrin	0.05	0.1	0.0036	0.0014
∑DDT (complex)	0.5	0.018	0.051	0.019
Pentachlorophenol	0.3	0.24	0.02	0.02
Dioxins and dioxin-like PCBs	30 pg TEQ/kg bw/month	0.02 (PCDDs) 0.05 (PCDFs) 0.07 (PBCs)	10 pg (I-TEQ)/kg bw/month	10 pg (I-TEQ)/kg bw/month

NA – not applicable, TEQ – toxic equivalents

a Based on recommended nutritional intake for chromium

Table S2: Summary of toxicological intake values for non-threshold priority contaminants

Contaminant	Oral risk-specific dose (µg/kg bw/day)	Inhalation risk-specific dose (µg/kg bw/day)	Skin absorption factor
Arsenic	0.0086	NA	0.005
Benzo(a)pyrene	0.0048	NA	0.026

Arsenic (As) – Arsenic is considered to be a non-threshold contaminant with internal cancers, such as bladder and liver cancers, the most sensitive endpoints. Estimates of carcinogenic potency are primarily derived from human epidemiological data from exposure via drinking water. A daily risk-specific dose of 0.0086 micrograms per kilogram bodyweight (µg/kg bw), derived from the arsenic concentration in drinking water determined to represent "negligible risk" by Canadian agencies (0.3 micrograms per litre, µg/L), is recommended. This value is based on the most current risk modelling data, and includes an external comparison population. Dermal absorption is considered to be negligible, although the skin absorption factor of 0.5% could be used as a refinement in the development of soil contaminant standards.

Cadmium (Cd) – Cadmium is considered to be a threshold contaminant, with kidney damage as a result of long-term exposure considered the most sensitive endpoint. Unlike for most other substances, toxicokinetic modelling has typically been used to estimate tolerable intakes. Given the long-term effects of cadmium, it is more appropriate to express intakes as monthly intakes. The Joint Expert Committee on Food Additives (JECFA) of the Food and Agriculture

Organization (FAO) and the World Health Organization (WHO) recommend a provisional tolerable monthly intake (PTWI) of 25 μg/kg bw and it is recommended that this value is used for the derivation of soil contaminant standards. Dermal absorption is expected to be negligible, although a dermal absorption factor of 0.0012 could be used. Dietary intake is the primary source of background exposure to cadmium and was estimated to be 12.5 μg/kg bw/month for a child (aged 1–3 years, 13 kg) and 7.9 μg/kg bw/month for an adult.

Chromium (Cr) – Chromium in its trivalent state is an essential element, but at high concentrations, and particularly in its hexavalent state, it is toxic. There is limited data on which to base tolerable daily intakes for chromium. The United States Environmental Protection Agency (US EPA) recommends a toxicological intakes of 1,500 μg Cr(III)/kg bw/day and 3 μg Cr(VI)/kg bw/day and these values are recommended for use in New Zealand. Dermal absorption of chromium (III) is expected to be a negligible route of exposure for soil contamination and is not considered relevant here. It is recommended that the adverse effects arising from dermal exposure to chromium (VI) are considered separately to those arising from oral exposure and that allergic contact dermatitis is the main effect of interest. A soil contaminant standard protective from allergic contact dermatitis could be established, but as these effects are likely to be elicited at higher concentrations than those arising from oral exposure, a soil contaminant standard protective against effects arising from oral exposure will also protect against allergic contact dermatitis. Estimates of dietary intake of chromium (III) are based on nutrient reference values for different age groups from the US Institute of Medicine (IOM) as recommended by the Australian National Health and Medical Research Council (NHMRC).

Copper (Cu) – Copper is an essential element, and adverse effects can arise both from copper deficiency and from excess copper intake. Liver damage is the critical endpoint for intake of high levels of copper in animal and human studies. The tolerable upper limit of 10 mg/day, based on liver function and converted using a 70-kg bodyweight, is used to derive a toxicological intake value of 0.15 mg/kg bw/day. Dermal absorption and inhalation are expected to be negligible routes of exposure and are not considered relevant for soil contamination. Dietary intake is the primary source of background exposure to copper. Estimated dietary intake for a child aged 5–6 years was 0.06 mg/kg bw/day and for an adult (25–44 years) was 0.02 mg/kg bw/day, which is within the recommended dietary intake for copper.

Lead (Pb) – The most significant critical effect of low concentrations of lead is considered to be reduced cognitive development and intellectual performance in children. The JECFA was the only authoritative body that had previously derived a tolerable intake for lead; the PTWI of 25 μg/kg bw/week, and the TDI derived from this, has been the value most widely used by different international agencies. However, this value has been recently withdrawn. A toxicological intake of 1.9 μg/kg bw/day is instead recommended to be used in the derivation of soil contaminant standards in New Zealand. This intake is based on dose-response modelling by JECFA and is the dietary intake at which the IQ decreases 3 points in the population. This general shift in distribution was deemed to be of concern by JECFA, although the effects were considered to be insignificant at an individual level. Exposures of individuals are more relevant in the context of contaminated sites. Inhalation exposure and dermal absorption are expected to be negligible, and could be ignored in the derivation of soil contaminant standards for contaminated land in New Zealand, as has been done by other jurisdictions. Dietary intake is the primary source of background exposure to lead and was estimated to be 0.97 μg/kg bw/day for a child and 0.41 μg/kg bw/day for an adult.

Inorganic mercury (Hg) – Inorganic mercury is considered to be a threshold contaminant, with renal effects in rats considered the most sensitive endpoint. A tolerable daily intake of

2 μg/kg bw/day is recommended as this is the value most widely used by different international agencies. Inhalation exposure is expected to be negligible on contaminated sites due to limited volatility of the forms of mercury likely to be present (mercury II). Dermal absorption is also expected to be negligible. Dietary intake, in particular seafood, and dental amalgam are the primary sources of background exposure to mercury. Dietary intakes of inorganic mercury were estimated to be 0.05 μg/kg bw/day for a child and 0.025 μg/kg bw/day for adults. Intake from dental amalgam was considered to be negligible for children and 0.04 μg/kg bw/day for adults, giving rise to a total inorganic mercury intake of 0.065 μg/kg bw/day for adults.

Boron (B) – Boron is considered to be a threshold contaminant, with foetal weight decrease in rats the most sensitive endpoint. A tolerable daily intake of 0.2 mg/kg bw, based on benchmark dose modelling in two studies by the US EPA, is recommended. Inhalation exposure and dermal absorption of boron are expected to be negligible and are not considered relevant here. Dietary intake is expected to be the primary source of background exposure to boron and, in the absence of information specific to New Zealand, it is recommended that TDIs of 0.08 mg/kg bw for children and 0.017 mg/kg bw for adults, based on international data, are used.

Benzo(a)pyrene (BaP) – Benzo(a)pyrene is considered to be a genotoxic carcinogen, and therefore is a non-threshold contaminant. An oral-risk-specific dose of 0.0048 μg/kg bw/day (slope factor of 2.08 per mg/kg bw/day) is recommended for use. This value is the geometric mean of 14 $BMDL_{10}$ estimates from four studies divided by 10,000 and allometric scaling, maximising the use of available data. A dermal absorption of 0.026 (2.6%) is recommended for use. BaP is considered representative of a range of carcinogenic polycyclic aromatic hydrocarbons (PAHs), and potency equivalence factors (PEF) are used to estimate the potential carcinogenicity of environmental PAH mixtures. A consistent set of PEFs is recommended to enable assessment of potential carcinogenicity of PAH mixtures through comparison with a BaP-equivalent soil contaminant standard in New Zealand. Further, it is recommended that the range of PAHs routinely analysed is expanded to include additional PAHs considered carcinogenic by FAO/WHO.

Dieldrin – Dieldrin is a threshold contaminant, with the liver being the critical target of chronic toxicity in several animal species. Most jurisdictions have adopted the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) value for ADI of 0.1 μg/kg bw/day, based on hepatotoxicity in rats, and this is recommended for use in New Zealand. No dermal absorption data is available for dieldrin; hence, it is recommended that an absorption factor of 0.1 is used. The dietary intake for a child aged 1–3 years was estimated to be 0.0036 μg/kg bw/day and for an adult, 0.0014 μg/kg bw/day, while intake from drinking water is negligible.

∑DDT – DDT and its derivatives DDE and DDD are considered to be threshold contaminants, given the equivocal data on their genotoxicity. These substances enhance liver enzyme production, are weakly hormone disrupting, and act on the central nervous system. Ideally, toxicological criteria for DDT should be based on data regarding the effects of DDE, because it is the primary metabolite found in the environment. However, insufficient data is available to do so – other than to note that toxicologically the adverse effects of DDE and DDT are similar – hence criteria are set based on the effects of DDT. In line with a number of international agencies, an oral TDI of 0.5 μg/kg bw/day, based on hepatotoxicity in rats, is recommended for use in New Zealand. A dermal absorption of 0.018 (1.8%) is recommended for use. Dietary intake of DDT residues is considered to be the primary source of exposure. The dietary intakes of ∑DDT for a child aged 1–3 years are 0.0511 μg/kg bw/day and for an average adult 0.0193 μg/kg bw/day, while intake from drinking water is negligible.

Pentachlorophenol (PCP) –While there appears to be reasonable evidence of carcinogenic effects in humans arising from exposure to PCP, there is weak evidence of genotoxicity and it seems more plausible a non-genotoxic mechanism is responsible for carcinogenic effects. As such, it is recommended that PCP be considered a threshold contaminant, with an additional uncertainty factor of 10 applied to the TDI derived by Baars et al (2001)[3] to account for the observed carcinogenicity of PCP. This TDI is used, as it uses the most sensitive relevant toxicological endpoint (decreased thyroid hormones) from available data and appropriate uncertainty factors. This gives rise to a recommended tolerable daily intake of 0.3 μg/kg bw. Inhalation exposure is likely to be negligible on contaminated sites due to the low volatility of PCP. However, PCP is indicated to be readily absorbed dermally and an absorption factor of 0.24 is recommended. No data is available on food intake of PCP, and no PCP was detected in drinking water supplies. In circumstances where no data is available on background exposure, it has been agreed to allocate 5% of TDI allocated to background exposure; as such, background exposure is 0.02 μg/kg bw/day. These criteria (Table S1) are applicable to exposure to PCP only, and are not necessarily protective of effects associated with the contaminants of technical-grade PCP, such as the polychlorinated dibenzo-*p*-dioxins and polychlorinated dibenzofurans, which should be considered separately.

Dioxins and dioxin-like PCBs – Dioxins and dioxin-like polychlorinated-biphenyls (PCBs) are considered to be threshold contaminants, with developmental effects on the reproductive system in male offspring of exposed pregnant females considered the most sensitive toxicity endpoint. These effects are also considered to be protective against carcinogenic effects of dioxins. The maximum monthly intake value of 30 pg TEQ/kg determined by the Ministry of Health is recommended, for consistency between New Zealand agencies. Further it is recommended that toxic equivalency factors (TEFs) developed by WHO[4] for individual dioxins and dioxin-like PCBs are used to calculate toxic equivalent doses (TEQs), as these are based on the latest re-evaluation by WHO, and thus are likely to become the international standard. Inhalation exposure to dioxins and dioxin-like PCBs is likely to be negligible on contaminated sites, due to their low volatility. Dermal absorption of these compounds is dependent on the physicochemical properties of the individual congeners. It is recommended that dermal factors of 0.02, 0.05 and 0.07 are used as conservative estimates of dermal absorption of PCDDs, PCDFs and dioxin-like PCBs, respectively. Dietary intake is the primary source of background exposure to dioxins and dioxin-like PCBs and was estimated to be 0.33 pg/kg bw/day or 10.0 pg I-TEQ/kg bw/month for an adult, and is extended to children.

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[3] Baars AJ, Theelen PJCM, Janssen JM, van Apeldorn ME, Meijrink MCM, Verdam L, Zeilmaker MJ. 2001. Re-evaluation of human-toxicological maximum permissible risk levels. *RIVM Report 711701 025.* National Institute of Public Health and the Environment: Bilthoven, The Netherlands.

[4] WHO. 2005. *Project for the Re-evaluation of Human and Mammalian Toxic Equivalency Factors (TEFs) for Dioxin and Dioxin-like Compounds.* Retrieved from http://www.who.int/ipcs/assessment/tef_update/en/ (February 2009).

1 Introduction

The Ministry for the Environment has confirmed a comprehensive policy framework for managing contaminated land in New Zealand. As part of this, a Technical Advisory Group (TecAG) has been set up to develop a national methodology for deriving and applying national soil contaminant standards (SCSs) designed to protect the health of New Zealanders. A critical part of the derivation of $SCSs_{(health)}$ is the use of toxicological criteria. A Toxicology Advisory Group (ToxAG) has been set up to provide recommendations to TecAG regarding toxicological criteria appropriate for use in the development of national $SCSs_{(health)}$ for New Zealand.

This document serves as a technical reference in support of the Ministry for the Environment's *Methodology for Deriving Standards for Contaminants in Soil to Protect Human Health* (2011). It presents a review of the toxicology literature, and recommendations for toxicological criteria for priority contaminants in soil. The term 'soil contaminant standards' to protect human health, or $SCSs_{(health)}$, specifically refers to soil contaminant concentrations that are mandatory under the *National Environmental Standard for Assessing and Managing Contaminants in Soil to Protect Human Health*. When talking about generic numerical values in guidelines or foreign jurisdictions, the term 'soil guideline values' (SGVs) is used.

This review briefly describes the toxicological status of the contaminants (ie, their mode of action and effects) and summarises reference health standards already considered by international agencies, especially those that have developed soil guideline values. "Reference health standards" (RHS) is used in this report to refer to any value set by a regulatory or advisory body that provides an estimated daily (sometimes weekly or monthly) amount of a substance that can be taken into the body either without any, or an unacceptable additional, risk of detrimental health effects occurring (based on available scientific information). "Toxicological intake value" (TIV) is used specifically for values recommended for use in New Zealand. Dermal absorption and background exposure to contaminants are also considered.

The information and recommendations presented in this document have been endorsed by the Toxicology Advisory Group.

1.1 Background to toxicological criteria used in the derivation of soil contaminant standards

1.1.1 Mode of action

When their effects on human health are being considered, contaminants are often referred to as either threshold or non-threshold contaminants. Threshold contaminants are those considered to manifest toxic effects only if exposure exceeds a threshold dose level, and include (by convention) non-genotoxic carcinogens and non-carcinogens. A variety of toxicological criteria have been derived by organisations worldwide for chemicals displaying threshold critical toxicity. The most well established of these, and most universally adopted in chemical risk assessment programmes, is the tolerable daily intake (TDI) that was originally used for contaminants within foodstuffs by the Joint Food and Agriculture Organization (FAO)/World Health Organization (WHO) Expert Committee on Food Additives (JECFA). The TDI is defined as an estimate of the amount of a contaminant – expressed on a bodyweight basis, eg, mg/kg bw/day – that can be ingested daily over a lifetime without appreciable health risk (based on the available scientific information). The

term “Acceptable Daily Intake” (ADI) is also used by JECFA and is also an estimate of the amount of a substance – expressed on a bodyweight basis, eg, milligrams per kilogram bodyweight per day (mg/kg bw/day) – that can be ingested daily over a lifetime without appreciable health risk (based on the available scientific information). The ADI is applied to food additives and veterinary drug residues, while the TDI is used for contaminants and naturally occurring toxicants. The United States Environmental Protection Agency (US EPA) uses largely the same methodology as JECFA/WHO but has adopted the terms “reference dose” (RfD, for oral and dermal exposure) and “reference concentrations” (RfC, for inhalation exposures instead of TDI or ADI), though using a very similar definition. US EPA (2009) defines RfD as an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive groups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The US Agency for Toxic Substances and Disease Registry (ATSDR), which is responsible for preparing toxicological profiles for priority hazardous substances commonly found at contaminated sites in the Unites States, derives minimal risk levels (MRLs) using a similar methodology to TDIs, RfDs and RfCs. Minimum risk levels are defined as 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, and are typically derived for each of chronic, intermediate (up to one year), and acute exposure (eg, ATSDR, 2007).

Non-threshold contaminants conventionally include genotoxic carcinogens, and are considered to have effects at all levels of exposure. Different organisations have used different approaches to determine the potency of non-threshold contaminants and potency is typically expressed either as (1) a slope factor (US) or maximum likelihood estimate, both of which are the increased risk per daily dose, or (2) a risk-specific dose (Canada) or index dose (UK), which is an estimate of the amount of a contaminant, expressed on a bodyweight basis, eg, mg/kg bw/day, that can be ingested daily over a lifetime with a minimal or negligible increase in risk. These values are typically obtained by dividing the acceptable increased risk level by the slope factor, although they may also be obtained by dividing a specified dose that produces a certain response by a given factor (eg, NHMRC, 1999; EA, 2008). Various approaches to estimation of carcinogenic potency have been adopted by different international agencies, although recent guidance has converged on the use of linear extrapolation from a point of departure from the dose-response curve with the $BMDL_{10}$ (the lower bound of a 95th confidence interval on a benchmark dose (BMD) corresponding to a 10% tumour incidence), the favoured point of departure (eg, EFSA, 2005; US EPA, 2005a; EA, 2009). However, a significant difference between US and Canadian agencies and other international agencies appears to be that the US EPA and Canadian agencies typically apply allometric cross-species scaling to cancer potency estimates derived from animal studies (US EPA, 2005a), while a number of European agencies, WHO, and Australian agencies do not (eg, NHMRC, 1999; Kroese et al, 2001 citing Health Council of Netherlands, 1994; EFSA, 2005; FAO/WHO 2006; EA, 2008).

The classification of carcinogens as genotoxic or non-genotoxic refers to their mode of action. Genotoxic carcinogens are those that act by causing damage to genetic materials and generally have effects at all levels of exposure (ie, non-threshold contaminants). In contrast, non-genotoxic carcinogens do not act on genetic material and are considered to have a threshold above which toxic effects are manifested (ie, threshold contaminants). This is the approach adopted in several current New Zealand government publications (eg, MfE and MoH, 1997; MoH, 2005). However, more recent understanding of the mechanisms of carcinogenesis leads to a blurring of the boundaries between genotoxicity and non-genotoxicity. For example, a carcinogen may elicit genotoxicity due to indirect action on DNA, and have a dose-response that is non-linear and most similar to a threshold response.

Recent guidance from the US EPA (2005a) addresses this difficulty in empirically distinguishing between a true threshold and a non-linear low-dose relationship by using a slightly different definition to distinguish between different modes of action of carcinogens. Specifically, the US EPA (2005a) defines three scenarios: (1) a linear dose-response is assumed if the carcinogen is DNA-reactive and directly mutagenic, or activity displays linearity at low doses, or there is insufficient evidence to define an alternative mode of action; (2) a non-linear dose-response is appropriate when there is sufficient data to ascertain the mode of action and conclude it is not linear at low doses and the substance is not mutagenic or displays other activity that would suggest linearity of response; (3) both linear and non-linear approaches may be used when there are multiple modes of action.

For the purposes of this report, the terms "non-threshold" and "threshold" are used. Non-threshold contaminants refer to substances for which the dose-response is demonstrated to be linear or there is insufficient evidence to indicate non-linearity – including genotoxic carcinogens that act both directly *and* indirectly with DNA. Threshold contaminants include those substances for which dose-response is demonstrated to be non-linear at low doses or which exhibit a threshold for response – including non-genotoxic carcinogens.

As noted above, different agencies have adopted different approaches to the use of allometric scaling to account for inter-species differences in deriving cancer potency estimates. The decision to use allometric scaling to account for inter-species differences in this report is made on a case-by-case basis.

The US EPA (2005b) also provides guidance around considerations for early life-exposure to carcinogens. The view of the Toxicological Advisory Group is that this is complex and further consideration is needed to determine the contaminants for which it would be appropriate to apply this approach and the additional factors that should be applied. Consequently, it has not been used in this report.

Finally, contaminants may elicit both carcinogenic (typically non-threshold) and non-carcinogenic (typically threshold) effects. Typically the most sensitive toxicological endpoint is used to set the final value (based on comparison of the dose associated with the acceptable excess lifetime risk level (risk-specific dose) with the TDI or equivalent).

1.1.2 Acceptable risk level

An acceptable risk level is often used to define the acceptable increased risk associated with exposure to non-threshold contaminants. In New Zealand, an acceptable increased risk level of 1 in 100,000 was first used in the national drinking water standards (MoH, 1995) and this has since been adopted in a number of government publications (eg, MfE and MoH, 1997; MoH, 2005). This falls in the "mid-range" of acceptable risk levels used by international agencies, which range from one in a million (eg, US, Canada) to 1 in 10,000 (The Netherlands).

There are numerous approaches and models that have been used to estimate carcinogenic potency, yielding markedly different estimates (EFSA, 2005). More recently there has been a tendency to move towards simple linear extrapolation from a point of departure on the dose-response curve to the origin (eg, Kroese et al, 2001; US EPA, 2005; EA, 2008). Typically, the benchmark dose approach is used and a BMD_{10} (the dose that gives rise to a 10% response) or $BMDL_{10}$ (the lower 95% confidence limit of the BMD_{10}) is used as the point of departure in an appropriate animal carcinogenicity study, although other doses, eg, BMD_{05}, BMD_{25}, may be used (NHMRC, 1999; EFSA, 2005). A variety of models may be used to estimate the BMD/L_{10}

of interest (NHMRC, 1999; IPCS, 2004; US EPA, 2005). This approach is less well developed for use with human cancer data, and traditional quantitative risk models may need to be used.

More recent guidance from European agencies and WHO for non-threshold contaminants often do not specify an acceptable risk level *per se*, but focus either on the margin of exposure (MOE, the ratio of the $BMDL_{10}$ to the estimated intake in humans) (EFSA, 2005; FAO/WHO, 2006) or application of a large default factor to the $BMDL_{10}$ (EA, 2009). The magnitude of the MOE is then subject to consideration as to what constitutes an acceptable level of risk, with the EFSA (2005) stating that an MOE of 10,000 or more is of low concern from a public health point of view. This factor (10,000) is the default factor applied to a critical $BMDL_{10}$ derived from animal studies in UK guidance (EA, 2008), and is equivalent to calculating a risk-specific dose for an excess lifetime cancer risk of 1 in 100,000 from the $BMDL_{10}$ using low-dose linear extrapolation. Where dose-response modelling of human data is used, estimates of the dose corresponding to an excess lifetime cancer risk of 1 in 100,000 are used (EA, 2009).

The consensus of the Toxicology Advisory Group was that the acceptable increased risk level should remain at 1 in 100,000 ($=10^{-5}$) or that, where appropriate, a default factor of 10,000 could be applied to $BMDL_{10}$ values to derive toxicological intake values for non-threshold contaminants (taking account of the need to use allometric scaling for inter-species differences or not, as noted above). It is recognised that in most cases in New Zealand, selection of appropriate carcinogenic potency estimates for a given contaminant will be based on the available literature as opposed to the derivation of values *per se*. Thus, these recommendations provide some guidance as to the preferential selection of carcinogenic potency estimates.

Finally, to facilitate comparison of different estimates of the potency of non-threshold substances in this document, where slope factors are used, a toxicological intake value (risk-specific dose) has been calculated assuming an acceptable risk level of 10^{-5}.

1.1.3 Background exposure

People may be exposed to contaminants from sources such as food, air and water; collectively this exposure from other sources is termed background exposure. For the majority of contaminants of concern from land contamination, the background exposure will primarily be from food and water.

Exposure to non-threshold contaminants is based on an agreed acceptable increase in risk, and therefore exposure should be limited as much as reasonably practicable. It is assumed that exposure from other sources (food, air, water) is also similarly controlled by the same principle. Therefore, background exposure is not taken into account for non-threshold contaminants.

For threshold contaminants, different countries have taken different approaches, which can be grouped into three main approaches:

- Background exposure is ignored – this is a non-conservative approach.
- Background exposure may be taken into account by subtracting the estimated background exposure from the tolerable daily intake, and the residual amount used to derive the soil guideline value.
- A proportion of the TDI may be allocated to exposure from soil.

Canadian agencies combine the latter two approaches by subtracting the background exposure from the TDI, and then allocating 20% of this residual TDI to exposure from soil (with air, water, food and consumer products also assigned 20%) (CCME, 2006). The UK protocol also

combines these approaches, but where the estimated background exposure is less than 50% of the TDI, all the residual amount is allocated to exposure from soil. Where the estimated background exposure is more than 50% of the TDI, 50% of the TDI is allocated to exposure from soil (EA, 2009). In New Zealand, three contaminant-focussed publications about contaminated land (MfE, 1997; 1999; MfE and MoH, 1997) assign 100% of the TDI as being from soil sources and do not consider background or dietary intakes, with an exception made in the case of copper (MfE and MoH, 1997), where only 10% of the TDI is assigned to soil sources. The allocation of 10% is nominally based on the approach adopted in the relevant *Drinking Water Guidelines* (MoH, 1995) and appears to be overly conservative in relation to exposure from soil sources. A fourth publication (MfE 2006) subtracted the estimated background exposure from the TDI and used the residual to calculate soil guideline values.

The Toxicology Advisory Group recommends that New Zealand adopts a variation on the UK approach (EA, 2009). Specifically, background exposure is subtracted from the TDI with the residual allocated to exposure from soil. However, in contrast to the UK approach, the Toxicology Advisory Group recommends that where background exposure comprises greater than 50% of the TDI, the proportion allocated to exposure from soil is considered on a case-by-case basis. Further, in cases where background exposure is negligible or no data on background exposure exists, the Toxicology Advisory Group recommends that a maximum of 95% of the TDI should be allocated to exposure from soil. This is expected to provide a slight degree of precaution for substances for which determining the background exposure may be problematic.

Dietary intake

Where applicable, estimates of the dietary intake of various substances are primarily based on the 2003/04 New Zealand Total Diet Survey (NZTDS) (Vannoort and Thomson, 2005) or national nutrition studies (copper only: Russell et al, 1999; MoH, 2003). Mean dietary intakes are used and are considered to represent a long-term average. Where data from the NZTDS is used, dietary intakes are provided for a child 1–3 years old and the mean of an adult male and female aged 25+. Dietary intakes provided in the national nutrition surveys are expressed as total intake, and the bodyweights provided in those reports were used to derive intakes expressed as mg/kg bw/day.

Dietary intake from water is based on data provided in a survey of the chemical quality of drinking water supplies (Davies et al, 2001), which provides details of chemical analysis of water collected from consumers' taps across New Zealand. It is noted that reviews of drinking water quality have been carried out subsequent to this survey (eg, MoH, 2006; 2007); however, the Davies et al (2001) report is the most recent that provides data in a usable manner.

1.1.4 Primary routes of exposure

At a contaminated site the oral, inhalation and dermal routes of exposure are of primary interest in deriving soil guideline values. Ingestion is generally considered to be the primary route of exposure for most contaminants of concern at contaminated sites, although inhalation and dermal absorption may also contribute to toxic effects. Where exposure via inhalation or dermal exposure contributes to a systemic response, the intakes from each of these exposure pathways can be added to the intake arising from ingestion to estimate the total intake used in derivation of soil guideline values. Where toxic effects are dependent on the route of exposure, separate soil guideline values should be derived for each route of exposure. Discussion on some general aspects of oral, inhalation and dermal exposures relevant to determining toxicological criteria

are discussed below. Further details on the derivation of soil guideline values and soil contaminant standards are discussed in MfE (2011).

Oral bioavailability

Ingestion is generally considered to be the primary route of exposure for most contaminants of concern at contaminated sites. While it is generally acknowledged that not all of the contaminants present in soil are absorbed into the human body (ie, are bioavailable), there is generally insufficient data to assume anything less than 100% bioavailability. Cadmium and lead are exceptions. The tolerable intakes established for cadmium are primarily based on toxicokinetic modelling of dietary cadmium intake, in which gastrointestinal absorption of cadmium from food in humans is considered to be in the range of 1 to10%. Various approaches have been used for lead, including the application of physiologically based toxicokinetic or other models (US EPA, 1994; DEFRA and EA, 2002) or application of a single factor to account for the reduced bioavailability of lead (Baars et al, 2001). Other agencies have assumed the lead is 100% bioavailable (NCSRP, 1996).

Further there may be differences in the bioavailability of substances used in studies to establish the tolerable intake or cancer potency factor, and soil – particularly for exposure via ingestion. For example, substances in drinking water will be more bioavailable than that substance in soil; substances in food may be more bioavailable than that same substance in soil. Further, substances administered in animal laboratory tests are likely to be more bioavailable than those substances in soil. Fasting and nutritional status may also influence oral absorption. Practically, these differences make little difference to the recommended intake as there is typically insufficient data to be able to take this factor into account quantitatively; it is generally assumed that the bioavailability of the substance is the same. However, such information enables a better assessment of the degree of conservativeness associated with the intake value when applied to the derivation of soil guideline values. This is discussed for individual contaminants where relevant in this report.

Inhalation exposure

Inhalation will be a negligible route of exposure for contaminants of limited or no volatility (semi-volatile and inorganic substances) in soil. In contrast to some occupational situations, often associated with specific industries, the amount of dust considered to be inhaled from contaminated sites typically represents a very small fraction of exposure. For example, based on inhalation parameters for New Zealand residential sites (MfE, 1997; 1999; MfE and MoH, 1997), such as inhalation rates of 3.8 m^3/day for a child, 20 m^3/day for an adult, and dust concentration of 0.026 mg/m^3 exposure, a child will inhale 0.098 mg of dust and an adult 0.52 mg. This is <0.1% of the amount of soil ingested by a child (100 mg/day) and about 2% of the soil ingested by an adult resident (25 mg/day). Similarly for industrial sites, using the parameters in MfE and MoH (1997), such as an inhalation rate of 9.6 m^3 during a working day, and a respirable dust concentration of 0.071 mg/m^3 exposure, an adult worker would inhale 0.68 mg, which is about 3% of the soil ingested. Furthermore, the majority of soil dust particles that are likely to be inhaled will be captured in the nose or throat, thus theywould actually contribute to oral exposure.

Dermal absorption

Dermal absorption of a substance may contribute to a systemic response associated with the ingestion of that substance. The skin absorption factor is the only contaminant-specific

parameter required for the dermal absorption pathway. Dermal absorption of semi-volatile and inorganic substances is considered on a case-by-case basis.

Dermal absorption of volatile organics is especially difficult to assess, because most studies have involved occluding (covering) the skin: this may give artificially high skin absorption values, since these compounds would also be expected to volatilise from the skin. The US EPA Region III recommends using a dermal absorption value of 0.05% for substances with a vapour pressure similar to that of benzene (vapour pressure approximately 95.2 mm Hg) (US EPA, 1995). This would include chemicals such as 1,1-dichloroethane 1,1,1-trichloroethane, and other volatiles with vapour pressure similar to or greater than that of benzene. For volatiles such as ethylbenzene, tetrachloroethene, toluene, and xylenes – which have vapour pressures lower than that of benzene (and less volatilisation from the skin may occur) – a default skin absorption value of 3% is recommended. These numbers are considered to only apply to non-occluded skin, which would be the scenario expected for most environmental exposures. However, if the skin is occluded for any reason, higher dermal absorption values (up to 100%) should be used.

2 Priority Contaminants

Fourteen contaminants were identified by the National Environmental Standards Technical Reference Group in 2005 as of high priority for developing soil contaminant standards (MfE, 2005). These contaminants comprised seven metals and metalloids (arsenic, cadmium, chromium, copper, lead, mercury, boron), three hydrocarbons (total petroleum hydrocarbons, benzene, benzo(a)pyrene), three chlorinated pesticides (dieldrin, DDTs, pentachlorophenol) and polychlorinated dibenzo-*p*-dioxins, polychlorinated dibenzo-*p*-furans (collectively dioxins) and selected (dioxin-like) polychlorinated biphenyls (dioxin-like PCBs). Toxicological intake values have been recommended for 12 of these contaminants and a summary of some details of these contaminants, including CAS numbers, are shown in the appendix.

2.1 Arsenic (As)

Observations of the toxicological effects of arsenic primarily come from epidemiological investigations of human populations exposed to arsenic in drinking water. Several comprehensive reviews of the toxicity of arsenic have been undertaken (NRC, 1999; 2001; EA, 2009; FPTCDW, 2006; ATSDR, 2007; Fowler et al, 2007). The discussion below summarises relevant data from these reviews. Particular attention is given to those studies that have been used in deriving reference health standards. Readers are referred to the original reviews for more details on adverse health effects.

2.1.1 Toxicological status

Arsenic exists in organic and inorganic forms. Inorganic forms, particularly trivalent forms (arsenites), are considered to be the most toxic. However, it has recently been suggested that methylated metabolites may be more toxic than previously thought (NRC, 1999; 2001; Rossman, 2003) with dimethylarsenous acid (DMA^{III}) demonstrating greater toxicity than arsenite in some bioassays.

Arsenic can cause cancerous and non-cancerous effects. A large number of the latter are associated with exposure to arsenic and include dermal lesions, pigmentation, keratoses, peripheral vascular disease (eg, blackfoot disease), and cardiovascular effects (US EPA, 2001; WHO, 2001; ATSDR, 2007). Skin lesions are considered to be a sensitive indicator of chronic arsenic exposure.

Arsenic is classified as a known human carcinogen by the International Agency for Research (IARC, 1987; 2004 – Group 1) and by the US EPA (1993 – Group A). Skin cancer is a well-documented feature in human populations exposed to arsenic via drinking water with naturally high concentrations of arsenic (WHO, 2001). More recently the US National Research Council (NRC) concluded that there was sufficient evidence from epidemiological studies that chronic ingestion of inorganic arsenic causes bladder and lung cancer, in addition to skin cancer (NRC, 1999; 2001). The increase in cancer risk observed in epidemiological studies is primarily attributed to the presence of arsenite. Any arsenate that is present is rapidly reduced to arsenite once it enters the cells (Rossman, 2003). In humans, arsenic compounds are metabolised by methylation, primarily in the liver, and it has recently been suggested that these metabolites may play a role in bladder and perhaps some other cancers (Rossman, 2003). Inhalation of arsenic primarily results in tumours in the lung (WHO, 2001).

While carcinogenicity is considered to be the primary toxicological effect of concern in humans, in animal studies carcinogenicity of arsenic is often not found. There is considerable debate over the mechanism of carcinogenicity of arsenic (eg, Basu et al, 2001; Hughes, 2002; Rossman, 2003) and, therefore, whether it should be treated as a threshold or non-threshold contaminant in the context of deriving soil guideline values. NRC (1999) concluded that the most plausible explanation for the mode of action of arsenic carcinogenesis is that it induces chromosomal abnormalities without interacting directly with the DNA. Such indirect effects are typically considered to give rise to sublinear dose responses, ie, act as a threshold contaminant. Baars et al (2001) also considered the general consensus to be that the carcinogenic action of arsenic is based on non-genotoxic mechanisms, and arsenic should, therefore, be considered a threshold contaminant. This conclusion is supported by other studies on epidemiological data relating arsenic ingestion to skin and internal cancers (eg, Rudel et al, 1996) and studies that indicate arsenic is active late in the carcinogenic process, ie, acts as a cancer promoter (Basu et al, 2001). Similarly, Mead (2005) states: "there is general agreement that arsenic does not interact directly with DNA, and that its toxic effects occur through indirect alteration of gene expression". An emerging consensus is also that arsenic is not an initiator of cancer, but rather works with other factors (eg, smoking, UV-radiation) to promote cancer (NRC, 1999; Mead, 2005).

2.1.2 New Zealand classification

The Hazardous Substances and New Organisms Act 1996 (HSNO) classification of arsenic set by the Environmental Risk Management Authority New Zealand (ERMA NZ) is shown in Table 1, but only has meaning when expressed in respect to a particular form of the element, ie, arsenic metal, whereas the form present in the environment as a soil contaminant is most likely to be arsenic oxide or a salt such as sodium arsenate/arsenite. Overall, arsenic is of relatively high toxicity (6.1B oral classification) with the following long-term endpoints: it is mutagenic (6.6B), a proven human carcinogen (6.7A), and is highly toxic from chronic exposures (6.9A). These endpoints are believed to be the most relevant findings concerning most chemical forms of arsenic likely to be encountered.

Table 1: HSNO classification of arsenic metal

Hazardous property	HSNO classification
Acute toxicity	6.1B
Skin irritation	ND
Eye irritation	ND
Sensitiser	–
Mutagenicity	6.6B
Carcinogenicity	6.7A
Reproductive/developmental toxicity	–
Target organ systemic toxicity	6.9A

ND – no classification due to no data/insufficient data/inconclusive data; – not assigned.

2.1.3 Reference health standards

Numerous studies have reported the effects of chronic exposure to arsenic in populations in regions with elevated concentrations of arsenic in drinking water. WHO (2001) cites the following places and references: Cordoba, Argentina (Arguello et al, 1938; Bergoglio, 1964), Antofagasta, Chile (Borgono et al, 1977; Zaldivar and Guiller 1977; Zaldivar et al, 1981), Mexico (Cebrian et al, 1983), and south-western Taiwan (Tseng et al, 1968; Tseng, 1977).

These epidemiological studies form the basis for the development of reference health standards by different agencies.

Normally, most arsenic in drinking water is present as the two inorganic species arsenate and arsenite, with only low proportions of various organoarsenic compounds. Of the two inorganic forms, arsenate usually dominates in oxidised (including chlorinated) waters, but the more toxic arsenite form can become dominant in some circumstances as a result of chemical reduction reactions that occur in the environment. For exposure studies of arsenic in drinking water, the total arsenic dose therefore represents the mix of arsenic species that a given population was exposed to in drinking water.

The most comprehensive dataset is that from south-western Taiwan, initially reported by Tseng et al (1968; 1977 cited in WHO, 2001) who focused on skin cancer and skin disease. As cited in NRC (1999), Chen et al (1985; 1986; 1992) and Wu et al (1989) subsequently reworked these data to examine the risk of internal cancers. This study has been recommended for risk quantification for several reasons, including the large stable population (>40,000 people) that had lifetime exposures to arsenic, pathology data collection that was "unusually thorough", and populations that were reasonably homogenous with respect to lifestyle (NRC, 2001; US EPA, 2001). Nonetheless, there are recognised weaknesses, including the use of median exposure data at the village level, the low income and relatively poor diet of the study population, and high exposures to arsenic via food. Further, NRC (2001) cites two recent studies (Ferreccio et al, 2000; Chiou et al, 2001) that are also of sufficient quality to warrant consideration in quantitative risk assessment for arsenic in drinking water.

Ingestion

Numerous agencies have derived reference health standards for the ingestion of arsenic, but have variously considered arsenic to be either a threshold or non-threshold contaminant. A summary of these values, and the bases for their derivation, are shown in Tables 2 and 3. To make it easier to compare the non-threshold values, the risk-specific dose at the acceptable excess risk level adopted in the given jurisdiction is given first, followed by that at an acceptable excess risk level of 10^{-5} (shown in brackets).

The majority of agencies that derived threshold values for arsenic based their reference health standards on the previous JECFA provisional tolerable weekly intake (PTWI) (FAO/WHO, 1988) (Table 2). This PTWI was based on a lowest observable adverse effects level (LOAEL): 25 out of 86 people had symptoms possibly associated with arsenic poisoning. However, this value was recently withdrawn (FAO/JECFA 2010) as JECFA determined that it is in the region of the benchmark dose for a 0.5% increased incidence of lung cancer ($BMDL_{0.5}$), which was determined from epidemiological studies to be 3.0 μg/kg bw per day (2–7 μg/kg bw per day based on the range of estimated total dietary exposure) using a range of assumptions to estimate total dietary exposure to inorganic arsenic from drinking water and food.

The US EPA (1993) quantitatively evaluated five epidemiological studies, including some of those evaluated by JECFA, to derive their reference dose. The US EPA (1993) ultimately considered that studies on the south-western Taiwanese population (WHO, 2001 citing Tseng et al, 1968; Tseng, 1977) were superior due to the provision of appropriate data, eg, exposure times, arsenic concentrations, and the large number of people studied. The ATSDR (2007) used an identical approach to that of the US EPA to derive its chronic oral risk level.

The majority of agencies have considered arsenic as a non-threshold contaminant. As (Table 3) shows, US EPA (1988) is the basis for the subsequent derivation of many drinking water and

soil guideline values. However, despite a common source of data being used, the toxicological intake values used by the different jurisdictions are different. Some of this discrepancy seems to arise from the original (US EPA, 1988) study itself. Specifically, this study determined that maximum likelihood estimates (MLE) of cancer risk, for a 70-kg person who consumes 2 L of water per day contaminated with 1 μg/L of arsenic, range from 3×10^{-5} (on the basis of Taiwanese females) to 7×10^{-5} (based on Taiwanese males). The midpoint of this range gives rise to the US EPA drinking water unit risk of 5×10^{-5}. The study also states the MLE of 1 μg/kg bw/day of arsenic from water ranges from 1×10^{-3} to 2×10^{-3}. The midpoint of this range gives rise to the US EPA oral slope factor of 1.5 per mg/kg bw per day. However, US EPA risk assessment guidance documents (US EPA, 1989) indicate that a drinking water unit risk can be converted to a slope factor by multiplying by bodyweight (70 kg), and dividing by the volume of water drunk (2 L) and a conversion factor (1000) to convert micrograms into milligrams. Using this latter approach gives rise to a slope factor of 1.75, which is the slope factor used by Environment Canada (1999).

WHO drinking water guidelines (pre-2003) have also based risk estimates on US EPA (1988). Specifically WHO (1996) indicates that the drinking water guideline of 10 μg/L nominally gives rise to a skin cancer risk of 6×10^{-4} based on data for males provided in US EPA (1988). This is stated to give rise to estimated lifetime skin cancer risks of 10^{-5} and 10^{-6} for arsenic concentrations of 0.17 and 0.017 μg/L, respectively. It is unclear how these are derived, as US EPA (1988) indicates that, based on data for Taiwanese males, estimated skin cancer risks for a 70-kg adult consuming 2 L per day of water containing 1 μg/L of arsenic is 7×10^{-5}, giving rise to a risk of 10^{-5} at 0.14 μg/L; arguably this difference is attributable to rounding errors. However, it should also be noted that WHO (2003) cites risk estimates from more recent studies (NRC, 2001); specifically, that the maximum likelihood estimates for the incidence of bladder and lung cancer in US populations exposed to 10 μg/L of arsenic range from 12 to 23 per 10,000, or a risk of 12×10^{-4} to 23×10^{-4}. The *New Zealand Drinking Water Guidelines* datasheet for arsenic states the old risk estimates (MoH, 2005). The WHO drinking water guideline is used in MfE and MoH (1997) to derive a slope factor for arsenic of 0.15 per mg/kg bw/day, which also takes into account a mortality rate from skin cancer of 7%.

More recent evaluations of arsenic in drinking water have focused on the risk of internal cancers, specifically bladder and lung cancers (NRC, 1999; 2001; US EPA, 2001; FPTCDW, 2006). The south-western Taiwanese population still forms the basis for new risk estimates, although data from Chen et al (1988; 1992) and Wu et al (1989) (all cited in NRC, 1999) are used instead of Tseng et al (1968) and Tseng (1977) (both cited in WHO, 2001) as the former are considered to provide better estimates of arsenic exposure and are focused on internal cancers. The risk models developed by Morales et al (2000) form the basis for dose-response models used by US EPA (2001) and Health Canada (2003, 2005) to develop risk estimates for arsenic in drinking water. The risk models used can have a marked influence on the derived risk estimates, in addition to the extrapolation of exposure data for a Taiwanese population to other populations. Both agencies used a Poisson model, a Taiwanese to Canadian/US conversion factor, and the same risk metrics to develop their risk estimates for drinking water. However, Health Canada (2005) included an external unexposed comparison population, while US EPA (2001) didn't. Their justification was that models with no comparison population were more reliable, as models with comparison populations resulted in supralinear (higher than a linear) dose-response, and there is no biological data to support a supralinear curve as being biologically plausible (US EPA, 2001). In contrast, Health Canada (2005) included a comparison population based on the recommendations of NRC (2001) and the fact that "an external comparison population is classically used in the analysis of cohort data (Breslow and Day 1987), since it provides a more accurate estimate of the baseline cancer rates and minimises

the impact of exposure misclassification in the low dose range within the study population" (FPTCDW, 2006).

The USEPA circulated a memorandum in 2008 containing a human health risk assessment relating to a decision on the re-registration eligibility of inorganic arsenicals as wood preservatives (US EPA, 2008). The human cancer risk assessment employed an oral cancer slope figure of 3.67 per mg/kg bw/day, based on earlier risk modelling by the agency in developing new rules for arsenic in drinking water. However, it is unclear as to exactly where this information was presented. From this slope factor, an extra cancer risk of 1 in 100,000 would be associated with an oral arsenic dose level of 0.003 μg/kg bw/day.

Based on recent evaluations of the carcinogenicity of arsenic, the EA (2009) considered that an oral index dose based on excess lifetime cancer risk would lie in the range of 0.0006 to 0.003 μg/kg bw/day. However, their final recommended oral index dose for deriving soil guideline values was 0.3 μg/kg bw/day, based on equivalence with the UK drinking water standard of 10 μg/L assuming 2 L/day is consumed by a 70-kg adult, to avoid disproportionately targeting soil exposures.

It is interesting to note that the risk-specific doses determined from internal cancers are higher than determined for skin cancer from US EPA (1988) (Table 3), ie, arsenic nominally has the potential to cause skin cancer at doses lower than required for internal cancers, yet internal cancers are the focus of recent studies. The rationale for this is not explicitly stated, although it may be attributable to a higher mortality rate from internal cancers. Further, NRC (1999) questioned the validity of the US EPA (1988) results in light of new information that adds more uncertainty to the data used in this report. Specifically, it has been recognised that arsenic exposure among persons and villages grouped together in the data reported in the Tseng studies is more variable than previously realised. New risk estimates are based on studies by Chen et al (1988; 1992) and Wu et al (1989) (all cited in NRC, 1999), which provide more detailed estimates for exposure; thus it is anticipated that these estimates are more robust.

Table 2: Summary of oral reference health standards for arsenic as a threshold contaminant, used by different international agencies

Jurisdiction	Tolerable daily intake (μg/kg bw)	Key study[1]	Critical effect[1]	Basis of value[1]	Reference
Joint FAO/ WHO Expert Committee on Food Additives (JECFA) – now withdrawn	2.1 (provisional tolerable weekly intake: 0.015 mg/kg bw)	Grantham and Jones (1977)	Not stated – basis was that of 33 people in Nova Scotia using water with arsenic concentrations >0.1 mg/L, 23 (70%) had mild symptoms and signs *possibly* attributable to arsenic poisoning, whereas only 25 out of 86 people (29%) consuming water with arsenic at 0.05–0.1 mg/L were similarly affected Additional epidemiological studies were used to support evidence for arsenic toxicity	JECFA (FAO/WHO, 1983) concluded that, based on the available epidemiological evidence, water supplies containing concentrations of 0.1 mg/L may give rise to presumptive signs of toxicity. An assumed daily water consumption of 1.5 L was used to convert this value to a daily intake of 0.15 mg, and a bodyweight of 75 kg converts this to a provisional daily intake of 2 μg/kg bw This value was "confirmed" by JECFA (FAO/WHO, 1988) by assigning a PTWI of 0.015 mg/kg bw, with the "clear understanding that the margin between the PTWI and intakes reported to have toxic effects in epidemiological studies was narrow"	FAO/WHO (1983; 1988)
Australia	2.1	Grantham and Jones (1977)	Not stated	FAO/WHO (1988)	NEPC (1999)
The Netherlands – current	2.1	Grantham and Jones (1977)	Not stated	FAO/WHO (1988)	Baars et al (2001)
The Netherlands – proposed[2]	1	Grantham and Jones (1977)	Not stated	FAO/WHO (1988) with an additional safety factor of 2 to account for observation errors inherent in epidemiological studies	Baars et al (2001)
US ATSDR – chronic duration MRL and US EPA	0.3	Tseng et al (1968), Tseng (1977), both cited in WHO (2001)	Hyperpigmentation, keratosis and possible vascular complications Human chronic oral exposure in drinking water	No observable adverse effect level (NOAEL) 0.009 mg/L converted[3] to 0.0008 mg/kg bw/day Uncertainty factor (UF) of 3 applied to account for both the lack of data to preclude reproductive toxicity as a critical effect and to account for some uncertainty in whether the NOAEL of the critical study accounts for all sensitive individuals	ATSDR (2007) US EPA (2005)

1 As reported in the reference cited in the reference column.

2 This value is yet to be officially adopted.

3 Conversion assumed a water intake of 4.5 L/day, a bodyweight of 55 kg, and a daily intake of 0.002 mg As/kg from food: NOAEL – [9 μg/L x 4.5 L/day + 2 μg/day (contribution of food)] x (1/55 kg) = 0.8 μg/kg bw/day.

Table 3: Summary of oral reference health standards for arsenic as a non-threshold contaminant, used by different international agencies

Jurisdiction	Acceptable risk level[a]	Guideline value (μg/L)[b]	Risk-specific dose[a] (μg/kg bw/day)	Cancer slope factor (per mg/kg bw/day)	Key study[c]	Critical effects[c]	Basis of value[b]	Reference
New Zealand	10^{-5}		0.067	0.15	WHO (1993) drinking water guideline	Skin cancer in southwestern Taiwan population	Fatal skin cancers, slope factor derived from WHO (1993) drinking water guideline (risk of 6×10^{-4} at 10 μg/L), assuming a 7% mortality rate	MfE and MoH (1997)
New Zealand drinking water	10^{-5} [d] (6×10^{-4})	10	0.0048[e]	2.1	US EPA (1988)	Skin cancer in southwestern Taiwan population	WHO (1996)	MoH (2005)
WHO drinking water	10^{-5}	10	0.0012–0.0024[f]	4.2–8	NRC (2001)	Internal cancers (lung, bladder) in southwestern Taiwan population	Practical quantification limit – incidence of bladder and lung cancer in US populations at this concentration range from $12–23 \times 10^{-4}$, based on maximum likelihood estimates from NRC (2001)	WHO (2003)
	10^{-5} [d] (6×10^{-4})	10	0.0048[d]	2.1	US EPA (1988)	Skin cancer in southwestern Taiwan population	Practical quantification limit – risk of skin cancer at this concentration is 6×10^{-4}, which is stated to give rise to estimated lifetime skin cancer risks of 10^{-4}, 10^{-5}, 10^{-6} for arsenic concentrations of 1.7, 0.17 and 0.017 μg/L, respectively	WHO (1996)
UK	10^{-5}		0.3 ($40–400 \times 10^{-5}$)[g]			Internal cancers	Based on equivalence with the UK drinking water standard of 10 μg/L assuming 2 L/day is consumed by a 70-kg adult, to avoid disproportionately targeting soil exposures	EA (2009)
Canada soil	10^{-6} [10^{-5}]		0.0006 [0.006]	1.75	Tseng et al (1968) and Tseng (1977), both cited in WHO (2001)		US EPA (1988)	Environment Canada (1999)
Canada drinking water	10^{-5} –10^{-6} [10^{-5}]	0.3	0.0086 [0.006–0.045][h]	[i]	Morales et al (2000)	Internal cancers (lung, bladder) in southwestern Taiwan population	0.3 μg/L was considered to pose negligible risk (95th confidence interval of the lifetime risk is 1.9×10^{-6} to 13.9×10^{-6}) Health Canada (2005) concluded that a Poisson model recommended by the US. EPA (2001) and fit by Morales et al (2000) with an external unexposed comparison population is the most appropriate for estimating the cancer risks associated with the ingestion of arsenic in drinking water. Health Canada (2005) adopted assumptions similar to those of the US EPA (2001) regarding the choice of risk metric and the use of a southwestern Taiwanese to Canadian conversion factor	FPTCDW (2006)

Jurisdiction	Acceptable risk level[a]	Guideline value (μg/L)[b]	Risk-specific dose[a] (μg/kg bw/day)	Cancer slope factor (per mg/kg bw/day)	Key study[c]	Critical effects[c]	Basis of value[b]	Reference
US EPA – IRIS, R6, R9	10^{-6} [10^{-5}]		0.00067 [0.0067]	1.5	US EPA (1988)	Skin cancer in southwestern Taiwan population	Quadratic-linear multi-stage model that included adjustment for larger water consumption, lower bodyweight and intake from food, in the Taiwanese population	US EPA (1998)
US EPA		10	0.01–0.045[j]	[k]	Chen et al (1985; 1988; 1992), Wu et al (1989), all cited in NRC (1999)	Internal cancers (lung, bladder) in southwestern Taiwan population	Poisson model with no comparison population, Taiwanese to US conversion, risk estimates from Morales et al (2000)	US EPA (2001)
US EPA			0.003[m]	3.67		Internal cancers (lung, bladder) in southwestern Taiwan population	Based on US EPA (2000), proposed rule for changes to the arsenic drinking water guideline	US EPA (2008)

a Where the acceptable risk level for a given jurisdiction is not 10–5, the risk-specific dose for a risk of 10^{-5} is shown in square brackets.

b Where a guideline value is provided, the risk-specific dose has been derived assuming consumption of 2 L/day by a 70-kg adult at the acceptable risk level or actual risk level if appropriate (see d).

c As reported in the reference cited in the reference column.

d Nominal acceptable risk level, actual risk level associated with the guideline value shown in parentheses.

e Calculated from the actual risk level associated with the guideline value.

f Calculated from cited cancer incidence rates (maximum likelihood estimates of bladder and lung cancer in males and females 12–23 per 10,000 population at 10 μg/L in drinking water), ie, 12/10,000.

g Actual risk level associated with the risk-specific dose.

h Range determined from 95% confidence interval for risk at 0.3 μg/L.

i Slope factor is not calculated as no specific risk was provided for the guideline value of 0.3 μg/L.

j Calculated from the risk estimate range presented in Table IIID.2 in US EPA (2001).

k Slope factor is not calculated as no specific risk was provided for the guideline value of 10 μg/L.

m Based on an excess lifetime cancer risk of 10^{-5}.

Inhalation

Inhalation will be a negligible route of exposure as arsenic is not volatile and the amount of dust considered to be inhaled typically represents a very small fraction of exposure (see section 1.1.4), so is not considered further.

Dermal absorption

The skin absorption factor is the only contaminant-specific parameter required for the dermal absorption pathway. Despite the fact that skin cancer is a primary toxicological effect of concern as a result of exposure to arsenic, dermal absorption of arsenic is generally considered to be negligible. US EPA (2004) guidance uses a dermal absorption factor of 3% based on Wester et al (1993), who examined the dermal uptake of arsenic in solution. However, recent studies on the dermal absorption of soil-absorbed arsenic in rhesus monkeys indicate that the mean dermal absorption is 0.5%, ie, negligible (Lowney et al, 2007).

Other routes of exposure – background exposure

For threshold contaminants it is important to account for background exposure. As arsenic has been considered a threshold contaminant by some agencies, such exposure is considered here.

Dietary intake of arsenic is considered to be the primary source of exposure. Vannoort and Thomson (2005) estimated that dietary intake of arsenic comprised 15% of the provisional tolerable weekly intake (PTWI: 15 μg/kg bw/week) for a young child (1–3 years, 13 kg) and around 10% for young males (25+ years, 82 kg) and females. This suggests a daily intake of inorganic arsenic of approximately 0.32 μg/kg bw for a young child and 0.21 μg/kg bw for young males and females. Davies et al (2001) found arsenic in 152 drinking water zones (18% of those assessed), although they noted that most results were comfortably below 50% of the maximum acceptable value (MAV) for drinking water (10 μg/L). Data on the detection of arsenic up to 50% of the MAV indicates that the majority of detections are 0–10% of the MAV.

Assuming a daily consumption of 1 L per day at arsenic concentrations of 1 μg/L by a young child gives rise to a daily arsenic intake from drinking water of 0.067 μg/kg bw, and a total daily arsenic intake of 0.38 μg/kg bw. Consumption of 2 L per day for a young male gives rise to a daily arsenic intake from drinking water of 0.024 μg/kg bw and a total daily arsenic intake of 0.23 μg/kg bw.

It is notable that these intakes are higher than all risk-specific doses shown in Table 3, suggesting that the acceptable increased risk level of 1 in 100,000 is already exceeded by intake from food. Similarly, estimated arsenic intake for a child exceeds the US EPA reference dose, while arsenic intake for an adult male comprises ~75% of the reference dose.

However, it should be noted that dietary intake in the New Zealand Total Diet Survey (Vannoort and Thomson, 2005) is likely to be overestimated for two main reasons: assumptions regarding the proportion of inorganic arsenic, and detection limits. Only total arsenic is determined in the NZTDS, and assumptions regarding the proportion of inorganic arsenic in different foods are made to estimate inorganic arsenic intake. Specifically, the NZTDS uses US Food and Drug Administration (US FDA) assumptions, which are acknowledged to be conservative, to determine the proportion of inorganic arsenic in the diet. The US FDA assumptions are that 10% of total arsenic in fish/seafood is inorganic, and that the arsenic in all other foods is 100% inorganic. A survey of total and inorganic arsenic in 40 different foods (Schoof et al, 1999 cited in Vannoort and Thomson, 2005) reported that of the total arsenic,

inorganic arsenic ranged from <1% to 100% as follows: marine fish (<1%), beef, chicken (1%), tomatoes (10%), rice (24%), potatoes (28%), apples and grapes (38%), carrots (53%), spinach and peas (100%). These assumptions also alter the importance of different food types; for example, for a young (19–24 years) male, fish forms approximately 83% of total arsenic intake and approximately 50% of the inorganic arsenic intake, while rice forms 2% of total arsenic intake and 13% of inorganic arsenic intake. Detection limits influence estimated dietary intake of an element, as, where a contaminant is determined to be below the detection limit for a particular food, half the detection limit is assigned to that food to estimate the total intake. This approach is commonly used and has been used in previous New Zealand dietary surveys. If the detection limit is high for a particular food and arsenic is not detected in this food, then it is likely the contribution of this food to total arsenic intake is overemphasised. Irrespective of the detection limit, inclusion of these "non-detects" is likely to overestimate the total arsenic intake. Nonetheless, this approach is used in the NZTDS for consistency with previous and international studies.

Summary of effects

Arsenic exposure can have numerous cancerous and non-cancerous effects including dermal lesions, pigmentation, keratoses, peripheral vascular disease (eg, blackfoot disease), and cardiovascular effects, skin cancer and internal cancers (bladder, lung, liver) (US EPA, 2001; WHO, 2001; ATSDR, 2007). Table 4 provides a summary of the effects at different levels of arsenic exposure and has primarily been sourced from ATSDR (2007). Cancer is the endpoint most consistently seen as a consequence of long-term chronic exposure, and is also the endpoint with the most extensive quantitative information available on dose-response.

Table 4: Summary of the health effects of arsenic

Dose (mg /kg/day	Type of poisoning	Effects
>2	Acute	Vomiting, diarrhoea, and abdominal pain, headache, lethargy, mental confusion, hallucination, seizures, and coma
>0.065–0.14	Chronic	Cardiovascular diseases such as "blackfoot disease", which is endemic in an area of Taiwan where average arsenic concentrations in drinking water range from 0.17 to 80 μg/L
0.03–0.1	Chronic	Peripheral neuropathy, characterised initially by numbness of the hands and feet and a "pins and needles" sensation and progressing to muscle weakness, wrist-drop and/or ankle-drop, diminished sensitivity, and altered reflex action. Reports of neurological effects at lower arsenic levels (0.004–0.006 mg/kg per day) have been inconsistent Minor respiratory symptoms such as cough, sputum, rhinorrhoea, and sore throat
0.01	Chronic	Vomiting, diarrhoea, and abdominal pain – symptoms diminish after cessation of exposure
>0.002	Chronic	Skin lesions (hyperkeratinisation and hyperpigmentation)
0.0012	Chronic	Lowest reported dosage associated with increased incidence of skin lesions
0.0000086	Chronic	Bladder and lung cancers – negligible risk based on consumption of 0.3 μg/L in drinking water (FPTCDW, 2006)
0.000001–0.000002	Chronic	Bladder and lung cancers (NRC, 2001)

Weight of evidence

- Arsenic is a known human carcinogen, based on human epidemiological studies that show increases in skin cancers and internal cancers (particularly bladder, liver and lung) as a result of chronic exposure to inorganic arsenic in drinking water (IARC, 1987; 2004; NRC, 1999; 2001; WHO, 2001; Mead, 2005; FPTCDW, 2006).
- Inorganic arsenic does not induce point mutations in bacterial and mammalian assays, although it does induce clastogenic effects (chromosome breakage, chromosomal aberrations and sister-chromatid exchange) in *in vitro* studies (ie, is genotoxic) (Rudel et al, 1996; Basu et al, 2001; Hughes, 2002; Rossman, 2003).
- Arsenic enhances the clastogenicity and mutagenicity of other DNA-damaging agents, ie, acts as a co-carcinogen (Rudel et al, 1996; NRC, 1999; Hughes, 2002; Rossman, 2003).
- The mechanisms of genotoxicity and carcinogenicity of arsenic are unknown, although several modes of action have been suggested including inhibition of DNA repair, altered DNA methylation patterns, and oxidative stress (Basu et al, 2001; Hughes, 2002; Rossman, 2003).
- While there is a general consensus that arsenic is likely to act indirectly on DNA in a sub-linear or threshold manner (eg, Rudel et al, 1996; Mead, 2005), it is also generally considered that there is insufficient data available to determine a "well-defined non-linear dose-response" (US EPA, 2001). Hence, a linear dose-response is assumed, ie, arsenic is treated as a non-threshold contaminant (eg, NRC 1999; 2001; US EPA, 2001; EA, 2009; FPTCDW, 2006).
- Given the consensus of international regulatory agencies, it is recommended that until further data is available on its mode of action, arsenic should be treated as a non-threshold contaminant in New Zealand.

Recommendations for toxicological intake values

Classification of arsenic as a non-threshold contaminant is consistent with its classification by ERMA NZ, since a mutagenicity (6.6B) classification has been applied indicating arsenic is a genotoxic carcinogen. As such, a risk-specific dose is proposed.

The risk-specific dose of 0.0086 μg/kg bw/day, derived from the arsenic concentration in drinking water determined to represent "negligible risk" (0.3 μg/L) by Canadian agencies (FPTCDW, 2006), is recommended (Table 5). This value is based on the most current risk-modelling data, and includes an external comparison population. It should be noted that as the risk estimates used in FPTCDW (2006) were based on exposure to arsenic via drinking water, the recommended risk-specific dose is likely a conservative estimate for intake via contaminated soil, as arsenic in contaminated soil will be less bioavailable than arsenic in drinking water. However, there is insufficient data to be able to quantitatively take account of this. Dermal absorption is considered to be negligible, although the skin absorption factor of 0.5% (Lowney et al, 2007) could be used as a refinement in the development of soil contaminant standards. An inhalation dose is not considered relevant for soil contamination by non-volatile substances (section 1.13). Because it is recommended that arsenic should be considered as a non-threshold contaminant, background exposure is irrelevant: exposure from all sources should be as low as reasonably practicable.

Table 5: Recommended toxicological criteria for arsenic

Parameter	Value	Basis
Contaminant status	Non-threshold	See weight of evidence
Oral risk-specific dose (μg/kg bw/day)	0.0086	From Health Canada (2005) risk-modelling for internal cancers, which includes an unexposed comparison population
Inhalation intake	NA	Lack of volatility of arsenic indicates inhalation exposures are minimal
Skin absorption factor	0.005	Lowney et al (2007)
Background exposure (μg/kg bw/day)	NA	Exposure to non-threshold contaminants from all sources should be as low as reasonably practicable

NA – not applicable.

2.2 Boron (B)

Few reviews of the toxicity of boron have been undertaken, with US EPA (2004a) and ATSDR (2007) being the most recent and most comprehensive. The discussion below is primarily drawn from these reviews and readers are referred to the original reviews for more details on adverse health effects.

2.2.1 Toxicological status

Acute boron poisoning has been reported in humans after application of dressings, powders or ointments containing borax and boric acid to large areas of abraded skin and following ingestion. Symptoms of boron poisoning include gastrointestinal disturbances, skin eruptions, and central nervous system stimulation followed by depression. Long-term exposure of humans to boron compounds leads to mild gastrointestinal irritation. Data from males occupationally exposed to high levels of vapours and aerosols of boron salt showed low sperm count and reduced sperm motility. Most other occupational studies failed to find an association of boron with observed effects, save for some irritant effects (US EPA, 2004a).

Studies in laboratory animals conducted by oral exposure have identified the developing foetus and the testes as the two most sensitive targets of boron toxicity in multiple species (US EPA, 2004a). The testicular effects that have been reported include reduced organ weight and organ-to-bodyweight ratio, atrophy, degeneration of the spermatogenic epithelium, impaired spermatogenesis, reduced fertility and sterility. The mechanism for boron's effect on the testes is not known, although altered physiological control of sperm maturation and release is suggested (US EPA, 2004a).

The developmental effects that have been reported following boron exposure include high prenatal mortality; reduced foetal bodyweight; and malformations and variations of the eyes, central nervous system, cardiovascular system, and axial skeleton (US EPA, 2004a). Rib cage malformations were the most common effects observed in both rats and mice while cardiovascular malformations were most common in rabbits. Decreased foetal growth, the most sensitive developmental endpoint, has been attributed to a general inhibition of mitosis by boric acid, as documented in studies on the mammalian testis, insects, yeast, fungi, bacteria, and viruses (US EPA, 2004a).

No data was located regarding the existence of an association between cancer and boron exposure in humans. No increased tumour incidence was observed in long-term carcinogenicity studies in mice and rats. Boric acid and borates were not mutagenic in various *in vitro* test systems.

Although the function of boron remains undefined, boron is becoming recognised as an element of potential nutritional importance because of the findings from human and animal studies. Findings from human experiments show that boron is a dynamic trace element that can affect the metabolism or utilisation of numerous substances involved in life processes, including calcium, copper, magnesium, nitrogen, glucose, triglycerides, reactive oxygen, and oestrogen (IOM, 2001).

2.2.2 New Zealand classification

The Hazardous Substances and New Organisms Act classification of boron set by ERMA NZ is shown in Table 6, but only has meaning when expressed in respect to a particular form of the element. Boron in the environment is always found chemically bound to oxygen, usually as an alkali or alkaline earth borates, or as boric acid. Overall boric acid has low acute toxicity (6.1E), although it is considered a skin (6.3B) and eye irritant (6.4A) and chronic exposure may cause developmental toxicity directly (6.8B). These findings are believed to be the most relevant, concerning most chemical forms of boron likely to be encountered.

Table 6: HSNO classification of boric acid

Hazardous property	HSNO classification
Acute toxicity	6.1E
Skin irritation	6.3B
Eye irritation	6.4A
Sensitiser	No
Mutagenicity	ND
Carcinogenicity	No
Reproductive/developmental toxicity	6.8B
Target organ systemic toxicity	ND

ND – not determined; No – not a sensitiser or carcinogen.

2.2.3 Reference health standards

Ingestion

With the exception of the New Zealand Timber Treatment Guidelines (MfE and MoH, 1997), the reference health standards from various sources essentially use the same studies, and are similar in value (Table 7). MfE and MoH (1997) used a now outdated reference dose from the US EPA, which was based on toxicity to dogs. The US EPA reviewed the toxicity of boron in 2004 (US EPA, 2004a), and used benchmark dose modelling of data from two studies (Heindel et al, 1992; Price et al, 1996a; both cited in US EPA, 2004b) with foetal weight decrease in rats as the endpoint to derive a revised RfD of 0.2 mg/kg bw/day. The ATSDR (2007) used the same method to derive their draft intermediate-duration minimal risk level. All other sources used the no observable adverse effect level from Price et al (1994 or 1996, cited in US EPA, 2004b) to derive their tolerable intakes ranging from 0.16 to 0.4 mg/kg bw/day. This range arises from the use of different uncertainty factors (Table 7).

Inhalation

Inhalation will be a negligible route of exposure as boron is not volatile and the amount of dust considered to be inhaled typically represents a very small fraction of exposure (see section 1.1.4), so inhalation is not considered further.

Table 7: Summary of oral reference health standards for boron as a threshold contaminant, used by different international agencies

Jurisdiction	Tolerable daily intake (mg/kg bw)	Key study[1]	Critical effect[1]	Basis of value[1]	Reference
New Zealand	0.09	Not stated	Not stated	US EPA (1992). US EPA reference dose was developed by application of an uncertainty factor of 100 to the highest no observed adverse effect level (NOAEL) in a lifetime study of dogs exposed to boron	MfE and MoH (1997)
New Zealand drinking water	0.21	Not stated	Foetal weight decrease in rats	$BMDL_{05}$ of 10.3 mg/kg/day and application of an uncertainty factor of 50	MoH (2005)
WHO – drinking water	0.16	Not stated	Foetal weight decrease in rats	NOAEL of 9.6 mg/kg bw/day and application of an uncertainty factor of 60 to account for inter-species (10) and intra-species (6) variation	WHO (2003)
International Programme on Chemical Safety (IPCS)	0.4	Not stated	Foetal weight decrease in rats	NOAEL of 9.6 mg/kg bw/day and application of an uncertainty factor of 25 to account for inter-species (3.16) and intra-species (7.94) variation	IPCS (1998)
Australia	0.2	Price et al (1994)	Not stated	NOAEL of 9.6 mg/kg bw/day and application of 48-fold uncertainty factor for inter-species (8) and intra-species (6) differences	Mangas (1998)
US ATSDR – intermediate-duration MRL US EPA	0.2	Heindel et al (1992); Price et al (1996a)	Foetal weight decrease in rats	$BMDL_{05}$ of 10.3 mg/kg/day estimated from foetal bodyweight data from two studies in which pregnant rats were exposed to boron in the diet on gestation days 0–20 and application of an uncertainty factor of 66 (3.3 for toxicokinetic extrapolation from animals to humans, 3.16 for toxicodynamic extrapolation from animals to humans, 2.0 for variability in human toxicokinetics, and 3.16 for variability in human toxicodynamics)	ATSDR (2007) USEPA (2004a)

1 As reported in the reference cited in the reference column.

Dermal absorption

The skin absorption factor is the only contaminant-specific parameter required for the dermal absorption pathway. The dermal absorption of boron in considered to be negligible (IPCS, 1998), thus it is considered that dermal exposure to boron is also negligible in the context of developing generic soil contaminant standards for New Zealand.

Other routes of exposure – background exposure

No data on the intake of boron from food in New Zealand is available, although food is estimated to be the greatest source of exposure to boron (IPCS, 1998; WHO, 2003). IPCS (1998 and WHO (2003) considered that the mean daily intake of boron in the diet was near 1.2 mg/day. Similarly, IOM (2001) indicated that the median intake of dietary and supplemental

boron by US adults was approximately 1.0–1.5 mg/day. These intakes include intake from drinking water and range from 0.014 to 0.021 mg/kg bw/day for a 70-kg adult.

Water quality monitoring data (Davies et al, 2001) indicated that boron was detected in 129 zones or 15% of those assessed, with 3300 people estimated to be exposed to drinking water with boron concentrations greater than 50% of the maximum acceptable value (1.4 mg/L). Data on the detection of boron up to 50% of the MAV indicates that most detections are between 0 and 10% of the MAV. Assuming consumption of 1 L of water per day at boron concentrations at 10% of the MAV (1.4 mg/L) by a young child (15 kg bodyweight), the boron intake from drinking water is 0.009 mg/kg bw/day. Assuming a daily consumption of 2 L at boron concentrations at 10% of the MAV (1.4 mg/L) by a 70-kg adult, the boron intake from drinking water is 0.004 mg/kg bw/day.

In the absence of information on the intake of boron from food in New Zealand, an intake of 1.2 mg/day is taken as the representative intake for dietary exposure (food and drinking water) for adults, and is also used for children. Expressed on a per bodyweight basis this intake is 0.08 mg/kg bw/day for children and 0.017 mg/kg bw/day for adults.

2.2.4 Summary of effects

There appear to be limited effects associated with exposure to boron, particularly in humans; the primary effects of boron in animal studies are developmental and reproductive effects, in particular testicular. The summary in Table 8 is based on information provided in ATSDR (2007).

2.2.5 Weight of evidence

- There is no evidence of carcinogenicity of boron in animals or humans. The IARC has not evaluated the carcinogenicity of boron, and the US EPA considers that there is inadequate animal or human data to classify boron (Class D – US EPA, 2004a).
- Studies of boron compounds for genotoxicity were overwhelmingly negative, including studies in bacteria, mammalian cells and mice *in vivo* (US EPA, 2004a; 2004b).
- Developmental and testicular effects are the most sensitive endpoints for the toxicity of boron (US EPA, 2004a; 2004b; ATSDR, 2007).

Table 8: Summary of the health effects of boron

Dose (mg/kg/day	Duration of exposure[1]	Effects
183	Acute	Lowest reported LOAEL for all effects reported for humans, vomiting and diarrhoea in infants
81	Chronic	Lowest reported LOAEL for reproductive effects (decreased testicular weight, testicular atrophy) in animals (rats) during chronic exposure
79	Chronic	Lowest reported LOAEL haematological and hepatic effects in animals (mice), highest reported NOAEL for reproductive effects (testicular atrophy) in animals (mice)
29	Intermediate	Lowest reported LOAEL for reproductive effects (mildly inhibited spermiation) in animals (rats)
13	Intermediate	Lowest reported LOAEL for developmental effects (foetal weight decrease) in animals (rats)
10	Intermediate	NOAEL for developmental effects (foetal weight decrease) in animals (rats)

1 Acute <14 days; Intermediate 15–364 days, Chronic >365 days; NOAEL – No observable adverse effect level.

2.2.6 Recommendations for toxicological intake values

Boron is considered to be a threshold contaminant, and a tolerable daily intake of 0.2 mg/kg bw, based on the reference dose established by the US EPA, is recommended. This total daily intake is recommended as it is based on benchmark dose modelling of two studies; both benchmark dose modelling and the use of two studies provide greater robustness in the value.

Inhalation exposure and dermal absorption of boron are expected to be negligible and are not considered relevant here. Dietary intake is expected to be the primary source of background exposure to boron and, in the absence of information specific to New Zealand, it is recommended that adult intakes of 1.2 mg/day from WHO (2003) and IPCS (1998) are used and also extrapolated to children. This gives rise to estimated intakes of 0.08 mg/kg bw/day for children and 0.017 mg/kg bw/day for adults. The recommended criteria are shown in Table 9.

Table 9: Recommended toxicological criteria for boron

Parameter	Value	Basis
Contaminant status	Threshold	See weight of evidence
Oral intake (mg/kg bw/day)	0.2	US EPA (2004a)
Inhalation intake	NA	Lack of volatility of boron indicates inhalation exposures are minimal
Skin absorption factor	NA	Negligible absorption (IPCS, 1998)
Background exposure (mg/kg bw/day)	0.08 0.017	Child (1–3 years, 15 kg) Adult (25+ years, 70 kg) Based on an intake of 1.2 mg/day (IPCS, 1998; WHO, 2003)

NA – not applicable.

2.3 Cadmium (Cd)

The following discussion on the toxicity of cadmium summarises relevant data from various reviews (US EPA, 1985; 1992; 1994; WHO, 1992; Jarup et al, 1998; ATSDR, 1999; Baars et al, 2001; DEFRA and EA, 2002; FAO/WHO, 2004). Particular attention is given to those studies that have been used in deriving reference health standards. Readers are referred to the original reviews for more details on adverse health effects.

2.3.1 Toxicological status

Cadmium is toxic to a wide range of organs and tissues, and a variety of toxicological endpoints (reproductive toxicity, neurotoxicity, carcinogenicity) have been observed in experimental animals and subsequently investigated in human populations (WHO, 1992; Jarup et al, 1998; ATSDR, 1999; DEFRA and EA, 2002). Fatal inhalation exposures have occurred in occupational accidents, with severe pulmonary oedema and chemical pneumonitis leading to respiratory failure and death (DEFRA and EA, 2002). Intake by humans of food or drink containing cadmium in concentrations in excess of about 15 mg/kg gives rise to acute gastrointestinal symptoms, including vomiting, diarrhoea, and abdominal cramps (DEFRA and EA, 2002). However, adverse effects on kidneys as a result of low-level long-term exposure to cadmium are typically considered to be the critical health effect in humans (Jarup et al, 1998; FAO/WHO, 2004; WHO, 2004).

Cadmium absorption after dietary exposure in humans is relatively low (3–5%) but cadmium is efficiently retained in the kidney and liver in the human body, with a very long biological half-life ranging from 10 to 30 years. Even low exposure levels may, in time, cause accumulation, especially in the kidneys. Both the kidneys and liver act as cadmium stores (together storing 50–85% of the body burden), with 30–60% being stored in the kidneys; cadmium stored in the liver is gradually released to the kidneys (WHO, 2004).

Non-cancer effects

Cadmium is primarily toxic to the kidney, especially to the proximal tubular cells where it accumulates over time and may cause renal dysfunction. Cadmium accumulated in the kidneys damages the proximal tubule cells, affecting tubular function. The first sign of this dysfunction is increased levels of low-molecular-weight proteins such as B2-microglobulin in the urine (tubular proteinuria). Cadmium-induced proteinuria is not readily reversible and continues to progress even after cadmium exposure has ceased, likely due to the redistribution to the kidneys of cadmium accumulated in the liver (FAO/WHO, 1989a; 1989b citing both Nogawa et al, 1979 and Roels et al, 1982).

Tubular dysfunction usually only develops after the cadmium concentration in the renal cortex reaches a critical level (Jarup et al, 1998; FAO/WHO, 2004). The critical tissue concentration of cadmium at which renal injury occurs is subject to inter-individual variation, although a value of 200 μg Cd/g wet weight in the renal cortex was suggested to correspond to a 10% incidence of proteinuria (FAO/WHO, 1989a; 1989b). This concentration was estimated to correspond to a concentration of cadmium in the urine of about 10 μg/g creatinine (Jarup et al, 1998). There appear to be three thresholds of urinary cadmium for the development of cadmium-induced kidney effects: about 2 μg/g creatinine, which is mainly associated with biochemical changes; about 4 μg/g creatinine, above which the function of the glomerular barrier is compromised and cytotoxic effects appear in the proximal tubules; and 10 μg/g creatinine, for the onset of proteinuria (ATSDR, 1999). In their most recent evaluation of cadmium, JECFA (FAO/WHO, 2004) considered that renal tubular dysfunction is the critical health outcome with regards to the toxicity of cadmium, and that an excess prevalence would not be expected to occur if urinary cadmium concentrations remain below 2.5 μg/g creatinine.

Loss of calcium from the bone and increased urinary excretion of calcium are also associated with chronic cadmium exposure. The adverse effects on bone and calcium metabolism may be the result of a direct effect of cadmium or may be secondary to the renal damage and subsequent disruption of calcium metabolism and kinetics. This may lead to osteomalacia (softening of the bones) or osteoporosis (increasingly brittle bones) (ATSDR, 1999; FAO/WHO, 2004).

Recent studies have reported the potential for endocrine disruption in humans as a result of exposure to cadmium (Jarup et al, 1998; Henson and Chedrese, 2004). While it is often difficult to interpret *in vitro* or *in vivo* studies on endocrine disruption to predict human effects, various effects on reproductive endocrinology have been described, and depend on the experimental model and dosage employed (Henson and Chedrese, 2004). Notably, depending on the dosage, cadmium exposure may either enhance or inhibit the biosynthesis of progesterone, a hormone linked to both normal ovarian cyclicity and maintenance of pregnancy. Exposure to cadmium during human pregnancy has also been linked to decreased birth weight and premature birth.

Carcinogenic effects

There is evidence for the carcinogenicity of cadmium, and the IARC (1993) has classified cadmium and cadmium compounds as carcinogenic to humans (Group 1), based on sufficient evidence of carcinogenicity in humans and animals. The US EPA (1994) has classified cadmium as only probably carcinogenic to humans (Group B1), based on limited epidemiological data for humans and sufficient animal data. Similarly, other authors (eg, Jarup et al, 1998) consider that evidence is weak for cadmium being a human carcinogen, and that an IARC classification of "probably carcinogenic to humans" (Group 2A) is more appropriate. However, there is no evidence of carcinogenicity by the oral route. These classifications are based on *occupational* exposure to cadmium with inhalation the primary route of exposure, although a recent study also reports an association between *environmental* exposure to cadmium and cancer via inhalation exposure (Nawrot et al, 2006). These authors compared cancer incidence in an area contaminated with cadmium (geometric mean cadmium soil concentration 7.97 mg/kg) with incidence in an area with low exposure to cadmium (geometric mean cadmium soil concentration 0.81 mg/kg). Specifically, Nawrot et al (2006) found a significant association between 24-h urinary cadmium excretion and all cancers, and lung cancer in particular. Additionally, the authors found a significant association between cadmium concentration in the soil, or residence in a high-exposure area, and lung cancer even after adjustment for age, sex, smoking, and exclusion of cadmium-exposed workers. The authors concluded that in areas with historically contaminated soil, house dust is a potential source of persistent exposure with the lungs being both the route of entrance and potential target. It is interesting to note that urinary cadmium excretion in the high-exposure group is around 0.99 μg/g creatinine, which is below the minimal threshold of 2.5 μg/g creatinine suggested by JECFA (FAO/WHO, 2004) to reduce the incidence of renal tubular dysfunction (see above).

There is conflicting data on the genotoxicity of cadmium. Some studies indicate that chromosomal aberrations occur as a result of oral or inhalation exposures in humans, while others do not (ATSDR, 1999). Studies in prokaryotic organisms largely indicate that cadmium is weakly mutagenic. In animal studies genetic damage has been reported, including DNA strand breaks, chromosomal damage, mutations and cell transformations (ATSDR, 1999). IARC (1993) concluded that ionic cadmium causes genotoxic effects in a variety of eukaryotic cells, including human cells, although positive results were often weak and/or seen at high concentrations that also caused cytotoxicity (WHO, 2004 citing both Baars et al, 2001 and Krajinc et al, 1987).

2.3.2 New Zealand classification

The Hazardous Substances and New Organisms Act classification of cadmium, as cadmium nitrate, set by ERMA NZ is shown in Table 10, but only has meaning when expressed in respect to cadmium in the form of cadmium nitrate, which is likely to represent the most toxic form of cadmium present in the environment. Overall, cadmium is of moderately acute toxicity (6.1C oral classification) and is corrosive to the eye (8.3A). In terms of long-term endpoints, cadmium is considered to be carcinogenic (6.7A) and is a systemic toxicant (6.9A) via the oral and inhalation routes.

Table 10: HSNO classification of cadmium (II), as cadmium nitrate

Hazardous property	HSNO classification
Acute toxicity	6.1C
Skin irritation	ND
Eye irritation	8.3A
Sensitiser	ND
Mutagenicity	ND
Carcinogenicity	6.7A
Reproductive/developmental toxicity	ND
Target organ systemic toxicity	6.9A

ND – no classification due to no data/insufficient data/inconclusive data.

2.3.3 Toxicological intake values

Ingestion

A number of regulatory agencies have developed guideline values for cadmium as a threshold contaminant (Table 11). Unlike for the majority of contaminants, reference health standards for cadmium have largely been derived using toxicokinetic models.

JECFA established a provisional tolerable weekly intake of 7 µg/kg bw for cadmium in 1988 (FAO/WHO, 1989a; 1989b) based on not exceeding cadmium concentrations of 50 mg/kg (wet wt) in the renal cortex, assuming an absorption rate of 5% and a daily excretion of 0.005% of body burden, over 50 years. It was recognised, however, that the margin of safety between the PTWI and the actual weekly intake of cadmium by the general population is small, and is even smaller in smokers. This PTWI was reviewed by JECFA in 1993, 2000 and 2004, largely due to concerns about the small margin of safety between the PTWI and estimated dietary intakes. On each occasion it was considered that the new data that had become available was insufficient to require revision of the PTWI (FAO/WHO, 1993; 2000; 2004); this was despite acknowledgment that the new information indicated a proportion of the general population might be at an increased risk of tubular dysfunction at the current PTWI of 7 µg/kg bw (FAO/WHO, 2000; FAO/WHO 2004). However, at it's meeting in June 2010, JECFA withdrew the provisional tolerable weekly intake and established a provisional tolerable monthly intake of (PTMI) 25 µg/kg bw (FAO/WHO 2010). A monthly intake was established due to consideration of the long half-life of cadmium, and consequently the small to negligible influence of daily ingestion on overall exposure.

This value is based on the lower bound of the 5th percentile dietary cadmium exposure (on a population level, 0.8 µg/kg bw/day or 25 µg/kg bw/mth) that equates to an urinary cadmium concentration 'breakpoint' of 5.24 (confidence interval 4.94–5.57) µg of cadmium per gram creatinine based on toxico-kinetic modelling. The breakpoint point was considered to be the threshold below which urinary Cd levels were not associated with an increased excretion of β2-microglobulin, and above which a steep increase in β2-microglobulin occurred in individuals who were 50 years and older. This breakpoint was based on meta-analysis of the dose-response relationship between the excretion of β2-microglobulin and cadmium in urine. The apparently long half-life of Cd in kidneys of 15 years means that steady state is achieved after 45–60 years of exposure.

The US EPA (1994) also used a toxicokinetic model to develop reference concentrations for food and water, based on an earlier study (US EPA, 1985) that used a cadmium concentration

of 200 µg/g (wet wt), and various assumptions regarding its absorption and excretion (Table 11). Specifically, they considered that since the fraction of ingested cadmium that is absorbed varies with the source (eg, food vs drinking water), it was necessary to allow for this difference when using the toxicokinetic model – thus RfDs for water and food were determined separately. So, although US EPA used different assumptions regarding absorption and excretion, their final daily RfD for food is the same as that derived by JECFA: 1 µg/kg bw (Table 11).

Concerns over the potential for adverse effects to be observed in a small (4%; Baars et al, 2001) section of the population led Dutch agencies to apply an additional safety factor of 2 to the JECFA values (Table 11; Baars et al, 2001).

The ATSDR (2008) derived a chronic-duration minimum risk level (MRL) for cadmium of 0.1 µg/kg bw/day. This value was derived from the 95% lower confidence limit of the urinary cadmium level associated with a 10% increased risk of low-molecular-weight proteinuria (0.5 µg/g creatinine) estimated from a meta-analysis of selected environmental exposure studies. An intake that would result in this urinary cadmium concentration was estimated using a modification of the Nordberg–Kjellström pharmacokinetic model, which is an eight-compartment toxicokinetic model. This dose of 0.3 µg/kg/day was divided by an uncertainty factor of 3 for human variability.

The most recent derivation of a tolerable intake was undertaken in 2009 by the European Food Safety Authority's Panel on contaminants in the food chain (CONTAM, 2009). Beta-2-microglobulin (B2M) was used as a sensitive biomarker for cadmium-induced tubular toxicity, although there is debate about the health significance of slight cadmium-induced tubular damage (CONTAM, 2009). A hybrid benchmark-dose modelling approach was applied to a meta-analysis of human exposure studies to determine a benchmark-dose lower confidence limit for a 5% increase in the prevalence of elevated B2M (BMDL5) of 1.0 µg/g creatinine, after application of a chemical-specific adjustment factor (CSAF)[5] to account for inter-individual differences in urinary cadmium in the study populations (AMU, 2009; CONTAM, 2009). To be able to derive a dietary cadmium intake from a urinary cadmium concentration, a one-compartment toxicokinetic model was fitted to data from the population-based Swedish Mammography Cohort study, which comprises a large dataset of non-smoking Swedish women (age range 58–70 years). The average daily dietary intake that ensured that 95% of non-smoking Swedish women, at age 50, would have urinary cadmium concentrations below the reference point of 1 µg Cd/g creatinine was then determined (Amzul et al, 2009; CONTAM, 2009). This average daily dietary cadmium exposure was 0.36 µg Cd/kg bw, or a weekly dietary intake of 2.52 µg Cd/kg bw. The CONTAM Panel considered that as the model calculation took into consideration the human variability in absorption rates (1–10%) and because the data used in the dose-response and kinetic modelling relates to an early biological response and a sensitive population, no adjustment or uncertainty factor was required for individual variability in susceptibility. Therefore, a tolerable weekly intake (TWI) for cadmium of 2.5 µg/kg bw was established.

The EFSA value has also been adopted by the UK Environment Agency for use in the derivation of soil guideline values for cadmium (EA, 2009a). Interestingly, they also recommend that exposure to cadmium should be considered over a lifetime, whereas typically a child is the critical receptor for residential land uses.

[5] A CSAF of 3.9 was determined by dividing the 95th percentile benchmark dose by the median BMD.

Inhalation

Inhalation is anticipated to be a negligible route of exposure for cadmium in soil as cadmium is not volatile and inhalation of soil particles is anticipated to be minimal (see section 1.1.4, Baars et al 2001). Yet, a recent study found an association between environmental exposure to cadmium, through contaminated soil, and cancer (Nawrot et al, 2006; see also section 2.8.1). Specifically, the authors found a significant increase in the incidence of lung cancer for residents in high-exposure areas (geometric mean soil concentration of 8.0 mg/kg) compared to low-exposure areas (geometric mean soil concentration of 0.81 mg/kg) as indicated by a hazard ratio of 3.58 (95% CI 1.00–12.7, $P = 0.049$); and that inhalation of house dust was the likely route of exposure in these areas.

Additionally, the inhalation intake value of 1.43 ng/kg bw/day adopted by the UK Environment Agency (EA, 2009a) is significantly lower than the range of oral intake values, which suggests that inhalation exposure could form a significant route of exposure for some land uses despite minimal exposure. The inhalation value is based on air quality guidelines of 5 ng/m^3 and inhalation of 20 m^3/day by a 70-kg adult. The air quality guidelines are based on extrapolation of occupational data (EC, 2000; CSTEE, 2001) or prevention of further increases in cadmium in agricultural soil (WHO, 2000). Further, based on an inhalation unit cancer risk estimate of 1.8×10^{-3} from the US EPA (1992), 5 ng/m^3 yields an excess lifetime cancer risk in the order of 1 in 100,000, based on inhalation of 20 m^3/day by a 70-kg adult.

While the above information highlights the potential importance of inhalation as an exposure route for cadmium, there is very little, if any, chance that dust particles would be small enough to be inhaled right into the lung. Instead they would be ejected from the airways into the throat and then swallowed, hence largely presenting an oral exposure. Inhalation was estimated to account for <1% of the total exposure to cadmium for commercial land-use (the land-use for which inhalation is likely to have the highest contribution to exposure) by the Environment Agency (2009b). Similarly, preliminary calculations during the development of soil contaminant standards for New Zealand found that inclusion of inhalation made a negligible difference to derived values.

Dermal absorption

The skin absorption factor is the only contaminant-specific parameter required for the dermal absorption pathway, which is typically considered to be negligible for inorganic contaminants such as cadmium. The US EPA (2004) recommends a dermal absorption factor of 0.001 (0.1%) for cadmium, based on Wester et al (1992). These authors determined the *in vitro* percutaneous absorption of cadmium as the chloride salt from soil and water, using human skin. Cadmium from soil penetrated the skin at 0.06% and 0.13% of the applied dose, with 0.01% and 0.07% respectively absorbed into the receptor fluid after 16 hours of exposure. Taking the geometric mean of the summed amounts bound to skin and that in the receptor fluid yields an average absorption factor of 0.0012 or 0.12%, similar to that recommended by the US EPA (2004). This low rate of absorption indicates that dermal exposure is a negligible route of exposure, and could be ignored in the derivation of soil contaminant standards for contaminated land in New Zealand, as has been done by other jurisdictions (Baars et al, 2001; DEFRA and EA, 2002).

Table 11: Summary of oral reference health standards for cadmium as a threshold contaminant, used by different international agencies

Jurisdiction	Tolerable weekly intake (μg/kg bw)	Tolerable daily intake (μg/kg bw)	Key study[1]	Critical effect[1]	Basis of value	Reference
New Zealand drinking water	7	1	FAO/WHO (1989)	Kidney damage (proteinuria)	FAO/WHO (1988) Drinking water standard based on allocation of 10% of the PTWI to drinking water.	MoH (2005)
European Food Safety Authority	2.5	0.36	FAO/WHO (1989)	Elevation in β2-microglobulin as a biomarker for tubular effects	Toxicokinetic model – average daily dietary cadmium exposure that ensures that 95% of the population at age 50 would have urinary cadmium concentrations below the reference point of 1 μg Cd/g creatinine, based on modelling of a large dataset of non-smoking Swedish women. The reference point of 1 μg Cd/g creatinine was the lower confidence interval of a 5% elevation (BMDL5) in β2-microglobulin that was determined from benchmark dose modelling and meta-analysis of human exposure data.	CONTAM (2009)
Joint FAO/WHO Expert Committee on Food Additives (JECFA)	25 (monthly)	0.8	Not stated	Kidney damage (proteinuria)	Toxicokinetic model – estimated daily intake that gives rise to a 'breakpoint' of urinary Cd excretion of 5.24 (confidence interval 4.94–5.57) μg Cd/g creatinine in individuals aged 50 years and older using a single-compartment model, and meta-analysis of dose-response data on β2-microglobulin and dietary Cd intake. Urinary Cd excretions below this breakpoint were not associated with an increase in β2-microglobulin, while higher urinary Cd excretion were associated with a steep increase in excretion.	FAO/WHO 2010
WHO drinking water	7	1	FAO/WHO (1989)	Kidney damage (proteinuria)	FAO/WHO (1988) Drinking water standard based on allocation of 10% of the PTWI to drinking water.	WHO (2004)
Australia	7	1	FAO/WHO (1989)	Kidney damage (proteinuria)	FAO/WHO (1989)	NEPC (1999)
UK	2.5	0.36	FAO/WHO (1989)	Elevation in β2-microglobulin as a biomarker for tubular effects	CONTAM (2009)	EA (2009)
The Netherlands – current	7	1	FAO/WHO (1989)	Kidney damage (proteinuria)	FAO/WHO (1989)	Baars et al (2001)
The Netherlands – proposed[2]	3.5	0.5	FAO/WHO (1989)	Kidney damage (proteinuria)	FAO/WHO (1989), with an additional uncertainty factor of 2 applied to account for adverse effects potentially occurring in 4% of the population at a TDI of 1 μg/kg bw/day.	Baars et al (2001)
Canada	7	1	FAO/WHO (1989)	Kidney damage (proteinuria)	FAO/WHO (1989)	NCSRP (1996)
US ATSDR – intermediate duration MRL		0.5	Brzoska and Moniuszko-Jakoniuk (2005d); Brzoska et al (2005a; 2005c)	Decreased bone mineralisation in rats	The BMDL of 0.05 mg Cd/kg/day was divided by an uncertainty factor of 100 (10 to account for extrapolation from animals to humans and 10 for human variability).	ATSDR (2008)

Jurisdiction	Tolerable weekly intake (μg/kg bw)	Tolerable daily intake (μg/kg bw)	Key study[1]	Critical effect[1]	Basis of value	Reference
US ATSDR – chronic duration MRL		0.1	Buchet et al (1990); Jarup et al (2000); Suwazono et al (2006)	Increased incidence of proteinuria in human exposure studies	95% lower confidence limit of the urinary cadmium level associated with a 10% increased risk of low-molecular-weight proteinuria (0.5 μg/g creatinine) estimated from a meta-analysis of selected environmental exposure studies. An intake that would result in this urinary cadmium concentration was estimated using a modification of the Nordberg–Kjellström pharmacokinetic model. This dose of 0.3 μg/kg/day was divided by an uncertainty factor of 3 for human variability.	ATSDR (2008)
US EPA		1 (food)		Kidney damage (proteinuria)	A concentration of 200 μg Cd/g wet weight human renal cortex is the highest renal level not associated with significant proteinuria. A toxicokinetic model is available to determine the level of chronic human oral exposure (NOAEL) that results in 200 μg/g wet weight human renal cortex; the model assumes that 0.01% of the Cd body burden is eliminated per day (US EPA, 1985). Assuming 2.5% absorption of Cd from food or 5% from water, the toxicokinetic model predicts that the NOAEL for chronic Cd exposure is 0.005 and 0.01 mg Cd/kg/day from water and food, respectively (ie, levels that would result in 200 μg Cd/g wet weight human renal cortex). Thus, based on an estimated NOAEL of 0.005 mg/kg/day for Cd in drinking water and an UF of 10, an RfD of 0.0005 mg/kg/day (water) was calculated; an equivalent RfD for Cd in food is 0.001 mg/kg/day.	US EPA (1994)

1 As reported in the reference cited in the reference column.

2 This value is yet to be officially adopted.

Other routes of exposure – background exposure

Food normally represents the major source of cadmium exposure, with drinking water typically only forming a minor contribution to total dietary intake (FAO/WHO, 1989a; 1989b). Non-food sources, in particular smoking, may also be a source of cadmium, eg, smoking 20 cigarettes per day may contribute a further 1–4 μg/day (FAO/WHO, 1989a; 1989b).

Vannoort and Thomson (2005) estimated the average dietary intake for cadmium in New Zealand was 2.6 μg/kg bw/week or 0.37 μg/kg bw/day for a toddler (1–3 years, 13 kg) and 2 μg/kg bw/week for young males (25+, 82 kg) and 1.5 μg/kg bw/week for young females (25+, 70 kg). The average dietary intake of cadmium for an adult is 1.75 μg/kg bw/week or 0.25 μg/kg bw/day.

Water quality monitoring data (Davies et al, 2001) indicated that cadmium was detected in 188 zones or 22% of those assessed, with 140,600 people estimated to be exposed to drinking water with cadmium concentrations greater than 50% of the then maximum acceptable value of 3 μg/L (note: the current New Zealand drinking water standard is 4 μg/L: MoH, 2005). Data on the detection of cadmium up to 50% of the MAV indicates that the majority of detections are 20% of the MAV.

Assuming a daily consumption of 1 L water per day at cadmium concentrations of 20% of the MAV used in Davies et al (2001) (ie, 0.6 μg/L) by a young child (15 kg bodyweight) gives rise to a cadmium intake from drinking water of 0.04 μg/kg bw/day, and a total cadmium intake for a child of 0.41 μg/kg bw/day or 12.5 μg/kg bw/month. Assuming a daily consumption of 2 L at cadmium concentrations of 20% of the MAV (0.6 μg/L) by a 70-kg adult gives rise to a cadmium intake from drinking water of 0.009 μg/kg bw/day, and a total cadmium intake of 0.26 μg/kg bw/day or 7.9 μg/kg bw/month.

2.3.4 Summary of effects

A variety of toxicological endpoints have been observed in experimental animals (reproductive toxicity, neurotoxicity, carcinogenicity) and subsequently investigated in human populations (WHO, 1992; Jarup et al, 1998; ATSDR, 1999; DEFRA and EA, 2002). However, adverse effects on kidneys as a result of low-level long-term exposure to cadmium are typically considered to be the critical health effect in humans (Jarup et al, 1998; FAO/WHO, 2004; WHO, 2004). Table 12 summarises effects observed in animals and humans resulting from exposure to cadmium (ATSDR, 1999).

2.3.5 Weight of evidence

- Cadmium is consdered to be carcinogenic to humans (Group 1) by the IARC (1993), and probably carcinogenic to humans (Group B1) by the US EPA (1992), based on inhalation exposure.
- There is weak evidence for the genotoxicity of cadmium (IARC, 1993; Baars et al, 2001).
- Insufficient data is available to assess carcinogenicity via the oral route. Therefore, cadmium is treated as a threshold contaminant, and renal tubular dysfunction is considered to be the critical endpoint foir oral exposure to cadmium (Baars et al, 2001; FAO/WHO, 2004; WHO, 2004).

Table 12: Summary of cadmium health effects in animals and humans (ATSDR, 1999)

Daily dose (mg/kg)	Type of poisoning[1]	Effects
29	Acute	Lowest reported LD_{50} for a single dose for animals (rats)[2]
25	Acute	Lowest single dosage reported to cause human death
3.4	Chronic	Lowest dosage reported to cause carcinogenic effects (increased rates of prostatic adenomas) in animals (rats)
2.3	Intermediate	Lowest dosage reported to cause endocrine effects (pancreatic atrophy and pancreatitis) in animals (rats)
1.18	Intermediate	Lowest dosage reported to cause renal effects (vesiculisation of proximal tubules) in animals (rats)
0.8	Intermediate	Lowest dosage reported to cause haematological effects (decreased haematocrit and haemoglobin) and muscular/skeletal effects (decreased bone strength in young animals) in animals (rats)
0.04–0.71	Intermediate	Lowest dosages reported to cause developmental effects (altered off-spring behaviour, delayed development of sensory motor coordination reflexes) in animals (rats)
0.01	Chronic	Lowest dosage reported to cause cardiovascular effects (hypertension, increased systolic pressure) in animals (rats)
0.0078	Chronic	Lowest dosage reported to cause renal effects (renal tubule lesions) in humans exposed to cadmium for 25 years
0.0021	Chronic	Lowest reported NOAEL for renal effects in humans exposed to cadmium for a lifetime[3]

1 Length of exposure: acute (<14 days), intermediate (15–365 days), chronic (>365 days).

2 LD50 – lethal dose at which 50% of the exposed population dies.

3 NOAEL – no observable adverse effect level.

2.3.6 Recommendations for toxicological intake values

JECFA's provisional tolerable weekly intake of 7 μg/kg bw/week, and the total daily intake derived from this, has been the value most widely used by different international agencies. However, there is recognition that this value may not be sufficiently protective of the general population (eg, Jarup et al, 1998; Satarug and Moore, 2004; Satarug et al, 2010) and some other agencies have adopted different values. Dutch agencies have adopted a pragmatic approach and simply applied an additional safety factor of 2 to the JECFA value, while the ATSDR (2008) derived a TDI of 0.1 μg/kg bw/day based on toxicokinetic modelling. The most recent derivation is that of the EFSA (CONTAM 2009), who derived a TWI of 2.5 μg/kg bw/week, also using toxicokinetic modelling. As a result of the EFSA derivation, JECFA reviewed cadmium in June 2010 and withdrew the previous PTWI, replacing it with a provisional tolerable monthly intake (PTMI) of 25 μg/kg bw (FAO/WHO 2010). The JECFA PTMI is recommended for use in deriving soil contaminant standards as this value was considered to represent the consensus view of a broader range of toxiciologists than is represented by CONTAM (2009) and ATSDR (2001), and would also include consideration of the same data used in earlier evaluations (eg, CONTAM 2009).

Additionally, in terms of deriving soil contaminant standards, given that the toxicological intake value for cadmium is based on the cumulative effects over 50 years, it is recommended that a combined child plus adult exposure period is considered when deriving a soil contaminant standard for residential scenarios.

The few data available on inhalation of cadmium suggest that inhalation of cadmium may contribute to detrimental health effects. However, it remains likely that inhalation is a low

contributor to total exposure and it is not recommended that inhalation of cadmium is considered in the derivation of soil contaminant standards.

Dermal absorption is expected to be negligible, and could be ignored in the derivation of soil contaminant standards for contaminated land in New Zealand, as has been done by other jurisdictions (Baars et al, 2001; DEFRA and EA, 2002). Conversely, a dermal absorption factor of 0.0012 based on Wester et al (1992) could be used (Table 13).

Dietary intake is the primary source of background exposure to cadmium and was estimated to be 0.41 μg/kg bw/day for a child (aged 1–3 years, 13 kg) and 0.26 μg/kg bw/day for an adult. Given the long-term effects of cadmium, it is more appropriate to express these intakes as weekly intakes: estimated at 2.87 μg/kg bw/week for a child and 1.82 μg/kg bw/week for an adult (Table 13).

Table 13: Recommended toxicological criteria for cadmium

Parameter	Value	Basis
Contaminant status	Threshold	See weight of evidence section
Oral (μg/kg bw/day) (μg/kg bw/month)	0.8 25	FAO/WHO (2010)
Inhalation intake (ng/kg bw/day)	1.43	EA (2009)
Skin absorption factor	0.001	Wester et al (1992). Dermal absorption is expected to be negligible
Background exposure (μg/kg bw/day(week))	0.41 (2.87) 0.26 (1.82)	Child (1–3 years) Adult Dietary intake of cadmium (Davies et al, 2001; Vannoort and Thomson, 2005)

ND – not determined.

2.4 Chromium (Cr)

The following discussion on the toxicity of chromium summarises relevant data from various reviews (WHO 1988; NCSRP, 1996; US EPA, 1998a; 1998b; ATSDR, 2000; Baars et al, 2001; DEFRA and EA, 2002). Particular attention is given to those studies that have been used in deriving reference health standards. Readers are referred to the original reviews for more details on adverse health effects.

2.4.1 Toxicological status

Chromium occurs most commonly in two valence states: trivalent, +3 (III) and hexavalent, +6 (VI). Chromium (III) is the most stable oxidation state and is the form most commonly found in the environment. Chromium (VI) in the environment primarily occurs as the by-product of several industrial processes. Chromium in its trivalent state is an essential element, but at high concentrations, and particularly in its hexavalent state, it is toxic. In humans and animals chromium (III) is an essential nutrient that plays a role in glucose, fat, and protein metabolism through potentiation of the action of insulin (IOM, 2001).

The US Institute of Medicine (IOM, 2001) established adequate intakes for chromium of 35 μg/day for men (19–50 years old, 76 kg) and 25 μg/day for women (19–50 years, 61 kg).

These adequate-intake values were based on estimated mean intakes from US data as the IOM concluded that insufficient information was available to set an estimated average requirement (EAR) for chromium (IOM, 2001). In the absence of information on the chromium content of children's diets, adequate intakes for children have been extrapolated from adults. The intake for a young child (1–3 years, 13 kg) is 11 μg/day. These values have been adopted by the Australian National Health and Medical Research Council (NHMRC) to provide nutrient reference values for Australia and New Zealand (NHMRC, 2006). These values are at the lower end of the estimated safe and adequate dietary daily intake (ESADDI) for chromium of 50–200 μg/day identified by the US National Research Council, which corresponds to 0.71–2.9 μg/kg/day for a 70-kg adult (US EPA, 1998a). The US Food and Drug Administration has selected a reference daily intake for chromium of 120 μg/day (US EPA, 1998a).

Relatively few studies address the oral or inhalation toxicity of chromium (III), and reductions in the absolute weights of livers and spleens of rats are the only effects reported following oral exposure to chromium (III) (US EPA, 1998a).

In contrast, chromium (VI) is a known toxicant, primarily via inhalation (US EPA, 1998b; 1998c; ATSDR, 2000). Results from occupational epidemiologic studies of chromium-exposed workers, across investigators and study populations, consistently demonstrate that chromium is carcinogenic by the inhalation exposure route (US EPA, 1998b; ATSDR, 2000). However, in these situations workers are exposed to both chromium (III) and chromium (VI) compounds, and the US EPA (1998b; 1998c) concluded that because only chromium (VI) was found to be carcinogenic in animal studies, only chromium (VI) should be classified as a human carcinogen (Group A). Metallic chromium and chromium (III) compounds were not classifiable as to their carcinogenicity to humans (Group D) (US EPA, 1998d). IARC (1990) similarly considered that chromium (VI) was carcinogenic to humans (Group 1) but that metallic chromium and chromium (III) compounds were not classifiable as to their carcinogenicity to humans (Group 3). Epidemiological studies of workers in chromium production facilities have demonstrated an association between inhalation of chromium (VI) and upper respiratory irritation and atrophy, lower respiratory effects, and renal effects (US EPA, 1998b; ATSDR, 2000).

Studies on occupational exposure to chromium have reported variable genotoxic effects: some reported none, others reported chromosomal aberrations or sister chromatid exchanges in workers exposed to chromium (VI) compared with controls (ATSDR, 2000). However, the studies in humans were generally limited in that exposures to chromium (VI) were not known and co-exposure to other potentially active compounds (namely ultraviolet rays and other potentially genotoxic metals) also occurred in several studies (ATSDR, 2000). Genotoxic effects are also observed in various *in vivo* studies and chromium (VI) is mutagenic in bacterial assays, and yeasts, and transforms both primary cells and cell lines (ATSDR, 2000). In contrast, studies with chromium (III) did not report mutagenic effects (ATSDR, 2000). While chromium (VI) exhibits genotoxicity, it has also been suggested that a threshold for carcinogenic effects for hexavalent chromium exists, based on the hypothesis that the administered dose must exceed the extracellular capacity to reduce chromium (VI) to chromium (III) (Baars et al, 2001 citing both De Flora et al, 1997 and Jones, 1990).

Chromium (VI) compounds were positive in the majority of tests reported, and their genotoxicity was related to solubility and, therefore, bioavailability to the targets. Chromium (III) was more genotoxic in subcellular targets, but lost this ability in cellular systems. Reduction of chromium (VI) in cells to chromium (III) and its subsequent genotoxicity may be greatly responsible for the final genotoxic effects (ATSDR, 2000 citing Beyersmann and Koster, 1987). Reduction of chromium (VI) can also result in the formation of

chromium (V), which is highly reactive and capable of interaction with DNA (ATSDR, 2000 citing both Jennette, 1982 and Norseth, 1986).

While reasonable data exists for the effects of hexavalent chromium via inhalation exposure, data is limited regarding health effects resulting from its ingestion (US EPA, 1998b; ATSDR, 2000). One epidemiological study that reported effects in humans resulting from ingestion of chromium-contaminated well water is reported in US EPA (1998b). Residents of a village in China were reported to have experienced oral ulcers, diarrhoea, abdominal pain, indigestion, vomiting, leukocytosis, and presence of immature neutrophils. Other reports of toxic effects of chromium (VI) in humans are limited to case reports from accidental poisonings.

With the exception of increased body burden of chromium, no significant adverse effects have been observed in animal studies following ingestion of chromium (US EPA, 1998b). High oral doses (eg, 74–34 mg/kg bw/day (provided as chromium (VI) in drinking water) have been reported to cause reproductive and developmental toxicity in mice, including decreased foetal weight, increased resorption, and increased abnormalities (eg, US EPA, 1998b citing both Junaid et al, 1996 and Kanojia et al, 1996). From these studies US EPA (1998b) derived no observable adverse effect levels (NOAELs) for fetotoxicity of 6.7 mg/kg bw/day and 3.7 mg/kg bw/day in mice and rats, respectively. However, other studies indicated that potassium dichromate administered at 100, 200, or 400 mg/kg in the diet to male and female mice was not a reproductive toxicant in either sex (US EPA, 1998b citing NTP, 1996a; 1996b). Other available studies on ingested chromium (VI) (McKenzie et al, 1958; US EPA, 1998b citing Anwar et al, 1961) are limited by a small number of animals per group and a lack of an observed effect at any dose level. However, the McKenzie study was considered to be most suitable for the dose-response assessment for ingested chromium and generated an adjusted NOAEL of 2.5 mg/kg bw/day (US EPA, 1998b).

While the toxicity of chromium (VI) is recognised, there are a number of barriers that limit the uptake of the hexavalent form (US EPA, 1998b). In particular, chromium (VI) is rapidly reduced to chromium (III) after penetration of biological membranes and in the gastric environment. Further, while chromium (VI) can readily be transported into cells, chromium (III) is much less able to cross cell membranes. The reduction of chromium (VI) to chromium (III) inside cells may be an important mechanism for the toxicity of chromium compounds. For example, a number of potentially mutagenic DNA lesions may be produced upon intracellular reduction to chromium (III) (US EPA, 1998b). In contrast, the reduction of chromium (VI) to chromium (III) outside cells is a major mechanism of protection. Most hexavalent chromium taken in with food is reduced to chromium (III) in the acid medium of the stomach. Gastrointestinal absorption of chromium (VI) occurs with greater efficiency than absorption of chromium (III), though absorption of ingested hexavalent chromium is estimated to be less than 5% (US EPA, 1998b). A significant amount of absorbed chromium is taken up in the bone, liver, kidneys, and spleen. Similar patterns are seen in rats with accumulation in kidneys, spleen, and bone as well as liver and testes (US EPA, 1998b citing: Hopkins, 1965; Kamath et al, 1997; Onkelinx, 1977).

Dermal exposure to chromium has been demonstrated to produce irritant and allergic contact dermatitis (US EPA, 1998b). Primary irritant dermatitis is related to chromium's direct cytotoxic properties, while allergic contact dermatitis is an inflammatory response mediated by the immune system. While chromium (VI) is believed to present the greatest skin sensitisation potential, it is the reduction to chromium (III) within the cell and the subsequent reaction with tissue protein that results in the allergic reaction (Guy et al, 1999). Allergic contact dermatitis is the most sensitive non-cancer effect resulting from dermal exposure (Guy et al, 1999).

2.4.2 New Zealand classification

The Hazardous Substances and New Organisms Act (HSNO) classifications of chromium (III) as chromium chloride and chromium (VI) as sodium dichromate dihydrate, set by ERMA NZ, are shown in Tables 14 and 15, respectively. The HSNO classification for chromium only has meaning when expressed with respect to the respective forms of the element. present in the environment. Chromium (III), as chromium chloride, has only been classified as eliciting acute toxicity effects (Table 14). In contrast, chromium (VI), as sodium dichromate dihydrate, is of high acute toxicity (6.1A oral classification), is corrosive to the skin and an eye irritant (8.2C, 8.3A), and is a respiratory and contact sensitiser (6.5A, 6.5B). In terms of long-term endpoints, chromium (VI) is considered to be mutagenic (6.6A), carcinogenic (6.7A), a reproductive and development toxicant (6.8A), and a systemic toxicant (6.9A), based on effects on the gastrointestinal system, kidneys and haematopoetic system.

Table 14: HSNO classification of chromium (III) chloride

Hazardous property	HSNO classification
Acute toxicity	6.1D
Skin irritation	ND
Eye irritation	ND
Sensitiser	ND
Mutagenicity	ND
Carcinogenicity	ND
Reproductive/developmental toxicity	ND
Target organ systemic toxicity	ND

ND – no classification due to no data/insufficient data/inconclusive data.

Table 15: HSNO classification of chromium (VI) as sodium dichromate dihydrate

Hazardous property	HSNO classification
Acute toxicity	6.1A
Skin irritation	8.2C
Eye irritation	8.3A
Sensitiser	6.5A 6.5B
Mutagenicity	6.6A
Carcinogenicity	6.7A
Reproductive/developmental toxicity	6.8A
Target organ systemic toxicity	6.9A

ND – no classification due to no data/insufficient data/inconclusive data.

2.4.3 Toxicological intake values

Ingestion

A number of regulatory agencies have developed guideline values for chromium, although the basis, eg, whether the guidelines refer to chromium (III), chromium (VI) or total chromium, is variable (Tables 16–19).

Adequate data from which to derive tolerable daily intakes is limited, and the US EPA is primarily the only agency that has derived TDIs for chromium (III) and (VI); most other agencies have adopted the US EPA values (Tables 16 and 17). The US EPA reference dose for

chromium (VI) is based on a NOAEL for systemic effects in rats exposed to daily doses of 2.5 mg Cr(VI)/kg as potassium chromate in their drinking water for 1 year, in the study by McKenzie et al (1958) (US EPA, 1998b). A chronic oral RfD of 1.5 mg Cr(III)/kg/day is based on a NOAEL for systemic effects in rats fed 1800 mg Cr(III)/kg/day as chromium oxide for five days per week for 600 feedings (840 total days) in the study by Ivankovic and Preussmann (1975, cited in US EPA, 1998a). These values were last revised in 1998.

With one exception, where a TDI for chromium (VI) has been used by individual jurisdictions (New Zealand, The Netherlands, UK), values have been sourced from US EPA's Integrated Risk Information System (IRIS) database. However, the US EPA updated the values in 1998 (US EPA, 1998b), and some jurisdictions are still using the older values (Tables 16 and 17). Interestingly, Canadian agencies specifically rejected the older US EPA RfD when establishing soil guideline values for chromium. This was largely due to the lack of confidence expressed by the US EPA in that value due to the poor quality of the original (McKenzie et al, 1958) study, as well as the facts that neither Health Canada nor WHO had established an oral TDI for chromium (VI), and that other Canadian agencies had not identified adequate animal studies with which to assess chromium (VI) carcinogenicity or non-tumour endpoints (NCSRP, 1996). Australian agencies base their soil guideline value for chromium (VI) on protection from contact dermatitis, although no information is given other than it provides a "10-fold safety margin over the likely threshold for skin sensitivity suggested by Sheehan et al 1991" (NEPC, 1999), and the Sheehan et al (1991) reference is not included in their reference list.

The TDIs for chromium (III) have a variable basis: Australia and New Zealand base their current TDI on the (older) US EPA values based on toxicity effects, the Netherlands also derived their values based on toxicity effects, while Canada and the ATSDR base intakes on safe and adequate dietary intakes. Specifically Canadian agencies established a TDI for chromium (III) of 6.2 μg/kg bw/day based on US National Research Council recommendations for the estimated upper limit of safe and adequate dietary intake for a child of 1–3 years old (NCSRP, 1996). Similarly, the ATSDR adopted the estimated upper limit of 200 μg/day for safe and adequate dietary intake reported by the National Research Council as provisional guidance for oral exposure to chromium (VI) and chromium (III). IOM (2001) did not set a tolerable upper limit for chromium as "few serious effects had been associated with excess intake from food", but did establish an adequate nutritional intake of 25–35 μg/day.

Different jurisdictions have handled the speciation issue differently. For example, UK agencies provide a value for total chromium based on chromium (VI) but acknowledge this is highly conservative given that chromium (VI) is not often present (DEFRA and EA, 2002). In contrast, Canadian and Australian agencies base their value for total chromium on chromium (III), given this is the form predominantly present in soil. The Drinking Water Standards (WHO and NZ) are for total chromium, but the basis for the maximum acceptable value is unclear. WHO (2008) and MoH (2005) provide the most detailed explanation for how the value was arrived at; specifically "the guideline value was first proposed in 1958 for hexavalent chromium, based on health concerns, but was later changed to a guideline for total chromium because of difficulties in analysing for the hexavalent form only" – this suggests that the original source for the derivation of the MAV is also the McKenzie et al (1958) study. However, back-calculation of the TDI based on the drinking water guideline, assuming 10% of the TDI is allocated to drinking water and that 2 L per day is consumed by a 70-kg adult, gives rise to a tolerable intake value of 14 μg/kg bw/day, which is higher than the values derived from the original McKenzie et al (1958) study. This may be due to differences in the parameters used, eg, bodyweight, amount of water considered to be consumed used in this report compared with in the original derivation.

Table 16: Summary of oral reference health standards for total chromium as a threshold contaminant, used by different international agencies

Jurisdiction	Guideline value (mg/L)[1]	Tolerable daily intake (µg/kg bw)	Key study[2]	Critical effect[2]	Basis of value[2]	Reference
New Zealand drinking water	0.05	14	Not stated	Not stated	WHO (2004)	MoH (2005)
WHO drinking water	0.05	14	Not stated	Not stated	Not stated	WHO (2004)
UK	–	3	Not stated	Not stated	Based on Cr (VI) from US EPA (1998b)	DEFRA and EA (2002)

1 Where a guideline value is provided, the tolerable daily intake has been derived assuming consumption of 2 L/day by a 70-kg adult, assuming that 10% of the TDI was allocated to exposure from drinking water, as typically occurs – no specific information in available in the cited references.

2 As reported in the reference cited in the reference column.

Table 17: Summary of oral reference health standards for chromium (III) as a threshold contaminant, used by different international agencies

Jurisdiction	Substance	Tolerable daily intake (µg/kg bw)	Key study[1]	Critical effect[1]	Basis of value[1]	Reference
New Zealand	Cr III	1,000	Not stated	Not stated	US EPA (1996)	MfE and MoH (1997)
Australia	Cr III	1,000	Not stated	Not stated	US EPA (yr not stated)	NEPC (1999)
The Netherlands – current	Cr III	5	Not stated	Not stated	Vermeire (1993)	Baars et al (2001)
The Netherlands – proposed[2]	Cr III – soluble compounds	5	Not stated Schroeder et al (1965)	Not stated (No effects on any target organs)	NOAEL of 0.46 mg/kg bw/day of Cr III as chromium acetate and application of an uncertainty factor of 100 (10 for interspecies variation and 10 for intraspecies variation).	Baars et al (2001)
	Cr III metallic and insoluble compounds	5,000	–	–	"Based on chronic NOAELs the toxicity of insoluble chromium III compounds is approximately 1,000 times less [than soluble Cr III compounds]".	Baars et al (2001)
Canada	Cr III	6.2	Not stated	Nutritional deficiency	Upper limit of the estimated safe and adequate dietary intake for a child of 1–3 years old.	NCSRP (1996)

Jurisdiction	Substance	Tolerable daily intake (µg/kg bw)	Key study[1]	Critical effect[1]	Basis of value[1]	Reference
US EPA	Cr III	1,500	Ivankovic and Preussmann (1975)	No effects at any dose in a 840-day feeding study in rats. Toxicological parameters included serum protein, bilirubin, haematology, urinalysis, organ weights, and histopathology	NOAEL: 5% Cr_2O_3 in diet 5 days/week for 600 feedings (1,800 g/kg bw average total dose or 1,468 mg Cr/kg/day) – converted as follows: 1,800 g Cr_2O_3/kg bw × 1,000 mg/g × 0.6849 g Cr/g Cr_2O_3/600 feeding days × 5 feeding days/7 days = 1,468 mg/kg/day NOEL. Application of uncertainty factor of 1000 (10 for interspecies variability and 10 for intraspecies variability, and an additional modifying factor of 10 to account for an inadequate database)	US EPA (1998a; 1998d)
US ATSDR	Cr III	200	Not stated	Nutritional deficiency	Upper limit of the estimated safe and adequate daily dietary intake	ATSDR (2000)

1 As reported in the reference cited in the reference column.

2 This value is yet to be officially adopted.

Table 18: Summary of oral reference health standards for chromium (VI) as a non-threshold contaminant, used by different international agencies

Jurisdiction	Acceptable risk level	Risk-specific dose[1] (µg/kg bw/day)	Cancer slope factor (per mg/kg bw/day)	Key study[2]	Critical effects[2]	Basis of value	Reference
The Netherlands – current	10^{-4} [10^{-5}]	0.0007 [0.00007]	–	Not stated	Not stated	Route-to-route extrapolation from inhalation studies, which established an extra lung cancer risk of 1 in 10,000 at 2.5 ng Cr VI/m^3 (no further detail provided)	Vermeire et al (1991 in Baars et al, 2001)

1 Where the acceptable risk level for a given jurisdiction is not 10^{-5}, the risk-specific dose for a risk of 10^{-5} is shown in square brackets.

2 As reported in the reference cited in the reference column.

Table 19: Summary of oral reference health standards for chromium (VI) as a threshold contaminant, used by different international agencies

Jurisdiction	Guideline value (mg/L)[1]	Tolerable daily intake (μg/kg bw)	Key study[2]	Critical effect[2]	Basis of value[2]	Reference
New Zealand		5	McKenzie et al (1958)	None reported in a 1-year drinking water study in rats	US EPA (1996)	MfE and MoH (1997)
New Zealand drinking water	0.05	14	Not stated	Not stated	WHO (2004)	MoH (2005)
WHO drinking water	0.05	14	Not stated	Not stated	1958 guideline value originally proposed for hexavalent chromium but extended to total chromium due to analytical difficulties in determining hexavalent chromium	WHO (2008)
Australia		?	Sheehan et al (1991)	Contact dermatitis	A health investigation level of 100 mg/kg for a standard residential scenario was proposed to provide a 10-fold safety margin over the likely threshold for skin sensitivity	NEPC (1999)
The Netherlands – proposed[3]		5	McKenzie et al (1958)	None reported in a 1-year drinking water study in rats	US EPA (1996)	Baars et al (2001)
US EPA		3	McKenzie et al (1958)	None reported in a 1-year drinking water study in rats	NOEL of 25 mg/L, converted to 2.5 mg/kg bw/day and application of uncertainty factor of 900: 10 for interspecies variability and 10 for intraspecies variability, 3 for a less-than lifetime exposure and an additional modifying factor of 3 to account for any uncertainties raised by the study of Zhang and Li (1987)	US EPA (1998b; 1998c)

1 Where a guideline value is provided, the tolerable daily intake has been derived assuming consumption of 2 L/day by a 70-kg adult, assuming that 10% of the TDI was allocated to exposure from drinking water, as typically occurs – no specific information in available in the cited references.

2 As reported in the reference cited in the reference column.

3 This value is yet to be officially adopted.

Inhalation

Inhalation is anticipated to be a negligible route of exposure as chromium is not volatile and the amount of dust considered to be inhaled typically represents a very small fraction of exposure (see section 1.1.4), so is not discussed further.

Dermal absorption

Dermal exposure to chromium has been demonstrated to produce irritant and allergic contact dermatitis (Guy et al, 1999; ATSDR, 2000; Baars et al, 2001). Primary irritant dermatitis is related to the direct cytotoxic properties of chromium, while allergic contact dermatitis is an inflammatory response mediated by the immune system (ATSDR, 2000). A number of studies have investigated the exposure level necessary to elicit a 10% response in sensitised individuals (see ATSDR, 2000). The prevalence of chromium sensitivity in the general US population is estimated to range from 0.08 to 1.6% (ATSDR, 2000). Estimates of the concentration of potassium dichromate that would induce a response in 10% of a sensitised population during patch testing in eight studies ranged from 10.1 to 449 mg/L, with a sample-size-weighted average of 154 mg $K_2Cr_2O_7$/L or 54 mg Cr(VI)/L (Paustenbach et al, 1992). These authors also suggest that a soil concentration of 500 mg Cr(VI)/kg would be protective of 90% of those individuals that are sensitised to chromium, and 99.84% of the general population assuming that 10% of the chromium (VI) is bioavailable. Another study estimated that 0.1% or less of the chromium (VI) in chromite ore processing residue would leach out in the presence of human sweat (Horowitz and Finley, 1993, cited in ATSDR, 2000), suggesting that soil concentrations up to 50,000 mg/kg may not elicit an allergic response.

As allergic contact dermatitis is an inflammatory response mediated by the immune system, this suggests that at least some chromium is absorbed through the skin. Studies that have investigated this response typically express dermal absorption as a function of skin surface area or flux, and thus are difficult to express as a percentage absorbed over time (see Guy et al, 1999). Dermal absorption of inorganic contaminants such as chromium is typically considered to be negligible and most international agencies have not considered dermal absorption in their derivation of soil guideline values (US EPA 1998a; 1998b; DEFRA and EA, 2002). However, two agencies have established guideline values for chromium (VI) to be protective against allergic contact dermatitis. These values are either in addition to soil guideline values based primarily on oral exposure (Baars et al, 2001) or in lieu of another guideline value (NEPC, 1999). These values are typically based on estimates that have the potential to induce a response in 10% of sensitised individuals. Baars et al (2001) present this guideline as the concentration of chromium (VI) in solution (10 mg/L) or as a skin loading (0.089 μg/cm^2), while the NEPC (1999) provides a guideline value based on soil concentration (100 mg Cr(VI)/kg).

It is recommended that the adverse effects arising from dermal exposure are considered separately to those arising from oral exposure and that allergic contact dermatitis is the main effect of interest, for which a soil guideline value could be established. However, it is likely that a soil guideline value protective of effects arising from oral exposure will also be protective against allergic contact dermatitis (see previous section).

Other routes of exposure – background exposure

The primary source of background exposure to chromium is diet, but no data is available on chromium intake from food in New Zealand. As discussed earlier, nutrient reference values (NRVs) for Australia and New Zealand have been established by the Australian National Health and Medical Research Council and are based on estimated mean intakes. As such, the NRV forms the best estimation of dietary intake of chromium. The adequate intake for a child aged 1–3 years (13 kg) is 11 μg/day or 0.85 μg/kg bw/day, for an adult male (19–50 years, 76 kg) is 35 μg/day or 0.46 μg/kg bw/day, and for an adult female (61 kg) is 25 μg/day or 0.41 μg/kg bw/day. The average intake for an adult is 0.44 μg/kg bw/day.

Water quality monitoring data (Davies et al, 2001) indicated that chromium was detected in eight zones (9% of those assessed), with only one zone with chromium concentrations (150 people) greater than 50% of the MAV (50 μg/L). Data on the detection of chromium up to 50% of the MAV indicates that most detections are between 0 and 10% of the MAV.

Assuming a daily consumption of 1 L of drinking water per day at chromium concentrations 10% of MAV (5 μg/L) by a young child (15 kg bodyweight) gives rise to a chromium intake from of 0.33 μg/kg bw/day, and a total dietary chromium intake of 1.2 μg/kg bw/day. Assuming a daily consumption of 2 L of drinking water per day at chromium concentrations 10% of MAV (5 μg/L) by a 70-kg adult gives rise to a chromium intake of 0.07 μg/kg bw/day, and a total dietary chromium intake of 0.53 μg/kg bw/day.

2.4.4 Summary of effects

Chromium in its trivalent state is an essential element, but at high concentrations, and particularly in its hexavalent state, it is toxic. In humans and animals chromium (III) is an essential nutrient that plays a role in glucose, fat, and protein metabolism through potentiation of the action of insulin (IOM, 2001). Limited data on the toxicity of chromium III is available. Similarly, limited data on the toxicity of ingested chromium (VI) is available, although toxic effects including reproductive and developmental effects and allergic contact dermatitis have been observed. Extensive data on the toxic effects of chromium (VI) resulting from inhalation exposure is available.

Tables 20 and 21 summarise the effects observed in animals and humans resulting from oral exposure to chromium (III) and (VI) (ATSDR, 2000).

Table 20: Summary of the health effects of chromium (III) in animals and humans

Dose mg Cr /kg/day	Type of poisoning[1]	Effects
2040	Chronic	No effects on cardiac, gastric, respiratory, hepatic or renal system observed in rats exposed to chromium (III) (as Cr_2O_3)
74	Intermediate	Lowest dosage reported to cause developmental effects (reduced ova and testes weights in offspring) in animals (mice)
5	Intermediate	Lowest dosage reported to cause reproductive effects (decreased number of implantations and viable foetuses) in animals (mice)
3.6	Chronic	No effects observed on blood, hepatic and renal system observed in rats exposed to chromium (III) as $CrCl_3$
0.46	Chronic	Lowest reported NOAELs for cardio, hepatic and renal effects in animals (rats) exposed to chromium as chromium acetate

1 Length of exposure: acute (<14 days), intermediate (15–365 days), chronic (>365 days).

Table 21: Summary of the health effects of chromium (VI) in animals and humans

Dose (mg Cr VI/kg/day	Type of poisoning[1]	Effects
37	Intermediate	Lowest dosage reported to cause developmental effects (increased number of post-implantation losses and decreased numbers of live foetuses) in animals (mice)
13.5	Intermediate	Lowest dosage reported to cause renal effects (inhibition of membrane enzymes) in animals (rats)
7.8	Intermediate	Lowest dosage reported to cause haematological effects (decreased mean corpuscular volume) in animals (mice)
6	Intermediate	Lowest dosage reported to cause reproductive effects (decreased number of implantations and viable foetuses) in animals (mice)
4.1	Acute	Lowest dosage reported to cause human death
3.6	Chronic	No effects on blood, liver or kidney observed in rats exposed to chromium (VI) as $K_2Cr_2O_7$
3.5	Intermediate	Lowest dosage reported to cause liver (cytoplasmic vacuolisation of hepatocytes) effects in animals (mice)
0.57	Chronic	Lowest dosage reported to cause gastrointestinal effects (abdominal pain, vomiting) and haematological effects (leukocytosis) in humans exposed to chromium (VI) over 1 year
0.036	Acute	Lowest dosage reported to cause contact dermatitis in humans

1 Length of exposure: acute (<14 days), intermediate (15–365 days), chronic (>365 days).

2.4.5 Weight of evidence

Chromium (III)

- Chromium (III) is considered not classifiable as to carcinogenicity (IARC, 1990; US EPA, 1998a), and therefore should be treated as a threshold contaminant.
- Chromium (III) is an essential element thus inadequate dietary intake will also result in adverse effects (IOM, 2001).

Chromium (VI)

- Chromium (VI) is classified as a known human carcinogen (IARC, 1990; US EPA, 1998b) via the inhalation route. Limited data on carcinogenicity for exposure via the oral route is available.
- Chromium (VI) compounds were positive in a number of genotoxicity assays in mammalian and non-mammalian systems. However, based largely on the absence of appropriate chronic data, and supported by the indication for a greater reducing capacity of chromium (VI) to chromium (III) via the oral route as compared to the inhalation route, the threshold approach has been used to derive reference health standards for chromium (VI) (Baars et al, 2001).

2.4.6 Recommendations for toxicological intake values

There is limited data on which to base tolerable daily intakes for chromium, and the recommended toxicological intakes of 1500 μg/kg bw/day and 3 μg/kg bw/day for chromium (VI) of the US EPA are recommended for use in New Zealand (Table 22). However, it should be noted that US EPA (1998a; 1998b) expresses a lack of confidence in the TDIs due to the poor quality of the original (McKenzie et al, 1958) study.

Dermal absorption of chromium (III) is expected to be a negligible route of exposure for soil contamination and is not considered relevant here. It is recommended that the adverse effects arising from dermal exposure to chromium (VI) are considered separately to those arising from oral exposure and that allergic contact dermatitis is the main effect of interest. A soil contaminant standard protective from allergic contact dermatitis could be established, but as these effects are likely to be elicited at higher concentrations than those arising from oral exposure, a soil contaminant standard protective against effects arising from oral exposure will also protect against allergic contact dermatitis.

Inhalation is expected to be a negligible route of exposure for soil contamination and is not considered relevant here. Dietary intake is the primary source of background exposure to chromium but no New Zealand data is available. However, Nutrient Reference Values (NRV) for chromium for different age groups have been recommended by the Australian NHMRC, based on those determined by the US Institute of Medicine (IOM, 2001) from estimated mean intakes. Therefore, in the absence of other information, it is recommended that these NRVs are used to provide estimates of dietary intake of chromium. It should be noted that these values are significantly lower than the suggested toxicity of chromium (III).

Table 22: Recommended toxicological criteria for chromium

Parameter	Value	Basis
Contaminant status	Threshold	–
Oral (μg/kg bw/day) – Cr III Cr VI	1500 3	US EPA (1998a) US EPA (1998b)
Inhalation intake (μg/kg bw/day)	NA	Lack of volatility of chromium indicates inhalation exposures are minimal
Skin absorption factor	NA	No data available although absorption is expected to be negligible
Background exposure (μg/kg bw/day)	1.2 0.53	Child (1–3 years) Adult Adequate intake of chromium (NHMRC, 2006); intake from drinking water based on NZ survey (Davies et al, 2001)

NA – not applicable

2.5 Copper (Cu)

The following discussion on the toxicity of copper summarises relevant data from various reviews (WHO, 1983; 1998; Baars et al, 2001; IOM, 2001; ATSDR, 2004). Particular attention is given to those studies that have been used in deriving reference health standards. Readers are referred to the original reviews for more details on the essentiality and adverse health effects of copper.

2.5.1 Toxicological status

Copper is both an essential element and a contaminant. Adverse effects can result from copper deficiency such that a daily copper intake of 2–3 g for adults, or 0.03–0.05 mg/kg bw/day for a 60-kg adult, is recommended to ensure minimum biological requirements are met (FAO/WHO, 1982a; 1982b). From a survey of dietary intake WHO (1996) established safe-range upper limits for mean population intakes of 12 mg/day for males (65 kg) and 10 mg/day for females (55 kg). This included the consideration that copper in food or dietary supplements is largely present in the form of organic compounds that are less toxic than ionic copper ingested in water. WHO (1998) concluded that the upper limit of the acceptable range of oral intake (AROI) is uncertain but "is most likely in the range of several but not many mg/day in adults (several meaning more than 2 or 3 mg/day)" based on studies of gastrointestinal effects of copper-contaminated drinking water. WHO (1996; 1998) concluded that from available data on human exposures worldwide, but particularly in Europe and the Americas, there is greater risk of health effects from deficiency of copper intake than from excess copper intake.

Because copper is an essential metal, cells, tissues and organisms have mechanisms to maintain copper levels within defined limits and for maintaining its availability while limiting its toxicity (homoeostasis). However, there are several disorders of homoeostatic mechanisms – such as Wilson's disease, Indian childhood cirrhosis and idiopathic copper toxicosis, which can result in deficiency or toxicity from exposure to copper at levels that are tolerated by the general population. Nonetheless, gross overexposure (either as a result of acute or chronic exposure) to copper can overwhelm the homoeostatic mechanisms in the normal individual (WHO, 1998).

Thus, toxic effects arising from copper tend to be observed only in people who have disorders in copper metabolism, and/or whose copper intake levels are excessive (WHO, 1998). Liver damage (eg, hepatitis, jaundice, hepatic necrosis) is the primary manifestation of copper toxicity in susceptible sub-populations, although this has rarely been reported in normal populations chronically exposed to copper (WHO, 1996). Liver and kidney toxicity may be observed in animal studies, although there are species-specific differences in sensitivity, with rats being more sensitive than mice (WHO, 1998; ATSDR, 2004). No association between the level of copper intake and spontaneous abortions has been found, and data is inadequate to assess the reproductive or developmental effects of copper in humans (WHO, 1998).

Gastrointestinal effects (eg, nausea, vomiting, diarrhoea) are commonly reported in human studies on exposure to copper in drinking water (eg, see WHO, 1998; 2004; IOM, 2001; ATSDR, 2004). These effects are suggested to be due to the irritant effect of copper on the gastrointestinal mucosa (WHO, 1996). The results of studies on drinking water suggest that the threshold for gastrointestinal effects from copper in water is about 6 mg/L (Araya et al, 2001; 2003a; 2003b), although one study reported an apparent threshold between 1 and 3 mg/L (Pizzarro et al, 1999). There is also a suggestion that individuals may be able to adapt to even higher concentrations – with no adverse gastrointestinal effects reported in US adults who consumed water containing approximately 8.5–8.8 mg/L of copper for over 20 years beginning in childhood (starting aged 0–5 years) (Scheinberg and Sternlieb, 1996, cited in IOM, 2001).

Copper or copper salts may result in contact dermatitis in susceptible individuals (WHO, 1998). The results of mutagenicity tests with different strains of bacteria are generally negative, although tests for mutagenicity using mammalian cells, both *in vitro* and *in vivo*, give predominantly positive results (WHO, 1998). Copper was not found to be carcinogenic in tests with mice and dogs (WHO, 1998) and copper 8-hydroxyquinoline was not classifiable as to its carcinogenicity (Group 3) (IARC, 1977). The US EPA (1991) has also not classified copper with regards to its carcinogenicity (Group D) on the basis that there is no human data, inadequate animal data from assays of copper compounds, and equivocal mutagenicity data.

2.5.2 New Zealand classification

The Hazardous Substances and New Organisms Act (HSNO) classification of copper, as copper sulphate, set by ERMA NZ is shown in Table 23; it only has meaning when expressed with respect to copper as copper sulphate, which is likely to be representative of the forms of copper present in the environment. Overall, copper is of moderately acute toxicity (6.1C oral classification), is a skin and eye irritant (6.3A, 6.4A), is a sensitiser (6.5B) and a systemic toxicant (6.9B) based on liver and kidney damage and gastrointestinal effects.

Table 23: HSNO classification of copper as copper (II) sulphate

Hazardous property	HSNO classification
Acute toxicity	6.1C
Skin irritation	6.3A
Eye irritation	6.4A
Sensitiser	6.5B
Mutagenicity	ND
Carcinogenicity	ND
Reproductive/developmental toxicity	ND
Target organ systemic toxicity	6.9B

ND – no classification due to no data/insufficient data/inconclusive data.

2.5.3 Toxicological intake values

Ingestion

Approaches to setting "acceptable" intakes for copper can be split into two approaches: consideration of the toxicity of copper, and consideration of essentiality of copper (Table 24). The JECFA (FAO/WHO, 1982a; 1982b) developed a provisional maximum TDI in humans of 0.5 mg/kg bw based on no observable effects on liver function in dogs during a 1-year feeding study. This value formed the basis for establishing a provisional drinking water standard of 2 mg/L (allocating 10% of the TDI to drinking water) by WHO (1983). This TDI is used in the Timber Treatment Guidelines (MfE and MoH, 1997), based on its use in the *Drinking Water Standards for New Zealand* (MoH, 1995).

In a recent revision WHO (2004) removed the provisional status of this standard, based on several recent human studies that confirmed the dose-response relationship between copper in drinking water and acute gastrointestinal effects. Specifically, the threshold for acute gastrointestinal effects was typically around 5 mg/L (Araya et al, 2001; 2003a; 2003b), although one study reported an apparent threshold between 1 and 3 mg/L (Pizzarro et al, 1999). Furthermore, WHO (2004) state that this value should permit consumption of 2 or 3 L of water per day, use of a nutritional supplement, and copper from foods without exceeding the tolerable upper intake level of 10 mg/day (IOM, 2001) or eliciting an adverse gastrointestinal response.

The tolerable upper limit of 10 mg/day is based on no observed effects on liver function in humans after a daily intake of a copper supplement containing 10 mg of copper during a 12-week study (Pratt et al, 1985; IOM, 2001). Liver function was chosen as the relevant endpoint "because of the potential for excess intake from food and supplements" in the United States and Canada, and the indication that liver damage is the critical endpoint resulting from daily intake of high levels of copper salts (IOM, 2001). It should also be noted that WHO (2004) considered that the data on gastrointestinal effects of copper must be used with caution "since the effects observed are influenced by temporal aspects of exposure and the

concentration of ingested copper to a greater extent than the total mass or dose ingested in a 24-hour period", citing the example that a single glass of tap water with a concentration greater than 3 mg of copper per litre is more likely to elicit nausea than a litre of water containing the same mass of copper, but ingested episodically throughout a day.

In contrast, the ATSDR (2004) derive an acute-duration MRL and an intermediate-duration MRL based on gastrointestinal effects in human studies on exposure via copper in drinking water. Both MRLs were 0.01 mg/kg bw/day, even though they were based on different studies (Table 24).

Other jurisdictions (Canada, The Netherlands) base their TDI on the upper end of estimated safe-dietary-intake ranges in the respective countries (Table 24). Australian agencies use a value of 0.17 mg/kg bw/day, which is stated to be based on Sloof et al (1989, cited in NEPC, 1999), although no information for the basis of this value is given (NEPC, 1999).

The US EPA (R6 and R9) uses a TDI of 0.04 mg/kg bw, based on the US EPA's Health Effects Summary Tables (HEAST: US EPA, 1997, cited in US EPA, 2008). However, this reference could not be obtained and the basis for this TDI is unknown. No reference dose (RfD, equivalent to TDI) for copper has been derived, according to the US EPA's IRIS database (US EPA, 1991).

Table 24: Summary of oral toxicological intake values for copper as a threshold contaminant, used by different international agencies[1]

Jurisdiction	Guideline value[2] (mg/L)	Tolerable daily intake (mg/kg bw)	Key study[3]	Critical effect[3]	Basis of value[3]	Reference
New Zealand		0.5	Not stated	Gastrointestinal effects	MoH (1995)	MfE and MoH (1997)
New Zealand drinking water	2	0.057	Not stated	Gastrointestinal effects and liver function in humans	To be protective against acute gastrointestinal effects of copper; derivation provides an adequate margin of safety in populations with normal copper homoeostasis	MoH (2005)
Joint (FAO/WHO meeting on pesticide residues		0.5	Shanaman et al (1972)	Liver function in dogs, 1-year feeding study	NOAEL of 5 mg/kg bw/day, application of a UF is not stated, although presumably is a value of 10	WHO (1983)
WHO drinking water	2	0.057	(Pratt et al (1985) – tolerable upper limit)	Gastrointestinal effects and liver function in humans	To be protective against acute gastrointestinal effects of copper and provide an adequate margin of safety in populations with normal copper homoeostasis – based on a tolerable upper limit of 10 mg/day from IOM (2001)	WHO (2004)
Australia		0.17	Not stated	Not stated	Sloof et al (1989)	NEPC (1999)
The Netherlands – current		0.14	Not stated	Not stated	Vermeire et al (1991)	Baars et al (2001)
The Netherlands – proposed[4]		0.14	Not stated	Not stated	Vermeire et al (1991)	Baars et al (2001)

Jurisdiction	Guideline value[2] (mg/L)	Tolerable daily intake (mg/kg bw)	Key study[3]	Critical effect[3]	Basis of value[3]	Reference
Canada		0.1	Health and Welfare Canada (1990)	Dietary intake	Upper limit of a safe and adequate dietary intake for a child of 3–10 years old	NCSRP (1995)
US ATSDR – intermediate-duration MRL		0.01	Araya et al (2003b)	Gastrointestinal effects in humans – 2 months drinking water	NOAEL of 0.042 mg/kg bw/day, divided by an uncertainty factor of 3 to account for human variability	ATSDR (2004)
US EPA Regions 6, 9		0.04	Not stated	Not stated	Health Effects Assessment Summary Table (HEAST)	US EPA
US Institute of Medicine		10 (0.15)[a]	Pratt et al (1985)	Liver function, 12-week study in humans	NOAEL of 10 mg/day, uncertainty factor of 1. A larger UF was considered unnecessary in view of the large international database in humans indicating no adverse effects from daily consumption of 10 to 12 mg/day of copper in foods and the rarity of observed liver damage from copper exposures in human populations with normal copper homoeostasis	IOM (2001)

1 UK agencies (DEFRA and EA) did assess copper for the purposes of managing contaminated land.

2 Where a guideline value is provided, the TDI has been derived assuming consumption of 2 L/day by a 70-kg adult.

3 As reported in the reference cited in the reference column.

4 This value is yet to be officially adopted.

a Tolerable intake is given as 10 mg/day, converted to mg/kg bw/day assuming 70 kg bodyweight.

Inhalation

Inhalation is anticipated to be a negligible route of exposure as copper is not volatile and the amount of dust considered to be inhaled typically represents a very small fraction of exposure (see section 1.1.4), so is not discussed further.

Dermal absorption

The skin absorption factor is the only contaminant-specific parameter required for the dermal absorption pathway. Organometallic copper salts are indicated to penetrate the skin, producing anti-inflammatory and anti-arthritic activity (Guy et al, 1999), but limited quantitative dermal absorption data is available. The available data indicates permeability coefficients for copper as copper chloride and copper sulphate in the order of 0.013×10^{-4} to 0.16×10^{-4} cm/h after 72 h, although higher permeability coefficients are observed during initial exposures which decrease over time (Guy et al, 1999). While these data provides an indication of dermal absorption of copper, they are not readily amenable to expression as a skin absorption factor. Further, in these studies the copper salts were applied in petrolatum, aqueous gels or emulsions; it is likely that lower absorption/permeability coefficients would be observed for copper present in contaminated soil. Finally, all the agencies considered in this report that have developed soil guideline values for copper (Canada, The Netherlands, US) have considered dermal exposure to

copper to be negligible (NCSRP, 1995; Baars et al, 2001; US EPA, 2003). Therefore, it is recommended that dermal exposure to copper is also considered negligible in the context of developing generic soil contaminant standards for New Zealand.

Other routes of exposure – background exposure

Background exposure to copper primarily occurs from food and water. The 2002 National Children's Nutrition Survey (MoH, 2003) provides median daily intakes of copper from food of 1.0 mg for boys (5–6 years, 23.1 kg) and girls (23.4 kg). The 1997 National Nutrition Survey (Russell et al, 1999) provides New Zealand median daily intakes of copper from food of 1.9 mg for males (25–44 years, 81.5 kg) and 0.8 mg for females (68.6 kg). Expressing these intakes on a bodyweight basis and for an average child and adult (see also section 1.1.3), copper intake for a child (aged 5–6 years) is 0.043 mg/kg bw/day, and for an adult (25–44 years) is 0.017 mg/kg bw/day.

Davies et al (2001) indicate that copper was detected in 97% of drinking water zones assessed (as measured at the consumer's tap), although typically between 0 and 10% of the MAV (2 mg/L) for drinking water. Using 10% of the MAV (0.2 mg/L) as a conservative estimate of copper in drinking water, and assuming a daily consumption of 1 L of water by a 15-kg child yields a conservative estimate of the daily water intake of copper for a child of 0.013 mg/kg bw. Assuming a daily consumption of 2 L of water by a 70-kg adult yields a conservative estimate of the daily water intake of copper for an adult of 0.003 mg/kg bw.

Therefore, the total dietary intake of copper (in food plus water) for a child is considered to be 0.056 mg/kg bw/day and for an adult is 0.02 mg/kg bw/day.

2.5.4 Summary of effects

Copper is both an essential element and a contaminant. Adverse effects can result from copper deficiency such that a daily copper intake of 2–3 g for adults, or 0.03–0.05 mg/kg bw for a 60-kg adult, is recommended to ensure minimum biological requirements are met (FAO/WHO, 1982a; 1982b). Gastrointestinal effects such as nausea, vomiting, and diarrhoea are the primary effects reported as a result of acute exposure to copper. However, gastrointestinal effects observed are influenced by temporal aspects of exposure and the concentration of ingested copper to a greater extent than the total mass or dose ingested in a 24-hour period (WHO, 2004). Liver damage is the primary manifestation of copper toxicity in people with copper homoeostatic disorders. Liver and kidney toxicity has been reported in animals exposed to copper. Table 25 summarises the effects observed in animals and humans resulting from exposure to copper (ATSDR, 2004).

Table 25: Summary of the health effects of copper in animals and humans

Dose (mg Cu /kg/day	Type of poisoning[1]	Effects
17	Intermediate	Lowest reported dosage to cause renal effects in animals (rats)
8	Intermediate	Lowest reported dosage to cause hepatic effects (increased aspartate aminotransferase activity) in animals (rats)
0.14	Intermediate	Lowest reported NOAEL for haematological and hepatic effects in humans after exposure to copper for 12 weeks
0.091	Intermediate exposure	Gastrointestinal effects of copper in humans exposed to copper (as copper sulphate in drinking water) over 2 months
0.073–0.096	Acute	Nausea, abdominal pain and vomiting in females exposed to copper (as copper sulphate) in drinking water over 1–2 weeks
0.01–6	Acute	Nausea and vomiting in females as a result of a single dose of copper (as copper sulphate) in drinking water

1 Length of exposure; acute (<14 days), intermediate (15–365 days), chronic (>365 days).

2.5.5 Weight of evidence

- There is no evidence that copper is carcinogenic; IARC (1977) classified copper as Group 3 – not classifiable as to its carcinogenicity. Similarly, the US EPA (1991) did not classify copper as a carcinogen (Group D), given there was no human data, inadequate animal data from assays of copper compounds, and equivocal mutagenicity data.
- Copper is an essential element, and adverse effects can arise from copper deficiency as well as excess copper intake (WHO, 1998; IOM, 2001).
- Gastrointestinal effects are the primary manifestations of toxicity arising from excess copper intake, although these effects are reversible (WHO, 1998; IOM, 2001).
- Liver damage is the critical endpoint for intake of high levels of copper in animal and human studies (WHO, 1998; IOM, 2001).
- Toxicity is likely to occur only when homoeostatic control is overwhelmed or repair mechanisms are impaired, which suggests a threshold of effects (IOM, 2001). Therefore, copper is treated as a threshold contaminant.

2.5.6 Recommendations for toxicological intake values

There are two options for setting a toxicological intake value on which to base soil contaminant standards. One is to use the tolerable upper limit based on liver function proposed by IOM (2001), and which forms the basis for setting the WHO Drinking Water Standards, and thus the New Zealand Drinking Water Standards. An alternative approach is to use a reference health standard based on gastrointestinal effects (eg, the approach of the ATSDR). However, given that gastrointestinal effects observed are influenced by temporal aspects of exposure and the concentration of ingested copper to a greater extent than the total mass or dose ingested in a 24-hour period (WHO, 2004), it seems more appropriate to base the intake value on liver function, and the tolerable upper limit of 10 mg/day derived by IOM (2001) is recommended.[6]

[6] Tolerable upper limits (TUL) for children and adolescents have also been specified by IOM (2001), and are used as the basis for nutrient reference limits specified in NHMRC and MoH (2006). These values were extrapolated from the adult TUL by prorating the child and adult bodyweights and rounding down. It is most appropriate to use non-rounded values in the derivation of soil guideline values; if this is done, the rounding applies at the end of the calculation rather than at an intermediate stage.

This limit requires conversion to a daily intake value based on bodyweight (eg, mg/kg bw/day). No bodyweight data is available in the original study (Pratt et al, 1985), therefore a standard bodyweight of 70 kg is used to derive an intake of 0.15 mg Cu/kg bw/day (Table 26).

Dermal absorption and inhalation are expected to be negligible routes of exposure and are not considered relevant for soil contamination. Dietary intake is the primary source of background exposure to copper. Estimated dietary intake for a child aged 5–6 years was 0.06 mg/kg bw/day and for an adult (25–44 years) was 0.02 mg/kg bw/day, which are within the recommended dietary intake levels for copper.

Table 26: Recommended toxicological criteria for copper

Parameter	Value	Basis
Contaminant status	Threshold	–
Oral (mg/kg bw/day)	0.15	Tolerable upper limit derived by IOM (2001), converted to intake based on bodyweight assuming a 70-kg adult
Inhalation intake (mg/kg bw/day)	NA	Lack of volatility of copper indicates inhalation exposures are minimal
Skin absorption factor	NA	No suitable data was found although dermal absorption of copper is expected to be negligible
Background exposure (mg/kg bw/day)	0.056 0.020	Child (5–6 years) Adult (25–44 years) Dietary intake of copper (Russell et al, 1999; MoH, 2003)

NA – not applicable

2.6 Lead (inorganic) (Pb)

Lead exists in both inorganic and organic forms, but it is the inorganic form that is typically of most concern in contaminated soils, and is the focus of this review. The scientific literature on the adverse health effects of lead is extensive and numerous reviews have been published (IPCS, 1995; FAO/WHO, 2000; IARC, 2006; ATSDR, 2007). The discussion below summarises relevant data from these reviews. Particular attention is given to those studies that have been used in deriving reference health standards. Readers are referred to the original reviews for more details on adverse health effects.

2.6.1 Toxicological status

Health effects associated with exposure to inorganic lead and compounds include, but are not limited to: neurotoxicity, developmental delays, hypertension, impaired haemoglobin synthesis, and male reproductive impairment. The most sensitive targets for lead toxicity are the developing nervous system, the haematological and cardiovascular systems, and the kidney. However, due to the multi-modes of action of lead in biological systems, lead could potentially affect any system or organs in the body. The effects of lead exposure have often been related to the blood lead content, which is generally considered to be the most accurate means of assessing exposure. Thus, most of the discussion below relates effects to blood lead content (PbB).

Overt signs of acute intoxication include dullness, restlessness, irritability, poor attention span, headaches, muscle tremor, abdominal cramps, kidney damage, hallucinations, loss of memory, and encephalopathy occurring at PbB of 100–120 µg/dL in adults and 80–100 µg/dL in children (ATSDR, 2007). Signs of chronic lead toxicity, including tiredness, sleeplessness, irritability, headaches, joint pain, and gastrointestinal symptoms, may appear in adults at PbB of

50–80 µg/dL (ATSDR, 2007). After 1–2 years of exposure, muscle weakness, gastrointestinal symptoms, lower scores on psychometric tests, disturbances in mood, and symptoms of peripheral neuropathy were observed in occupationally exposed populations at blood lead levels of 40–60 µg/dL (ATSDR, 2007). At lower blood lead concentrations, adverse effects include delays and/or impaired development of the nervous system, delayed sexual maturation, neurobehavioral effects, increased blood pressure, depressed renal glomerular filtration rate, and inhibition of pathways in haem synthesis. The timing of exposure, in addition to the exposure intensity, appears to be an important variable in the exposure–response relationship for lead. Exposures that occur during pre- and post-natal development, which result at PbB of 10 µg/dL or less, produce delays or impairments of neurological and sexual development. Cognitive deficits, hypertension, and depressed glomerular filtration rate have also been observed in older adults (>60 years and/or post-menopause) in association with PbBs of <10 µg/dL. This may reflect a higher vulnerability with age and/or the effects of cumulative lifetime exposures that are less evident in younger populations that have lower time-integrated exposures. Studies of children have also shown associations between PbB and growth, delayed sexual maturation in girls, and decreased erythropoietin production. While lead can impair cognitive function in adults as well, children are more vulnerable partly due to the relative importance of exposure pathways (ie, dust-to-hand/mouth) and differences in toxicokinetics (ie, absorption of ingested lead). Children absorb a larger fraction of ingested lead than adults, although perhaps more important is the fact that the developing nervous system is especially susceptible to lead toxicity (ATSDR, 2007).

A primary symptom of chronic lead poisoning is anaemia, arising from reduction in eurythrocyte lifespan and inhibition of haem synthesis by δ-aminolevulinic acid dehydratase (ALAD). Inhibition of ALAD activity occurs over a wide range of PbBs beginning at 5 µg/dL, although haemoglobin concentrations are generally not limited sufficiently to result in clinically observable anaemia until >20 µg/dL (ATSDR, 2007). While the toxicological significance of inhibition of ALAD at low exposures is controversial in the absence of a detectable effect on haemoglobin levels, impairment of haem synthesis has a far-ranging impact not limited to the haemopoietic system. A potential consequence of the inhibition of haem synthesis is a decreased formation of mixed-function oxidases in the liver resulting in impaired metabolism of endogenous compounds, as well as impaired detoxification of xenobiotics (ATSDR, 2007). Further, lead has also been shown to interfere with calcium metabolism, both directly and by interfering with the haem-mediated generation of the vitamin D precursor 1,25-dihydroxycholecalciferol. A significant decrease in the level of circulating 1,25-dihydroxycholecalciferol has been demonstrated in children whose blood lead levels were in the range 12–120 µg/dL, with no evidence of a threshold (ATSDR, 2007).

There are variable reports on the reproductive effects associated with lead exposure, with some studies reporting associations between blood lead concentrations and abortion and pre-term delivery in women and alterations in sperm and decreased fertility in men; but other studies found no significant association between lead exposure and these endpoints (ATSDR, 2007). Nonetheless there appears to be a clearer effect in males, with a threshold blood lead concentration in the range of 30–40 µg/dL (ATSDR, 2007).

Effects on kidneys may arise from acute or chronic exposure. Acute renal nephropathy, which occurs after short exposure to lead causing dysfunction of the proximal tubules and is largely reversible, has been noted at blood lead levels of 40 µg/dL and above. Chronic lead-induced nephropathy involves reductions in glomerular filtration rates: irreversible atrophy of the proximal tubules with decreased glomerular filtration rates have been consistently observed in populations with mean PbB < 20 µg/dL and two studies have reported effects at PbB < 10 µg/dL. Above 30 µg/dL enzymuria and proteinuria may become evident, with severe

deficits in function and pathological changes occurring in association with blood lead concentrations exceeding 50 µg/dL (ATSDR, 2007).

At low exposures and low blood lead concentrations, an increase in systemic blood pressure may be observed. The effects on blood pressure and glomerular filtration rate may be mechanistically related and may be confounders and covariables in epidemiological studies. Decrements in glomerular filtration rate may contribute to elevations in blood pressure, and elevated blood pressure may predispose people to glomerular disease (ATSDR, 2007).

In vitro mutagenicity studies in micro-organisms have yielded mostly negative results for lead, but lead is a clastogenic agent, as shown by the induction of chromosomal aberrations, micronuclei, and by sister chromatid exchanges in peripheral blood cells from lead workers (IARC, 2006). Lead has produced primarily renal tumours in rodents by a mechanism not yet elucidated. Some non-genotoxic mechanisms that have been proposed for lead-induced cancer include inhibition of DNA synthesis and repair, alterations in cell-to-cell communication, and oxidative damage. The carcinogenicity of lead in humans has been examined in several epidemiological studies, which either have been negative or have shown only very small excess mortalities from cancers. In most of these studies, there were either concurrent exposures to other carcinogenic agents or other confounding factors such as smoking that were not considered (WHO, 2004).

However, the major concern regarding lead toxicity is the cognitive and neurobehavioural deficits that are observed in children exposed to lead. Studies indicate that an IQ decline of 1–5 points is associated with an increase in PbB of 10 µg/dL, and recent studies have reported neurobehavioural deficits in children associated with blood lead concentrations of <10 µg/dL (ATSDR, 2007). Lead also has caused neurobehavioural alterations in developing animals, and at blood lead concentrations similar to those reported in children. Studies in animals, particularly in monkeys, have provided key information for the interpretation of a cognitive basis for IQ changes.

2.6.2 New Zealand classification

The Hazardous Substances and New Organisms Act classification of lead set by ERMA NZ is shown in Table 27, but only has meaning when expressed in respect to a particular form of the element. Lead is predominantly present in soil as Pb (II).

Overall, lead as lead chloride has low acute toxicity (6.1C) with the following long-term endpoints: it causes developmental toxicity (6.8A) and general toxicity from chronic exposures (6.9B). It should also be noted that other Pb (II) compounds have also been considered mutagenic (6.6B), and suspected human carcinogens (6.7B). These (Table 27) are believed to be the most relevant findings concerning most chemical forms of lead likely to be encountered.

Table 27: HSNO classification of lead, as lead chloride

Hazardous property	HSNO classification
Acute toxicity	6.1C
Skin irritation	ND
Eye irritation	ND
Sensitiser	–
Mutagenicity	ND (6.6B)[1]
Carcinogenicity	ND (6.7B)[1]
Reproductive/developmental toxicity	6.8A
Target organ systemic toxicity	6.9B (6.9A)[2]

ND – not determined; – – not assigned.

1 Other Pb (II) compounds have been classified as mutagens and potential human carcinogens.

2 Other Pb (II) compounds have been classified as 6.9A.

2.6.3 Reference health standards

Ingestion

The Joint FAO/WHO Expert Committee on Food Additives was the only authoritative body that established a tolerable intake of lead and had previously set a provisional tolerable weekly intake (PTWI) of 0.025 mg/kg bw applicable for infants and children (FAO/WHO, 1986). This value was reconfirmed in 1993 and extended to adults (FAO/WHO 1993), and maintained in 1999 (FAO/WHO, 2000). However, this PTWI was withdrawn in June 2010 based on dose-response analyses and estimation that the previously established PTWI of 25 μg/kg bodyweight is associated with a decrease of at least 3 intelligence quotient (IQ) points in children and an increase in systolic blood pressure of approximately 3 mmHg (0.4 kPa) in adults (FAO/WHO, 2010). JECFA considered that while such effects may be insignificant at the individual level, these changes were important when viewed as a shift in the distribution of IQ or blood pressure within a population. Further, JECFA concluded that as the dose-response modelling failed to indicate a threshold of effect, it was not possible to establish a new PTWI that would be protective of human health.

Instead, JECFA suggests that their dose-response analyses should be used as guidance to identify the magnitude of effect associated with identified levels of dietary lead exposure in different populations. Based on the information provided, an exposure level of 0.3 μg/kg bodyweight/day was calculated to be associated with a population decrease of 0.5 IQ points, which was considered to be a negligible impact. In contrast, an exposure level of 1.9 μg/kg bodyweight/day was calculated to be associated with a population decrease of 3 IQ points, which was deemed by JECFA to be of concern. JECFA considered that effects on systolic blood pressure in adults were of less concern than that for the neurodevelopmental effects observed in children.

The previous PTWI was based on metabolic studies in infants (Ryu et al, 1983, in FAO/WHO, 1986) showing that a mean daily intake of 0.003–0.004 mg/kg bw was a no observable adverse effect level and was not associated with an increase in blood lead levels or in the body burden of lead, while an intake of 0.005 mg/kg bw or more resulted in lead retention (FAO/WHO, 1986). The small uncertainty factor (<2) reflected the conservatism of the endpoint, the quality of the metabolic data, and use of one of the most susceptible groups in the population. An estimate of

the blood lead concentrations associated with this intake was 5.7 μg/dL[7] and was considered to be below the concentration shown to be associated with an effect on intellectual performance in children (FAO/WHO, 1993). JECFA's PTWI, or the total daily intake derived from it, has been used by the Australian (NEPC, 1999), Dutch (Baars et al, 2001) and Canadian (NCSRP, 1996) regulatory agencies to derive soil guideline values. Further, in New Zealand this PTWI was used by Cavanagh and Proffitt (2005), and appears to have been the basis for a soil metal limit established in NZWWA (2003) (see also Cavanagh, 2004).

US EPA's IRIS database does not provide an RfD for inorganic lead, due to the significant amount of information on the health effects of lead already available, and assessment of this information by other US regulatory bodies (US EPA, 2004a). Further, the ATSDR (2007) did not derive MRLs for lead because a clear threshold for some of the more sensitive effects in humans has not been identified. Further, they considered that deriving an MRL would overlook the significant body of literature on health effects associated with blood lead concentrations. In lieu of MRLs, ATSDR developed a framework to guide decisions at lead-contaminated sites, which uses site-specific exposure data to estimate internal doses as measured by blood lead levels.

The Environmental Case Management of Lead Exposed Persons (MoH, 2007) provides a summary of recommended guideline values based on international values, but does not discuss the underlying toxicological basis for these values.

UK and US agencies use blood lead concentrations as the standard index of exposure and risk (DEFRA and EA, 2002a; CDC, 2005). Specifically, a blood lead concentration of 10 μg/dL (0.1 μg/mL) is considered to be the most appropriate, recognising that there is generally considered to be no threshold for the neurotoxic action of lead and exposures from all sources should be as low as reasonably practicable (DEFRA and EA, 2002a). In New Zealand, cases where blood lead concentrations of individuals are at or above 10 μg/dL are required to be notified to the Medical Officer of Health (MoH, 2007).

Bioavailability of lead

While it is generally acknowledged that not all of the contaminants present in soil are absorbed into the human body (ie, are bioavailable), there is generally insufficient data to assume anything less than 100% bioavailability. Lead is an exception. Probably due to the extensive literature on the health effects of lead exposure, and in particular the focus on blood lead concentrations as a more accurate means for assessing exposure, regulatory agencies have used a reduced bioavailability of lead in the derivation of soil guideline values (either through the use of a simple factor or a model estimating blood lead concentrations). Lijzen et al (2001) use a relative bioavailability (the bioavailability from a soil matrix with respect to the bioavailability from the matrix in toxicity studies used to assess tolerable intakes) for lead of 0.6 (60%) in the derivation of serious (human health) risk concentrations. UK and US agencies have developed models based on the relationship between exposure and blood lead concentrations to derive soil guideline values. In the US, the Integrated Exposure Uptake Biokinetic (IEUBK) model has primarily been used to establish soil guideline values for lead (US EPA, 1994b; 1996; 2004a; 2004b; 2004c), while in the UK a model developed by the Society for Environmental Geochemistry and Health (SEGH) was used (DEFRA and EA, 2002b). UK agencies are currently re-deriving soil guideline values for various contaminants including lead, thus it is

[7] Based on an intake for a two-year-old child weighing 10 kg at the PTWI, of 250 μg of lead per week, or 35.7 μg per day, and a conversion factor (based on one empirical study) of 0.16 μg/dL per microgram of lead intake per day (FAO/WHO, 1993).

unclear as to whether this approach will be maintained. Nonetheless, a brief discussion is provided below.

Further detail on these models is provided in Cavanagh (2004), although, briefly, the IEUBK model was developed to describe the exposure of children to lead from multiple sources, and incorporates data on the toxicokinetics of lead – five exposure pathways are considered (air, water, diet, soil and dust). Using the various generic default parameters, including absorption factors of 0.3 for soil and dust, and 0.5 for food and water, a soil guideline value of 400 mg/kg is derived, and is considered appropriate for use in a residential scenario. This is the value that has been recommended for use in the management of contaminated land (US EPA, 1994a), and has been adopted by regulatory agencies in the United States (US EPA, 1996; 2004a; 2004b; US HUD, 1995).

In contrast, the UK model considers the background exposure to lead from sources other than soil and dust, and the slope or response of the blood lead concentration versus soil and dust lead relationship:

$$S = 1000 \times ([T/Gn] - B) / \delta$$

where: S = soil or dust guideline (μg/g or mg/kg)

T = blood lead target concentration (10 μg/dL)

G = the geometric standard deviation of the blood lead distribution (1.4 μg/dL)

n = number of standard deviations corresponding to the degree of protection required for the population at risk (1.645 for protection of 95% of the population)

B = the background or baseline blood lead concentration in the population from sources other than soil and dust (3.44 μg/dL)

δ = the slope or response of the blood lead concentration versus soil and dust lead relationship (5 μg/dL increase per 1000 μg/g increment of soil or dust lead).

DEFRA and EA (2002b) consider that one of the main uncertainties in the UK model is the choice of δ, because δ is based only on empirical studies of environmental lead exposure and blood lead concentrations in children, and therefore it is not appropriate for adults. Furthermore, there is a wide variation in the value of δ, from 0.9 to 9 μg/dL (blood concentration) per 1000 μg/g (soil concentration), determined in available studies – this variation is attributable to differences in study methodologies.

Other sources also indicate a reduced bioavailability of lead. For example, FAO/WHO (2000) indicates that absorption of lead can range from 3 to 80% with typical absorption rates in adults and infants considered to be 10 and 50% respectively. Laboratory studies found the bioacessibility (the fraction of an external dose available for gastric absorption, a major component of bioavailability) of lead ranges from 2 to 75% (Sips et al, 2001; Grøn and Andersen, 2003). In terms of usage in the development of soil contaminant standards, the relative bioavailability value of 0.6 used by Lijzen et al (2001) appears to provide the most robust estimate of lead bioavailability in soil, of the available estimates. However, there is still uncertainty about the relevance of this value to New Zealand, particularly as it is based on data from Dutch soils, and New Zealand soils may differ.

While there is an extensive literature available on the effects associated with specific blood lead concentrations, there is arguably more extensive literature focusing on the relationship between intake and absorption than for other contaminants. Current studies indicate a wide range of lead

bioavailability/bioaccessibility, although there are no agreed laboratory methods for determining bioavailability/bioaccessiblity. Potentially, the model developed by the UK agencies, which relates blood lead to soil lead, and thus potentially provides a "real" measure of bioavailability, could be investigated for use in New Zealand. However, this information is currently not available, and the UK model has an uncertain status. Furthermore, it should be noted that while a blood lead concentration of 10 μg/dL is used as a threshold of effect, it is recognised that effects occur below this concentration. This level was not changed, however, for reasons including that setting a lower level would be arbitrary given the absence of an identifiable threshold and feasibility and effectiveness of interventions to further reduce levels already below 10 μg/dL have not been shown (CDC, 2005). Thus in the absence of a valid model to predict blood lead concentrations for New Zealand, and the suggested absence of a threshold of effect for neurodevelopmental impairment, it is recommended that, in the first instance, 100% bioavailability is assumed.

Table 28: Summary of oral reference health standards for lead as a threshold contaminant, used by different international agencies

Jurisdiction	PTWI (µg/kg bw)	TDI (µg/kg bw)	Blood lead (µg/dL)	Key study[1]	Critical effect[1]	Basis of value[1]	Reference
New Zealand	25	3.6		Not stated	No accumulation in body burden of lead	FAO/WHO (1986)	NZWWA (2003) and Cavanagh and Proffitt (2005)
New Zealand drinking water	25	3.6		Not stated	No accumulation in body burden of lead	FAO/WHO (1986)	MoH (2005)
Joint FAO/WHO Expert Committee on Food Additives (JECFA) – now withdrawn	25	3.6		Ryu et al (1983)	No increase in blood lead concentrations, which may have given rise to neurodevelopmental effects in children	Intake of lead that did not show an increase in blood lead concentrations	FAO/WHO (1986)[2]
WHO drinking water	25	3.6		Not stated	No accumulation in body burden of lead	FAO/WHO (1986)	WHO (2003)
Australia	25	3.6		Not stated	No accumulation in body burden of lead	FAO/WHO (1986)	NEPC (1999)
UK			10	Not stated	Neurodevelopmental effects in children	FAO/WHO (1993; 2000)	DEFRA and EA (2002a; 2002b)
The Netherlands – current	25	3.6		Not stated	No accumulation in body burden of lead	FAO/WHO (1986)	Baars et al (2001)
The Netherlands – proposed[3]	25	3.6		Not stated	No accumulation in body burden of lead	FAO/WHO (1986)	Baars et al (2001)
Canada	25	3.6		Not stated	No accumulation in body burden of lead	FAO/WHO (1986)	NCSRP (1996)
US			10	Not stated	Neurodevelopmental effects in children	Not stated	CDC (2005)

1 As reported in the reference cited in the reference column.

2 Reconfirmed in 1993 and extended to all age groups (FAO/WHO, 1993); maintained in 1999 (FAO/WHO, 2000).

3 This value is yet to be officially adopted.

Inhalation

Inhalation will be a negligible route of exposure as lead is not volatile and the amount of dust considered to be inhaled typically represents a very small fraction of exposure (see section 1.1.4), so is not considered further.

Dermal absorption

The skin absorption factor is the only contaminant-specific parameter required for the dermal absorption pathway, which is typically considered to be negligible for inorganic contaminants such as lead. Limited data is available on the dermal absorption of lead, and these indicate that organic lead compounds are more readily absorbed than inorganic lead (Guy et al, 1999). *In vitro* percutaneous absorption of lead oxide and lead acetate after 24 h in human skin was less than 0.01% and 0.05%, respectively, of the applied dose. This low rate of absorption indicates that dermal exposure is a negligible route of exposure, and could be ignored in the derivation of soil contaminant standards for contaminated land in New Zealand, as has been done by other jurisdictions (Baars et al, 2001; US EPA, 1994b).

Other routes of exposure – background exposure

Since the removal of lead from petrol in New Zealand in 1996, the main source of non-occupational exposure is lead-based paints on and around houses built before 1970 and particularly before 1945 (MoH, 2007). Beyond this, food intake, and drinking water, in particular where lead has been used in the plumbing system, may also result in exposure.

Vannoort and Thomson (2005) estimated that the average dietary intake for lead in New Zealand was 2.1 μg/kg bw/week or 0.3 μg/kg bw/day for a toddler (1–3 years, 13 kg) and 0.9 μg/kg bw/week for young males (25+ years, 82 kg) and 0.8 μg/kg bw/week for young females (25+ years, 70 kg). The average dietary intake of lead for an adult is 0.85 μg/kg bw/week or 0.12 μg/kg bw/day.

Water quality monitoring data (Davies et al, 2001) indicated that lead was detected in 731 zones or 85% of those assessed, with 612,000 people estimated to be exposed to drinking water with lead concentrations greater than 50% of the maximum acceptable value (10 μg/L), with 477,000 people estimated to be exposed to drinking water with lead concentrations greater than the MAV. While a significant number of people are exposed to lead concentrations greater than the MAV, there is no data on what those concentrations are, thus exposure at the MAV is used to determine intake from drinking water.

Assuming a daily consumption of 1 L of water per day at lead concentrations at the MAV (10 μg/L) by a young child (15 kg bodyweight) gives rise to a lead intake from drinking water of 0.7 μg/kg bw/day, and a total lead intake for a child of 0.97 μg/kg bw/day or 6.7 μg/kg bw/week. Assuming a daily consumption of 2 L at lead concentrations at the MAV (10 μg/L) by a 70-kg adult gives rise to a lead intake from drinking water of 0.28 μg/kg bw/day, and a total lead intake of 0.41 μg/kg bw/day or 2.85 μg/kg bw/week.

2.6.4 Summary of effects

Studies reporting health effects associated with exposure to lead have more often reported blood lead concentrations, as opposed to estimated intakes. As such, the health effects of lead, modified from ATSDR (2007) and summarised in Table 29, are based on blood lead concentrations.

Table 29: Summary of effects associated with lead, as measured by blood lead concentrations (modified from ATSDR, 2007)

Blood lead (µg/dL)	Duration of exposure	Effect
100–120	Acute	Restlessness, irritability, poor attention span, headaches, muscle tremor, abdominal cramps, kidney damage, hallucinations, and loss of memory, encephalopathy in adults
80–100	Acute	Restlessness, irritability, poor attention span, headaches, muscle tremor, abdominal cramps, kidney damage, hallucinations, and loss of memory, encephalopathy in children
50–80	Chronic	Signs of chronic toxicity including tiredness, sleeplessness, irritability, headaches, joint pain, and gastrointestinal symptoms in adults
>50	Chronic	Depressed haemoglobin in adults
40–60	Chronic	Muscle weakness, gastrointestinal symptoms, lower scores on psychometric tests, disturbances in mood, and symptoms of peripheral neuropathy in occupationally exposed adults
30–40	Chronic	Reduced fertility in adults
>40	Chronic	Depressed haemoglobin in children, neurobehavioural effects in adults
>30	Chronic	Depressed nerve conduction velocity in children, liver damage in adults
>15	Chronic	Depressed vitamin D in children
<10	Chronic	Neurodevelopmental effects in children; inhibition of sexual maturation in children; depressed δ-aminolevulinic acid dehydratase and glomerular filtration rate in adults
<5	Chronic	Depressed δ-aminolevulinic acid dehydratase in children, neurobehavioural effects in elderly adults

2.6.5 Weight of evidence

- Inorganic lead is considered to be probably carcinogenic to humans (Group 2A) by the IARC (2006), and a probable human carcinogen (Group B2) by the US EPA (1993).
- Inorganic lead does not induce point mutations in bacterial and mammalian assays, although it does induce clastogenic effects (chromosome breakage, chromosomal aberrations and sister-chromatid exchange) in occupationally exposed adults (ie, is genotoxic) (IARC, 2006).
- The most sensitive targets for lead toxicity are the developing nervous system, the haematological and cardiovascular systems, and the kidneys. However, due to the multiple modes of action of lead in biological systems, lead could potentially affect any system or organs in the body (FAO/WHO, 2000; IARC, 2006; ATSDR, 2007).
- Children are more vulnerable than adults due to increased absorption of lead and the effect of lead on the developing nervous system (WHO, 2003; IARC, 2006; ATSDR, 2007).
- The most significant critical effect of low concentrations of lead is considered to be reduced cognitive development and intellectual performance in children (FAO/WHO, 2000).

2.6.6 Recommendations for toxicological intake values

Although lead is considered to be a probable human carcinogen and has some genotoxic activity, the most significant critical effect of low concentrations of lead is considered to be reduced cognitive development and intellectual performance in children, for which determining a tolerable intake is deemed appropriate. JECFA is the only authoritative body that has previously derived a tolerable intake for lead and the PTWI of 25 μg/kg bw, and the TDI derived from this, has been the value most widely used by different international agencies. However, this PTWI has subsequently been withdrawn and not replaced. Instead, the dose-response modelling undertaken was suggested to be used as a guide to identify the magnitude of effect associated with identified levels of dietary lead exposure. Based on this modelling, an exposure level of 1.9 μg/kg bodyweight/day was calculated to be associated with a decrease of 3 IQ points in a population, which was deemed by JECFA to be of concern.

While blood lead concentration is considered to give the most accurate indication of lead exposure, and models to predict blood lead concentrations associated with lead exposure have been used in the US and UK, no such model has been investigated for use in New Zealand.

Given the absence of a validated model for predicting blood lead effects in New Zealand, it is recommended that a toxicological intake value of 1.9 μg/kg bw/day is used as the basis for deriving soil contaminant standards. While this value is the exposure level calculated by FAO/WHO (2010) to be associated with a decrease of 3 IQ points at a population level, the effects were considered to be insignificant at an individual level. Exposures of individuals are more relevant in the context of contaminated sites, thus it is considered that an intake value of 1.9 μg/kg bodyweight/day is sufficiently precautionary.

Further, while reduced bioavailability of lead has been used by some international agencies (either through the use of blood lead models or a simple factor) in the derivation of soil guideline values, it is recommended that 100% bioavailability of lead is assumed in the first instance, for consistency with other contaminants and to provide an additional degree of precaution, given the apparent absence of a threshold of adverse effects.

Inhalation exposure and dermal absorption are expected to be negligible, and could be ignored in the derivation of soil contaminant standards for contaminated land in New Zealand, as has been done by other jurisdictions (Baars et al, 2001).

Dietary intake is the primary source of background exposure to lead and was estimated to be 0.97 μg/kg bw/day for a child (aged 1–3 years, 13 kg) and 0.41 μg/kg bw/day for an adult. Given the long-term effects of lead, it is more appropriate to express these intakes as weekly intakes: estimated at 6.7 μg/kg bw/week for a child and 2.85 μg/kg bw/week for an adult (Table 30).

Table 30: Recommended toxicological criteria for inorganic lead

Parameter	Value	Basis
Contaminant status	Threshold	Refer to weight of evidence
Oral index dose (μg/kg bw per day)	1.9	Dose-response modelling by FAO/WHO (2010) that indicated this level of exposure may give rise to decreased IQ at a population level, but effects were considered insignificant at an individual level.
Inhalation intake	NA	Lack of volatility of inorganic lead indicates inhalation exposure is negligible
Skin absorption factor	NA	Available data indicate that dermal absorption of inorganic lead is negligible (Guy et al, 1999)
Background exposure (μg/kg bw per day) or [per week]	0.97 [6.7] 0.41 [2.85]	Child (1–3 years) Adult (25+ years) Dietary intake (Davies et al, 2001; Vannoort and Thomson, 2005)

NA – not applicable.

2.7 Mercury (inorganic) (Hg)

A number of reviews on the toxicity of inorganic mercury (IPCS, 1991; 2003; ATSDR, 1999; DEFRA and EA, 2002) have been published, and additional reviews are available for methyl-mercury (ATSDR, 1999; EA, 2009; FAO/WHO, 2004). Mercury exists in both organic and inorganic (including elemental) forms. Organic mercury (primarily methylmercury) is mainly formed under both aerobic and anaerobic conditions through bacterial biotransformation (although other biological and chemical processes may also result in the formation of organic mercury compounds), and is a natural process occurring in aquatic sediments. This conversion is suggested to account for the high level of organic mercury found in fish and other seafood (Guy et al, 1999). However, mercury primarily exists in inorganic forms in soil, which thus are the focus of this review. The discussion below summarises relevant data for inorganic mercury from these reviews. Particular attention is given to those studies that have been used in deriving reference health standards. Readers are referred to the original reviews for more details on adverse health effects.

2.7.1 Toxicological status

Inhalation of sufficient levels of metallic mercury vapour has been associated with systemic toxicity in both humans and animals. The major target organs of metallic-mercury-induced toxicity are the kidneys and the central nervous system. At high exposure levels, respiratory, cardiovascular, and gastrointestinal effects also occur.

Central nervous system effects are considered to be the most sensitive indicator of inhalation exposure to metallic mercury vapour. Symptoms reported as a consequence of occupational exposure include tremors, poor concentration, some loss of psychomotor skills and decreased nerve conduction. Neurotoxicity is suggested to be attributable to mercuric ion formation in the brain (EA, 2009).

Inorganic mercury compounds are rapidly accumulated in the kidneys, the main target organs for chronic exposure to these compounds. The primary effect is suggested to be the formation of mercuric-mercury-induced autoimmune glomerulonephritis. The first step is the production of

gamma globulin antibodies and their deposition on the glomerular membrane. If the process continues, the selectivity of the filtration process is damaged and serum proteins and other proteins are lost to urine (proteinuria), and oedema consequently develops. The latter condition is sometimes known as nephrotic syndrome. Autoimmune glomerulonephritis is the most sensitive endpoint in animals, with the brown Norway rat being considered particularly sensitive. Proteinuria has been associated with occupational exposure to metallic mercury, both in workers with other evidence of mercury poisoning and in those without such evidence. Other effects on the kidneys that have been observed during animal studies include increased kidney weight and increased incidence of tubular necrosis (IPCS, 2003).

Other toxic effects that have been observed in animals during subchronic or chronic exposure at higher concentrations than those responsible for renal effects include inflammation and necrosis of the glandular stomach, increases in hepatic lipid peroxidation and decreases in glutathione, decreases in liver weight, increases in adrenal weights, and effects on the thyroid (IPCS, 2003).

Studies undertaken to assess the carcinogenicity of mercuric chloride found that renal adenomas and adenocarcinomas occurred in male rodents only. A few renal adenomas occurred in female rats and there was a dose-related increase in the incidence of squamous-cell papilloma of the fore-stomach in males. Dose-related hyperplasia of the fore-stomach was seen in both males and females (IPCS, 2003; WHO, 2005).

Inorganic mercury compounds react with DNA (and other macromolecules) and have been shown to be clastogenic (chromosomal aberrations and sister-chromatid exchange) in *in vitro* and *in vivo* studies, although some studies have also shown negative results (IPCS, 2003; WHO, 2005).

2.7.2 New Zealand classification

The Hazardous Substances and New Organisms Act classification of inorganic mercury set by ERMA NZ only has meaning when expressed in respect to a particular form of the element. As both metallic mercury, Hg (0), and divalent mercury, Hg (II), are important environmental forms, the HSNO classifications are shown for both (Table 31).

Table 31: HSNO classification of metallic mercury and mercury as mercuric chloride

Hazardous property	Metallic mercury	Mercuric chloride
Acute toxicity	6.1B	6.1B
Skin irritation	ND	8.2C
Eye irritation	ND	8.3A
Sensitiser	6.5B	ND
Mutagenicity	ND	ND
Carcinogenicity	ND	ND
Reproductive/developmental toxicity	6.8A	ND
Target organ systemic toxicity	6.9A	6.9A

ND – not determined.

Overall, inorganic mercury is of relatively high toxicity (6.1B) and mercury is highly toxic from chronic exposures (6.9A). Metallic mercury is also considered to be a sensitiser (6.5B) and a reproductive toxicant (6.8A) while divalent mercury is corrosive to skin (8.2C) and eye tissue (8.3A). These findings are believed to be the most relevant, concerning most inorganic (excluding elemental) forms of mercury likely to be encountered.

2.7.3 Reference health standards

Ingestion

Reference health standards for inorganic mercury have been variably based on total mercury and inorganic mercury, although more recent RHSs have been specific for inorganic mercury (Tables 32 and 33). RHSs developed for total mercury are based on the toxicity of methylmercury (FAO/WHO, 1988; 2004), although in specific cases, eg, drinking water, it is assumed to apply to inorganic mercury (MoH, 2005). The total-mercury tolerable intake used by various agencies was that established by JECFA in 1972, which originally established a provisional tolerable weekly intake of 5 µg/kg bw/week of total mercury, of which no more than 3.3 µg/kg bw/week should be present as methylmercury (FAO/WHO, 1972). This was based on the amount of mercury in human hair, and calculations relating dietary intake to concentrations of mercury in hair. The PTWI for methylmercury was reconfirmed in 1988 (FAO/WHO, 1988), but was revised to 1.6 µg/kg bw in 2004 (FAO/WHO, 2004). The PTWI of 5µg/kg bw/week of total mercury was recently withdrawn by JECFA and a PTWI of 4µg/kg bw/week for inorganic mercury established (FAO/WHO 2010). This PTWI was based on the lowest $BMDL_{10}$ for relative kidney weight increase in male rats and gave a daily dose of 0.06 mg/kg bw/day, after adjustment from a 5 day per week dosing schedule to an average daily dose and for the percent contribution of inorganic mercury to dose, and application of a 100-fold uncertainty factor. This PTWI is stated to apply to dietary exposure to total mercury from foods other than fish and shellfish.

Evaluations of tolerable intakes for inorganic mercury have used data on its toxicity in animals, with immune effects in rat kidney being the critical response (Table 33). The TDIs established by the US EPA (1995) and the IPCS (2003) have been adopted by other agencies (Table 33), but these use different studies to establish their RHS. The US EPA (1995) used a selection of studies that provided lowest observable adverse effects levels for immunoglobulin G effects in the kidney of the brown Norway rat, which they considered a good surrogate for the study of mercury-induced kidney damage in sensitive humans. The LOAELs ranged from 0.23 to 0.63 mg/kg bw. These studies, along with other data on the toxicity of inorganic mercury, were considered during a workshop and, after intensive review, a Drinking Water Equivalent Level (DWEL) of 0.01 mg/L was recommended. The oral RfD provided in US EPA (1995) is derived by back-calculation of the DWEL, assuming 2 L per day is consumed by a 70-kg adult; it is also stated to be based on LOAELs of 0.226, 0.317, and 0.633 mg/kg bw/day of mercuric chloride. In contrast, Baars et al (2001) and the IPCS Working Group (IPCS, 2003) used the study of NTP (1993 cited in IPCS, 2003) which determined a NOAEL of 0.23 mg/kg bw/day for kidney effects in the Fischer rat (Table 33). No rationale for the selection of this study over other studies was given.

ATSDR derived the subchronic minimal risk level for inorganic mercury from the 26-week study in which dose-related effects on the kidney were observed in rats given mercuric chloride orally (NTP, 1993 cited in IPCS, 2003). The lowest dose level (0.23 mg/kg bw/day) was judged to be a NOAEL. This was multiplied by 5/7 (to take account of the dosing regime) and divided by an uncertainty factor of 100 (10 each for inter- and intra-species variations) to arrive at an MRL of 2 µg/kg bw/day (rounded value) considered protective for human exposures of up to one year. ATSDR (1999) considered there was no suitable chronic oral study on which to base a chronic oral MRL. The EA (2009) in the UK recently evaluated toxicological data for all forms of mercury and recommended a TDI of 2 µg/kg bw based on the Baars et al (2001) and IPCS (2003) recommendations. This represents a change from their previous recommendation of 0.3 µg/kg bw/day and is indicated to be “largely a reflection of changes in the weight of expert group opinion” (EA, 2009).

Table 32: Summary of oral reference health standards for inorganic mercury, based on total mercury, as a threshold contaminant, used by different international agencies

Jurisdiction	Tolerable daily intake (µg/kg bw)	Key study[1]	Critical effect[1]	Basis of value[1]	Reference
New Zealand drinking water	0.47 (3.3 µg/kg bw provisional tolerable weekly intake)	Not stated	Nursing mothers and pregnant women	FAO/WHO (1988) – PTWI for methylmercury	MoH (2005)
Joint FAO/WHO Expert Committee on Food Additives (JECFA)	0.57 (4 µg/kg bw provisional tolerable weekly intake)	Not stated	Increased liver weight in male rats	Lowest $BMDL_{10}$ for relative kidney weight increase in male rats, adjusted to daily dose, and application of a 100-fold uncertainty factor	FAO/WHO (2010)
Australia	0.47 (3.3 µg/kg bw provisional tolerable weekly intake)	Not stated	Not stated	FAO/WHO (1988) – PTWI for methylmercury	NEPC (1999)
The Netherlands – current	0.61 (5 µg/kg bw provisional tolerable weekly intake)	Not stated	Not stated	FAO/WHO (1988) – PTWI for total mercury	Baars et al (2001)

1 As reported in the reference cited in the reference column.

Table 33: Summary of oral reference health standards for inorganic mercury as a threshold contaminant, used by different international agencies

Jurisdiction	Tolerable daily intake (µg/kg bw)	Key study[1]	Critical effect[1]	Basis of value[1]	Reference
International Programme on Chemical Safety (IPCS)	2	NTP (1993)	Renal effects – rats	NOAEL of 0.23 mg/kg bw/day as the starting point, adjusting the 5 days per week dosing pattern to daily exposure, and applying an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability)	IPCS (2003)
WHO – drinking water	2	NTP (1993)	Renal effects – rats	IPCS (2003)	WHO (2005)
UK	2	Not stated	Renal effects – rats	Baars et al (2001); IPCS (2003)	EA (2009)
The Netherlands – proposed[2]	2	Not stated	Renal effects – rats	NOAEL of 0.23 mg/kg bw/day and application of 100-fold uncertainty factor to account for inter- and intra-species variation	Baars et al (2001)
Canada	0.3	Not stated	Renal effects – rats	US EPA (1995)	Health Canada (1996)
US ATSDR – intermediate duration MRL	2	Dieter et al (1992); NTP (1993)	Renal effects – rats	NOAEL of 0.23 mg/kg bw/day as the starting point, adjusting the 5 days per week dosing pattern to daily exposure, and applying an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability)	ATSDR (1999)

US EPA	0.3	Druet et al (1978), Bernaudin et al (1981) and Andres (1984) form the basis for the recommended DWEL	Renal effects – rats	Back calculations from a Drinking Water Equivalent Level, recommended to and subsequently adopted by the Agency,[3] of 0.010 mg/L (RfD = 0.010 mg/L x 2 L/day/70-kg bw = 0.0003 mg/kg bw/day)	US EPA (1995)

1 As reported in the reference cited in the reference column.

2 This value is yet to be officially adopted.

3 The most sensitive adverse effect for mercury risk assessment was identified as formation of mercuric-mercury-induced autoimmune glomerulonephritis. The brown Norway rat was identified as a good surrogate for the study of mercury-induced kidney damage in sensitive humans. Information from three studies (Druet et al, 1978; Bernaudin et al, 1981; Andres 1984; all cited in US EPA, 1995) using the brown Norway rat was selected as the basis for the panel's recommendation of 0.010 mg/L as the DWEL for inorganic mercury. The recommended DWEL of 0.010 mg/L was derived as the product of an intensive review and workshop discussions of the entire inorganic mercury database.

Inhalation

Exposure to elemental mercury vapour has been a significant cause of concern in relation to toxic effects from inorganic mercury (IPCS, 1991; 2003). However, inhalation exposures are most likely to occur in occupational settings and inhalation is expected to be a negligible route of exposure on contaminated sites as mercury has limited volatility, and the amount of dust considered to be inhaled typically represents a very small fraction of exposure (see section 1.1.4).

Dermal absorption

The skin absorption factor is the only contaminant-specific parameter required for the dermal absorption pathway, which is typically considered to be negligible for inorganic contaminants such as mercury. Inorganic mercury is considered to be a skin sensitiser, and may cause acute contact dermatitis (Guy et al, 1999). Mercury reacts with skin proteins, and as a result penetration does not increase commensurably with increasing exposure concentration but rather approaches a plateau value. Mercury has a permeability coefficient in the order of 10^{-5} cm/h (Guy et al, 1999), which compares to permeability coefficients in the order of 10^{-4} cm/h for lead. As lead was considered to have negligible absorption (see earlier), dermal absorption of mercury is considered to be a negligible route of exposure.

Other routes of exposure – background exposure

The general population is primarily exposed to mercury through diet and dental amalgam (IPCS, 1991; 2003). Data on mercury intake from dental amalgam is likely to be highly variable: ATSDR (1999) estimates values may range from 1.2 to 27 μg/day. CCME (1996) provides an estimate of an average daily intake of inorganic mercury from dental amalgam of 0.52 μg/day for children aged 5–11, and 2.81 μg/day for adults aged 20+ years. In the absence of data from New Zealand, a mercury intake of 0.04 μg/kg bw/day, based on the intake of 2.81 μg/day for adults from CCME (1996), could be used as an estimate of mercury intake from mercury amalgam fillings. It is considered that children aged 1–3 years will generally not have fillings, thus no mercury intake is expected from mercury amalgam fillings.

Vannoort and Thomson (2005) estimate the dietary intake of total mercury to be 1.3 μg/kg bw/week or 0.19 μg/kg bw/day for a young child (1–3 years, 15 kg) and 0.74 μg/kg bw/week or 0.11 μg/kg bw/day for adult males and 0.6 μg/kg bw/week or 0.09 μg/kg bw/day for adult females. This intake is primarily from seafood, with mercury not detected in most other food

samples. Assuming that 20% of total mercury in seafood is inorganic mercury (IPCS, 2003), this gives rise to daily intakes of inorganic mercury of 0.04 μg/kg bw/day for a young child (1–3 years, 15 kg) and 0.02 μg/kg bw/day for adults.

Davies et al (2001) detected mercury (total) in only three drinking water zones (3% of those assessed), with an estimated 100 people exposed to drinking water at greater than 50% of the maximum acceptable value. As a conservative estimate of drinking water intake, it is assumed the inorganic mercury is present at 10% of the MAV (2 μg/L).

Assuming that all mercury present in drinking water is inorganic, and a daily consumption of 1 L of water per day at mercury concentrations at 10% of the MAV (2 μg/L) by a young child (15 kg bodyweight), the inorganic mercury intake from drinking water is 0.01 μg/kg bw/day, and the total inorganic mercury intake for a child is 0.05 μg/kg bw/day. Assuming a daily consumption of 2 L at mercury concentrations at 10% of the MAV (2 μg/L) by a 70-kg adult, the inorganic mercury intake from drinking water is 0.006 μg/kg bw/day, and a total inorganic intake is 0.065 μg/kg bw/day.

2.7.4 Summary of effects

Exposure to inorganic mercury can give rise to a number of health effects in animals, including gastrointestinal effects, liver damage, kidney damage and tumours. There is limited data on the effects on humans of exposure to inorganic mercury: one study reports the effects of acute oral exposure to inorganic mercury and other studies report impaired neurological behaviour as a result of inhalation exposure to elemental mercury at concentrations of 0.014–0.076 mg/m^3. Table 34 provides a summary of the effects at different levels of mercury exposure and has primarily been sourced from ATSDR (1999) and IPCS (2003).

Table 34: Summary of the health effects of inorganic mercury

Dose (mg/kg/day	Duration of exposure[1]	Effects
30	Acute	Lowest reported LOAEL in humans – nausea, vomiting, acute renal failure
7	Intermediate	Lowest reported LOAEL for cardiovascular effects in animals (rats)
3.7	Chronic	Lowest reported LOAEL for cancer (for stomach tumours) in animals (rats)
2.2	Intermediate	Lowest reported LOAEL for endocrine and neurological effects in animals (rats)
1.9	Chronic	Lowest reported LOAEL for renal and gastric effects in animals (rats)
0.3–0.6	Intermediate	Lowest reported LOAEL for renal effects in animals (rats)

1 Acute <14 days; Intermediate 15–364 days, Chronic >365 days; LOAEL Lowest observable adverse effects level.

2.7.5 Weight of evidence

- Mercuric chloride was considered a possible human carcinogen (Class C), based on animal studies, by the US EPA (1995). IARC (1993) concluded that there is inadequate evidence in humans for the carcinogenicity of mercury and mercury compounds; that there is limited evidence in experimental animals for the carcinogenicity of mercuric chloride; and, as an overall evaluation, that elemental mercury and inorganic mercury compounds are not classifiable as to their carcinogenicity to humans (Group 3).
- Inorganic mercury compounds react with DNA (and other macromolecules) and are clastogenic (chromosomal aberrations and sister-chromatid exchange) in *in vitro* and *in vivo* studies (IPCS, 2003; WHO, 2005).

- Immune effects in kidney are the most sensitive endpoint (US EPA, 1995; IPCS, 2003; WHO, 2005).

2.7.6 Recommendations for toxicological intake values

Inorganic mercury is considered to be a threshold contaminant, and a total daily intake of 2 μg/kg bw is recommended (Table 35). This is the TDI derived by Baars et al (2001) and IPCS (2003), which has also been adopted by other agencies (WHO, 2005; EA, 2009); it also forms the intermediate-duration minimal risk level derived by ATSDR (1999) and is based on renal effects in rats. This recommendation does not apply to elemental mercury or organic mercury.

Inhalation exposure is expected to be negligible on contaminated sites due to limited volatility of the forms of mercury likely to be present (mercury II). Dermal absorption is also expected to be negligible, and could be ignored in the derivation of soil contaminant standards for contaminated land in New Zealand, as has been done by other jurisdictions (CCME, 1996; Baars et al, 2001; EA, 2009).

Dietary intake, in particular seafood, and dental amalgam are the primary sources of background exposure to mercury. Dietary intakes of inorganic mercury were estimated to be 0.05 μg/kg bw/day for a child and 0.025 μg/kg bw/day for an dult. Intake from dental amalgam was considered to be negligible for children and 0.04 μg/kg bw/day for adults, giving rise to a total inorganic mercury intake of 0.065 μg/kg bw/day for adults (Table 35).

Table 35: Recommended toxicological criteria for inorganic mercury (excluding elemental mercury)

Parameter	Value	Basis
Contaminant status	Threshold	See weight of evidence
Oral index dose (μg/kg bw/day)	2	Baars et al (2001); IPCS (2003)
Inhalation intake	NA	Low volatility of inorganic mercury indicates inhalation exposure will be negligible
Skin absorption factor	NA	Available data indicates that dermal absorption of inorganic mercury is negligible (Guy et al, 1999)
Background exposure (μg/kg bw/day)	0.05 0.065	Child (1–3 years) Adult (25+ years) Dietary intake (Davies et al, 2001; Vannoort and Thomson, 2005)

NA – not applicable.

2.8 Benzo(a)pyrene (BaP)

Several comprehensive reviews of the toxicity of benzo(a)pyrene have been undertaken (eg, ATSDR, 1995; WHO, 1998a; DEFRA and EA, 2002; EC 2002; FAO/WHO 2006a-c; CCME 2008). In the summary below, particular attention is given to those studies that have been used in deriving reference health standards. Readers are referred to the original reviews for more details on adverse health effects.

2.8.1 Toxicological status

Benzo(a)pyrene (BaP) is a well-documented carcinogen: it is classified as a probable human carcinogen (Class 2A) by IARC (1987) and as a probable human carcinogen (Group B2) by the US EPA (1994).

Benzo(a)pyrene is absorbed through the gastrointestinal tract, lungs, and skin and is primarily metabolised in the liver by the cytochrome P-450 system, although metabolism can also occur in the tissues of the lungs, gastrointestinal tract, skin and kidneys (ATSDR, 1995; WHO, 1998a). BaP has been demonstrated to be a skin irritant and dermal sensitiser, is embryotoxic to mice, and causes immuno-suppression in mice and humans (WHO, 1998a). BaP is an indirect carcinogen, that is, its carcinogenicity results from its metabolites, primarily various epoxides, as opposed to BaP itself. Several different types of tumours have been observed as a result of exposure to BaP, although tumour development is closely related to route of administration, ie, dermal application induces skin tumours and oral administration induces gastric tumours (FAO/WHO, 1991). Exposure to BaP causes disruption to cellular genetic material, in particular DNA adducts are formed as a result of exposure, and BaP is considered to be a genotoxic carcinogen (WHO, 1998a).

The genotoxic effects of BaP have been determined in tests for mutagenicity in urine and faeces, micronucleus formation, chromosomal aberration and sister chromatid exchange in peripheral blood lymphocytes, adducts of benzo(a)pyrene with DNA in peripheral lymphocytes and other tissues and with proteins such as albumin, and antibodies to DNA adducts (WHO, 1998a). In addition BaP has been demonstrated to be a skin irritant and dermal sensitiser (FAO/WHO, (1991).

BaP is a contaminant that occurs ubiquitously with a range of polycyclic aromatic hydrocarbons (PAHs) as a result of incomplete combustion (FAO/WHO, 1991). BaP is considered to be a marker for PAHs as it is one of the most strongly carcinogenic of the hundreds of PAHs that exist (of which only 16 are on the US EPA list of priority pollutants and therefore routinely analysed). The toxicity of PAH mixtures is often determined through the use of potency equivalence factors (PEFs), which express the toxicity of individual PAHs that are carcinogenic relative to that of BaP (BaP-equivalents). Non-carcinogenic PAHs are considered separately. However, recent studies indicate that different tumour sites result from exposure to BaP and coal tar (PAH mixture), suggesting that BaP is a point-of-contact carcinogen, while coal tar is a systemic carcinogen (Gaylor et al, 1998). This data, combined with new cancer potency estimates for BaP (see below), has led a number of authors to question the validity of existing PEFs based on BaP (eg, Goldstein, 2001). Other authors have also suggested the PEFs underestimate the toxicity of PAH mixtures, and that it is more appropriate to use BaP as a surrogate for the toxicity of the whole PAH (EC, 2002; Schneider et al, 2002).

2.8.2 New Zealand classification

The Hazardous Substances and New Organisms Act classification of BaP set by ERMA NZ is shown in Table 36. BaP is considered to be a carcinogen (6.7A) as well as being mutagenic (6.6A) and a reproductive toxicant (6.8A).

Table 36: HSNO classification of benzo(a)pyrene

Hazardous property	HSNO classification
Acute toxicity	ND
Skin irritation	ND
Eye irritation	ND
Sensitiser	ND
Mutagenicity	6.6A
Carcinogenicity	6.7A
Reproductive/developmental toxicity	6.8A
Target organ systemic toxicity	ND

ND – no classification due to no data/insufficient data/inconclusive data.

2.8.3 Toxicological intake values

Ingestion

A number of regulatory agencies have developed guideline values for BaP, and all of them consider BaP to be a non-threshold contaminant, although different cancer potency estimates are used. In addition, several recent studies have derived cancer potency estimates using new data, and different risk models. A summary of the reference health standards for BaP as a single compound and the bases for their derivation are shown in Table 37, while reference health standards for BaP as a surrogate for PAH mixtures are shown in Table 38. More detailed discussion is provided below.

The WHO drinking water guidelines use a slope factor of 0.46 per mg/kg bw/day as derived by Thorsland and Farr 1990 (in WHO 2003) without correction for differences in body surface area, as BaP is an indirect carcinogen, that is, the carcinogenicity appears due to a metabolite rather than BaP itself (WHO, 1996). While the Thorsland and Farr (1990) study (cited as Clement Associates 1990 in US EPA, 1994) study was rejected by the US EPA (1991b, cited in US EPA, 1994) in their estimates of cancer potency of BaP due to the use of "unrealistic conditions imposed upon certain parameters" the body-weight$^{3/4}$-scaled value (5.9 per mg/kg bw/day) was used in the final determination of the US EPA slope factor for BaP (see below). WHO maintained its (1996) guideline in a more recent evaluation of PAHs in drinking water and considered that recent studies by Culp et al (1998) and Weyand et al (1995, cited in WHO, 1998b; 2003) validated the Neal and Rigdon (1967) study, based on "nearly identical" risk estimates obtained using the more recent data. However, there is no detailed discussion on the derivation of these risk estimates, other than they were calculated using a two-stage birth–death mutation model (WHO, 1998b; 2003). The New Zealand Drinking Water Standards also use the WHO (1996) drinking water guideline for BaP (MoH, 2005).

The US EPA (1994) has adopted a slope factor of 7.3 per mg/kg bw/day, which is the geometric mean of three slope factors calculated from data contained in the Neil and Rigdon (1967, cited in US EPA, 1994) study and one slope factor derived from data in Brune et al (1981, cited in US EPA, 1994). All estimates use cross-species scaling using $(\text{bodyweight})^{2/3}$ to account for animal and human differences, and also adjust for the less than lifetime exposure of the test animals using an expected lifetime of 630 days. The California EPA used the same data but slightly different modelling procedures, including an expected lifetime of 730 days and cross-species scaling of $(\text{bodyweight})^{3/4}$, to derive a slope factor of 9.5 per mg/kg bw/day for development of a public health goal for water quality (CalEPA, 1997). The datasets contained in these studies are acknowledged to be acceptable, but less than optimal – due to the partial lifetime exposure and variable sacrifice patterns, by the US EPA (1994). In contrast, Goldstein (2001) and Kroese et al (2001) consider these studies to be inadequate for developing a BaP cancer potency factor.

Fitzgerald et al (2004), Gaylor et al (2000) and Kroese et al (2001) use cancer potency estimates derived from more recent studies that have been specifically conducted to establish cancer potency. These studies are Culp et al (1998) and Kroese et al (2001), which describe 2-year feeding studies on mice and rats respectively. These authors all use different methods to estimate the cancer potency of BaP, which results in different cancer potency estimates (Table 37). Gaylor et al (2000) use the data of Culp et al (1998) to provide an upper-bound estimate of the slope factor for BaP by linear extrapolation from the dose level estimated to produce a 10% excess tumour incidence (ED_{10}). Fitzgerald et al (2004) also use the data of Culp et al (1998), but determine maximum likelihood estimates of the dose at which there is 5% excess tumour incidence, using the modified benchmark-dose method (NHMRC, 1999). An uncertainty factor of 4500 is subsequently applied to account for various factors, including interspecies variability and database adequacy (Table 37). Kroese et al (2001) use their own data and determine the cancer potency of BaP linear extrapolation from the lowest dose level associated with statistically significant increased tumour incidence. This estimate of cancer potency was confirmed using the data of Culp et al (1998).

Despite the availability of these more recent studies, and the rejection of the Clement Associates (1990 cited in US EPA, 1994) methodology by the US EPA (1991 cited in US EPA, 1994), UK agencies have established a index dose of 0.02 μg/kg bw/day for BaP based on the WHO drinking water guidelines of 0.7 μg/L, for an acceptable risk level of 1 in 10^{-5} (DEFRA and EA, 2002). They considered that the risk model used by Clement Associates (1990 cited in US EPA, 1994) was appropriate for use, given the partial lifetime exposures and variable sacrifice regime of the study by Neal and Rigdon (1967 cited in US EPA, 1994). They also took into account that a more recent review of PAHs in drinking water by WHO (1998b) that found "nearly identical results" of risk estimations using the same modelling procedure but more recent studies, validated the use of the Neal and Rigdon (1967) results.

The Canadian Soil Quality Guidelines for the protection of human health and the environment for potentially carcinogenic, including BaP, and other PAHs has recently been reviewed (CCME, 2008). These authors discussed the Culp et al (1998) data but followed Health Canada recommendations for a slope factor based on the Neal and Rigdon (1967) study due to the greater number of dose level used in this study, and the high mortality associated with one of the three dose levels in the Culp et al (1998). Little information was able to be found on the derivation on this slope factors other than "a linear robust extrapolation was used by Health Canada with surface area correction". CCME (2008) also considered approaches to assessing PAH mixtures and concluded that due to the lack of viable alternatives, potency equivalence factors remained the preferred option.

Table 37: Summary of oral reference health standards for benzo(a)pyrene, used by different international agencies or developed in the scientific literature

Jurisdiction	Acceptable risk level	Guideline value	Risk-specific dose[1] (μg/kg bw/day)	Cancer slope factor (per mg/kg bw/day)	Key study[2]	Critical effects[2]	Basis of value[2]	Reference
New Zealand	10^{-5}		0.0014	7.3	US EPA (1994)	Fore-stomach tumours – mice	US EPA (1994)	MfE (1997; 1999)
New Zealand drinking water	10^{-5}	0.07	0.022	0.46	Not stated	Not stated	WHO (2003)	MoH (2005)
WHO drinking water	10^{-5}		0.022	0.46	Clement Associates (1990)	Fore-stomach tumours – mice	Two-stage birth–death mutation model to incorporate the partial lifetime exposure, without allometric scaling.	WHO (1998b, 2003)
UK	10^{-5}		0.02	–	Neal and Rigdon (1967)	Fore-stomach tumours – mice	WHO (1996)	DEFRA and EA (2002)
The Netherlands – current	10^{-4} [10^{-5}]		2 [0.2]	–	Not stated	Not stated	Vermeire (1993)	Baars et al (2001)
The Netherlands – proposed[3]	10^{-4} [10^{-5}]		0.5 [0.050]	–	Culp et al (1998), Kroese et al (2001)	Fore-stomach tumours – mice, rats	Kroese et al (2001)	Baars et al (2001)
US	10^{-6} [10^{-5}]		0.00014 [0.0014]	7.3	Neal and Rigdon (1967), Brune et al (1981)	Fore-stomach tumours – mice Fore-stomach tumours – rats	Geometric mean of four slope factors obtained by differing modelling procedures, using the two studies. Inter-species scaling of bodyweight to the 2/3 power was applied.	US EPA (1994)
California	10^{-6} [10^{-5}]		0.00011 [0.0011]	9.03	Neal and Rigdon (1967)	Fore-stomach tumours – mice	Risk estimate determined from Global86 computer model. Inter-species scaling of bodyweight to the 3/4 power was applied.	CalEPA (1997)
Canada	10^{-6} [10^{-5}]		0.000435 [0.00435]	2.3	Neal and Rigdon (1967)	Fore-stomach tumours – mice	"Robust linear extrapolation with a surface area correction".	CCME (2008)
Norwegian Food Control Authority	10^{-6} [10^{-5}]		0.00057 [0.0057]		Culp et al (1998)	Fore-stomach tumours – mice	Linear extrapolation from BMD_{25} (the dose that results in tumour incidence in 25% of animals), and interspecies scaling factor of bodyweight to the 3/4 power.	EC (2002)

Jurisdiction	Acceptable risk level	Guideline value	Risk-specific dose[1] (µg/kg bw/day)	Cancer slope factor (per mg/kg bw/day)	Key study[2]	Critical effects[2]	Basis of value[2]	Reference
US[4]	10^{-6} [10^{-5}]		0.00083 [0.0083]	1.2	Culp et al (1998)	Fore-stomach tumours – mice	US EPA standard method – low-dose linear extrapolation. Upper-bound estimate of the slope factor determined by linear extrapolation from the dose estimated to produce an excess tumour incidence of 10% (BMD_{10} from monotonic multi-stage modelling), and interspecies dose scaling of bodyweight to the 3/4 power.	Gaylor et al (2000)
The Netherlands[4]	10^{-6} [10^{-5}]		0.005 [0.050]	–	Culp et al (1998), Kroese et al (2001)	Fore-stomach tumours – mice Tumour-bearing animals – rats	"Virtually safe dose" – linear extrapolation from lowest dose level associated with a significant increased tumour response for an acceptable increased risk level of 1 in a million.	Kroese et al (2001)
Australia[4]			0.080		Culp et al (1998)	Fore-stomach tumours – mice	Modified benchmark dose (NHMRC, 1999) – maximum likelihood estimates of the dose level giving rise to an excess tumour incidence of 5% (BMD_{05}, as determined from a variety of models), divided by a factor of 4,500 to account for various uncertainties (5 for interspecies extrapolation, 10 for intraspecies variability, 2 for database (in)adequacy, 9 for malignancy, 5 for genotoxicity).	Fitzgerald et al (2004)

1 Where the acceptable risk level for a given jurisdiction is not 10^{-5}, the risk-specific dose for a risk of 10^{-5} is shown in square brackets.

2 As reported in the references cited in the reference column.

3 This value is yet to be officially adopted.

4 These are values developed in the scientific literature, as opposed to values developed for regulatory purposes.

Table 38: Summary of oral reference health standards for benzo(a)pyrene in a PAH mixture, used by different international agencies or developed in the scientific literature

Jurisdiction	Acceptable risk level	Risk-specific dose[1] (μg/kg bw/day	Cancer slope factor (per mg/kg bw/day)	Key study[2]	Critical effects[2]	Basis of value[2]	Reference
Joint FAO/WHO Expert Committee on Food Additives (JECFA)	[10^{-5}]	[3] [0.0014]	$BMDL_{10}$ = 0.1 mg/kg bw/day (6.7)	Culp et al (1998)	Fore-stomach tumours – mice	Eight different statistical models were fitted to the combined data for two coal tar mixtures – $BMDL_{10}$ ranged from 0.1 to 0.23 mg BaP/kg bw/day, with the lower end of this range used in the evaluation by JECFA.	FAO/WHO (2006b)
EU Scientific committee on food (SCF)	10^{-6} [10^{-5}]	0.00006–0.0005 [0.0006–0.005]	–	Alexander Knutsen (2001), Kroese et al (2001)	Fore-stomach tumours – mice	Application of carcinogenic potency factor of 10 to "virtually safe doses" established for BaP by Kroese et al (2001) (0.5 ng/kg bw/day), and Alexander and Knutsen (2001) (0.06 ng/kg bw/day), to account for the carcinogenic potency of a mixture of PAHs. Stated to be in agreement with that determined by Schneider et al (2002). Note: the SCF expressed reservations regarding the use of mathematical modelling for substances that are genotoxic and carcinogenic and concluded that exposures from food should be as low as practically achievable.	EC (2002)
Germany[4]	10^{-6} [10^{-5}]	0.00009 [0.0009]	11.5	Culp et al (1998)	Fore-stomach tumours – mice, rats arising from exposure to coal tar	Arithmetic mean of four estimates of slope factors of the potency of two coal tar mixtures determined using linearised multi-stage modelling and low-dose linear model using the dose estimated to produce an excess tumour incidence of 10% as the point of departure and accounting for bodyweight adjustment by caloric demand – allometric scaling.	Schneider et al (2002)

1 Where the acceptable risk level for a given jurisdiction is not 10^{-5}, the risk-specific dose for a risk of 10^{-5} is shown in square brackets.

2 As reported in the reference cited in the reference column.

3 Derived in the current study from the $BMDL_{10}$ of 0.1 mg/kg bw/day determined by FAO/WHO (2006a; 2006b), using low-dose linear extrapolation (slope factor = $0.1/BMDL_{10}$) of US EPA (2005) and cross-species scaling of bodyweight to the 3/4 power, ie, slope factor (humans) = 10^{-5} x (mouse slope factor x $(70/0.035)^{1-0.75}$).

4 These are values developed in the scientific literature, as opposed to values developed for regulatory purposes.

The EU Scientific Committee on Food and JECFA have adopted a different approach in their recent evaluations of benzo(a)pyrene (EC, 2002; FAO/WHO, 2006a; 2006b). Specifically, these evaluations considered PAHs as a mixture, and considered a total of 33 individual PAHs, selected on the basis of availability of information on their occurrence and toxic effects. Both committees considered that BaP could be used as a marker for the occurrence and effect of carcinogenic PAHs in food, and did not endorse the use of toxic equivalency factors, TEFs (see later section for more detailed discussion). Therefore, the reference health standards developed by these committees account for *all* carcinogenic PAHs, not just BaP. However, the EU Committee also expressed reservations about the use of mathematical modelling to extrapolate from animal tumour data, in order to estimate risks to humans at low exposure to substances that are both genotoxic and carcinogenic; it recommended that exposure to these substances in food should be as low as reasonably achievable. Nonetheless, the committee suggested a conservative estimate of the potency of total PAH in food is 10 times that of BaP alone. It applied this "potency" factor to "virtually safe doses" (for a risk of 1 in a million) provided by other authors to develop a "virtually safe dose" for BaP as a marker for carcinogenic PAH in food of 0.06–0.5 ng/kg bw/day.

JECFA used the data from Culp et al (1998) for coal tar mixtures to derive the benchmark dose and BMDL for a 10% extra risk of all tumours, using eight different statistical models (FAO/WHO, 2006a; 2006b). Estimates for the BMDL ranged from 0.1 to 0.23 mg/kg bw/day, and a BMDL equivalent to 0.1 mg BaP/kg/bw/day was derived for mixtures of PAHs in food (FAO/WHO, 2006b). No further risk estimation, ie, low-dose extrapolation, was undertaken by FAO/WHO (2006a; 2006b). However, following recent US EPA guidance (US EPA, 2005) for low-dose linear extrapolation using $BMDL_{10}$ as the point of departure, and cross-species scaling of bodyweight to the ¾ power (using a human bodyweight of 70 kg and mouse bodyweight of 35 g), a slope factor of 6.7 per mg/kg bw/day can be determined. This equates to a risk-specific dose of 0.0015 μg/kg bw/day at an excess risk level of 1 in 100,000. Without $bodyweight^{3/4}$ scaling, a slope factor of 1 per mg/kg bw/day and a risk-specific dose of 0.01 μg/kg bw/day is obtained. FAO/WHO (2006b) also derived BMDL for BaP from the data of Culp et al (1998) and Koesse et al (2001) (Table 38). It is notable that both committees also recommend that future monitoring should include certain PAHs that are currently not regularly monitored (ie, PAHs that are not part of the "US EPA 16").

Schneider et al (2002) also used the Culp et al (1998) data for coal tar mixtures to determine slope factors for BaP as a surrogate for PAH mixtures. These authors used two approaches for estimating the slope factors of the coal tar mixtures: linearised multi-stage modelling, a procedure that has previously been widely used by the US EPA, and linear extrapolation from the 95% lower confidence limit on the dose associated with 10% extra risk ($BMDL_{10}$). The $BMDL_{10}$ was determined from curve-fitting and values were determined to be 0.08 and 0.052 mg/kg bw/day for the two coal-tar mixtures. These values are lower than what was determined by JECFA (FAO/WHO, 2006b). The slope factors (based on mice data) determined for the two coal-tar mixtures using the two approaches ranged from 1.4 to 2 per mg BaP/kg bw/day. These authors used the arithmetic mean of these slope factors and allometric scaling to derive a human slope factor of 11.5 per mg/kg bw/day. This equates to a risk-specific dose (RSD) for 10^{-5} risk of 0.0009 μg/kg bw/day.

Evaluation

There is a considerable spread in the carcinogenic potency estimates for BaP listed in Table 37. This spread is attributable to differences in the models used to estimate carcinogenic potency, as well as the data used for modelling. The models used to estimate carcinogenic potency partly reflect policy decisions on how low dose extrapolation should be undertaken, as well as scientific uncertainty. More recently there has been a tendency to move towards simple linear extrapolation from a point of departure on the dose-response curve to the origin (eg, Kroese et al, 2001; US EPA, 2005; EA, 2008). Typically a BMD_{10} (the dose that gives rise to a 10% response) or $BMDL_{10}$ (the lower 95% confidence limit of the BMD_{10}) is used as the point of departure, although other doses eg, BMD_{05}, BMD_{25} may be used. Different statistical models can be used to calculate the BMD or BMDL which may give rise to slightly different values for a given dataset. Once the point of departure is selected, different agencies have adopted different approaches, for example the UK have proposed to divide the $BMDL_{10}$ by orders of magnitude to obtain the desired risk levels eg, divide the $BMDL_{10}$ to obtain the dose for 1 in a 100,000 risk (EA, 2008). In contrast, US EPA determines a slope factor from the point of departure according to (x/100)/BMDx and applies cross-species scaling of $(bodyweight)^{3/4}$. In older risk estimate modelling (eg, US EPA, 1994), the cancer slope factor is the primary output and cross-species scaling $(bodyweight)^{2/3}$ was used.

While different modelling approaches will yield different potency estimates, the application of allometric ($(bodyweight)^{3/4}$) scaling to account for inter-species differences appears to be the most significant factor influencing cancer potency estimates when comparing estimates developed by US and Canadian agencies, and other international agencies. For example, the slope factor used in the WHO drinking water guidelines (WHO, 1996; 1998b) is 0.46 per mg/kg bw/day, while for *the same study*, using $bodyweight^{2/3}$ scaling the US EPA slope factor is 5.9 per mg/kg/day. Table 39 provides a summary of risk estimates derived for BaP using different models and data by different agencies. From the risk estimates provided, the slope factors and risk-specific doses for a 1 in 100,000 risk have been calculated with and without cross-species scaling following US EPA (2005) guidance. It is relevant to note that the risk-specific dose for 1 in 100,000 risk (calculated from the slope factor determined from $BMDL_{10}$ following US EPA guidance, but without $bodyweight^{3/4}$ scaling) is equivalent to dividing the $BMDL_{10}$ by 10,000 as per the proposed UK guidance.

While the tendency of WHO (FAO/WHO, 2006c), a number of European agencies (eg, Health Council of Netherlands, 1994 cited in Kroese et al, 2001; EA, 2008), and Australian agencies (NHMRC, 1999) is to not apply allometric ($bodyweight^{3/4}$) scaling in determining cancer potency, the Toxicological Advisory Group agreed this approach should be used in estimating the cancer potency of BaP. This provides consistency with previous contaminated land guidance (MoH and MfE, 1997; MfE, 1997; 1999), although not with the current Drinking Water Standards (MoH 2005). Given that different modelling procedures do produce different results, it is recommended that the geometric mean of existing estimates of the $BMDL_{10}$ that are allometric-scaled (Table 39) are used to provide the cancer potency estimate for BaP.

Inhalation

Inhalation is anticipated to be a negligible route of exposure as benzo(a)pyrene has limited volatility and the amount of dust considered to be inhaled typically represents a very small fraction of exposure (see section 1.1.4), so is not discussed further.

Table 39: Risk estimates for BaP determined by different international agencies, developed in the scientific literature or derived in the current study, with and without allometric cross-species scaling

Primary reference	Key study[a]	Critical effects[a]	Model	BMDL[b]	Cancer slope factor (per mg/kg bw/day)		Risk-specific dose[c] (μg/kg bw/day)	
					Without scaling	With scaling	Without scaling	With scaling
US EPA (1994)	Neal and Rigdon (1967)	Fore-stomach tumours – mice	Conditional upper bound two-stage model.	–	0.464[d]	5.9	0.0216	0.0017
			Upper-bound estimate by extrapolation from 10% response point to background of empirically fitted dose-response curve using two-stage model described above.	–	0.707[d]	9	0.014	0.0011
			Generalised Weibull-type dose-response model.	–	0.354[d]	4.5	0.028	0.0022
	Brune et al (1981)	Tumour-bearing animals – rats	Linearised Multistage Model, extra risk	–	0.920[e]	11.7	0.011	0.0009
			Geometric mean of above 4 estimates[f]	–	0.574[d]	7.3	0.017	0.0014
CalEPA (1997)	Neal and Rigdon (1967)	Fore-stomach tumours – mice	Risk estimate determined from Global86 computer model		1.34[g]	9.03	0.0075	0.0011
CCME (2008)	Neal and Rigdon (1967)	Fore-stomach tumours – mice	"Robust linear extrapolation with a surface area correction".		0.181[g]	2.3	0.055	0.0043
Gaylor et al (2000)	Culp et al (1998)	Fore-stomach tumours – mice	US EPA standard method – low-dose linear extrapolation using BMDL10 from monotonic multi-stage modelling.		0.178[g]	1.2	0.056	0.0083
Kroese et al (2001)	Kroese et al (2001)	Tumour-bearing animals – rats	"Virtually safe dose"	–	–	–	0.05	0.0074
	Culp et al (1998)	Fore-stomach tumours – mice	"Virtually safe dose"	–	–	–	0.05	0.0074
				0.36[h]	0.139[i]	0.936[g]	0.08	0.0107
FAO/WHO (2006b)	Culp et al (1998)	Fore-stomach tumours – mice	Eight different statistical models were fitted to data for BaP, although not all models yielded a BMD or BMDL. All available BMDLs were used.	0.62	0.162[j]	1.09[g]	0.062	0.0092
				0.31	0.323[i]	2.17[g]	0.031	0.0046
				0.74	0.135[i]	0.910[g]	0.074	0.0110
	Kroese et al (2001)	Tumour-bearing animals – rats	Eight different statistical models were fitted to data for BaP, although not all models yielded a BMD or BMDL. All available BMDLs were used.	1.67	0.060[i]	0.514[j]	0.167	0.0195
				1.56	0.064[i]	0.550[j]	0.156	0.0182
				1.23	0.081[i]	0.697[j]	0.123	0.0143
Geometric mean all studies					**0.233**	**2.08**	**0.043**	**0.0048**

a As reported in the reference cited in the reference column.
b $BMDL_{10}$ unless otherwise stated.
c Risk-specific dose for excess risk of 10^{-5}.
d Derived in this study using bodyweight scaling to the 2/3 power, ie, slope factor (mouse) = human slope factor / $(70/0.035)^{1-0.666}$ (US EPA, 1994).
e Derived in this study using bodyweight scaling to the 2/3 power, ie, slope factor (rat) = human slope factor / $(70/0.4)^{1-0.666}$ (US EPA, 1994).
f Not used in calculation of geometric mean.
g Derived in this study using bodyweight scaling to the 3/4 power, ie, slope factor (mouse) = human slope factor / $(70/0.035)^{1-0.75}$ (US EPA, 2005).
h $BMDL_{05}$.
i Derived in this study following US EPA (2005) using low-dose linear extrapolation where slope factor = (x/100)/$BMDL_x$, and no scaling.
j Derived in this study using bodyweight scaling to the 3/4 power, ie, slope factor (rat) = human slope factor / $(70/0.4)^{1-0.75}$ (US EPA, 1994; 2005).

Dermal absorption

Skin absorption is a key contaminant-specific parameter required for the dermal absorption pathway; this is typically used to provide an estimate of "additional" oral exposure. Percutaneous absorption is the process whereby a chemical penetrates the skin and reaches the systemic blood supply, while dermal absorption also includes the chemical remaining in the skin. While different permeabilities are observed for different species, monkey, pig and human skin are considered to have similar permeabilities, with human skin considered to be the least permeable. As BaP is actively metabolised in the skin it is relevant to include both the amount that passes through the skin and that which remains bound to the skin to estimate dermal uptake. The US EPA (2004) recommends a dermal absorption factor of 0.13 (13%), which is based on data from Wester et al (1990). These authors indicate that 13.2% of BaP in soil was absorbed by rhesus monkeys over a 24-h period. However, they also indicate that a reduced amount (1.4%) was absorbed into human skin from soil over the same time period, although no partitioning into human plasma occurred, ie, the BaP remained bound to the skin. Another study on the dermal absorption of BAP from soils also showed that a minimal amount (0.1%) of BaP was absorbed through pig skin and 1.7% and 3.5% remained bound to the skin when BaP in aged sandy and clay soils was applied to the skin (Abdel-Rahman et al, 2002). A higher amount (3.3% and 8.3% in clay and sandy soils, respectively) was absorbed when non-aged soil (ie, freshly spiked) was applied to the skin. A more recent study with human skin showed greater absorption through the skin, with approximately 7% of BaP passing through when applied as freshly spiked soil (Moody et al, 2007). A further 7% remained bound to the skin.

As aging soils decrease the bioavailability of BaP, the dermal absorption data from freshly spiked soils can provide a "worst-case" estimate of dermal absorption. The geometric mean of dermal absorption using freshly spiked soils from the above studies (including *in vivo* studies) is 6%, while using data for aged soils yields a geometric mean of 2.6%.

Given that BaP is suggested to act largely as a point-of-contact carcinogen (Knafla et al, 2006), as opposed to systemically, it is more appropriate to derive soil guideline values for the dermal route of exposure using a route-specific slope factor, as opposed to considering it an addition to oral exposure. Typically such values are not available for dermal exposure, although a recent study has derived a dermal slope factor for BaP of 25 per mg/kg/day (Knafla et al, 2006). This study examined all relevant studies and ultimately derived an average slope factor from three mouse skin-painting studies. However, it should be noted that this is a relatively untested approach and greater uncertainties exist in the extrapolation of dermal data derived from animals to humans than for the oral or inhalation route (Knafla et al, 2006). These authors indicate that there are sufficient data on the relative toxicity of other PAHs compared with BaP, to develop dermal PEFs to assess the dermal toxicity of PAH mixtures, although they do not attempt to do so in their publication.

Given that no other international agency has currently adopted the use of a dermal slope factor, this approach is not recommended for use in New Zealand at this point in time, although it is pertinent to keep a watching brief on the further evaluation of the toxicity of BaP by regulatory agencies. Specifically, the CCME (2008) has indicated that Health Canada is currently developing a dermal slope factor for BaP and a separate soil quality guideline may be developed by CCME for dermal exposure. As such, it is recommended that a dermal absorption factor is used to account for dermal exposure to BaP in contaminated soil – specifically, a dermal absorption factor of 0.026 (2.6%), based on the geometric mean of dermal absorption estimates for aged soil by Abdel-Rahman et al (2002).

Other routes of exposure – background exposure

The primary source of background exposure to BaP for the general population is considered to be food, as a result of cooking (eg, char-grilling) and poor air quality (eg, winter-time pollution as a result of domestic home heating) (WHO, 1998a). Smoking is an additional source of exposure for individuals. However, as BaP is considered to be a non-threshold contaminant, background exposure is not taken into account in the derivation of soil contaminant standards (see above).

2.8.4 Mixtures of PAHs

Because a variety of polycyclic aromatic hydrocarbons are found together and because, at least to some extent, different PAHs act by the same mechanism, it is necessary to evaluate the toxicity of the mixture. Two general approaches are used. The first approach assesses the relative potency of each component relative to a standard component, and evaluates the mixture as the sum of its parts – the toxic equivalency factor (TEF) or potency equivalence factor (PEF) approach. The second approach is the use of a single component to provide a measure of concentration in relation to response of the whole mixture (surrogate approach).

Equivalence factors

An alternative approach to assessing mixtures of PAHs is to use benzo(a)pyrene as a marker for the range of PAHs that occur in the environment, as it is considered to be one of the most strongly carcinogenic of the hundreds of PAHs that exist. Specifically, the potencies of other PAHs are considered relative to that of BaP. These factors are often termed toxicity equivalence factors although they are more accurately potency equivalence factors as they compare the relative cancer potency of the different PAHs as opposed to all toxic endpoints, which should be considered in developing TEFs. The toxicity of the various PAHs is assumed to be additive, which has been demonstrated for defined synthetic mixtures of PAHs (WHO, 1998a citing McClure and Schoeny, 1995), although it may not be true for environmental mixtures of PAHs (WHO, 1998a). The potential toxicity of a mixture of PAHs can be nominally determined by applying the relevant potency equivalence factor to the concentration of that PAH and summing the "equivalent" concentration. Limitations exist in the use of potency equivalence factors, including the fact that only a limited number of PAHs, typically the "US-EPA 16" (Table 40), are routinely analysed for BaP-equivalency. Whether the BaP-equivalent concentration provides a reasonable estimate of the carcinogenicity of environmental mixtures of PAHs depends on what PAHs are causing the toxicity, and how potent they are. For example, while most PAHs are considered to be less potent than BaP, dibenzo(a,l) pyrene is considered to be significantly more toxic (PEF of 100) than BaP (WHO, 1998a citing McClure and Schoeny, 1995). Thus the presence of a small amount of dibenzo(a,l) pyrene can contribute significantly to the carcinogenicity of the mixture. However, this PAH is not one of the regularly monitored PAHs (ie, one of the "US EPA 16") thus information on environmental concentrations, and concentrations at which effects may be observed, is lacking.

Additionally, it should be noted that PEFs have been developed primarily using dermal exposure data, for which the most extensive data exist. However, as tumour formation is closely related to site of administration it should be noted that there is no basis for assuming the order of relative potency for PAHs is the same after oral and inhalation exposure. While there is an absence of data to otherwise consider the carcinogenicity of environmental mixtures of PAHs, some regulatory agencies have adopted the PEF approach to assess PAH mixtures in contaminated soil (eg, US EPA, 1993; Baars et al, 2001).

Potency equivalence factors have been proposed by a number of authors for a range of PAHs and generally represent an order-of-magnitude relative potency (see table AI.9 in WHO, 1998a). Nisbet and LaGoy (1992) were the first to round equivalency factors to an order of magnitude, which they considered "appropriately reflects the state of actual knowledge on relative potencies". However, one issue that arises is the discrepancy between sources as to what PAHs are considered to be carcinogenic and therefore have PEFs assigned. Further, some authors (Nisbet and LaGoy, 1992) have assigned equivalence factors to non-carcinogenic PAHs as well. The carcinogenicity classifications from different sources for selected PAHs are shown in Table 40. The JECFA (FAO/WHO, 2006a) classification is the most recent and differs from US EPA and IARC (1987) classifications by: confirming the US EPA (1993) classification of chrysene as a carcinogen; classifying fluoranthene as carcinogenic; and considering acenapthene, phenanthrene and pyrene as questionably carcinogenic. JECFA also considered that dibenzo(a,e)pyrene, dibenzo(a,h)pyrene, dibenzo(a,i)pyrene, dibenzo(a,l)pyrene, and 5-methylchrysene are carcinogenic and genotoxic, and that future monitoring should include all genotoxic and carcinogenic PAHs (FAO/WHO, 2006a).

The potency equivalence factors discussed by WHO (1998a) were similar for PAHs that are generally considered to be carcinogenic (ie, those considered in Table 40), with the greatest variation for chrysene (ranging from 0.001 to 0.1). PEFs from selected sources are shown in Table 41. These include PEFs from existing New Zealand documents (MfE, 1997; 1999) and US EPA (1993), the nominal source for PEFs in the New Zealand documents; PEFs proposed by Kalberlah et al (1995 cited, in WHO, 1998a), who adopted the same approach as US EPA (1993); and PEFs proposed by McClure and Schoeny (1995 cited in WHO, 1998a), as these authors nominally improved the estimates developed by US EPA (1993). Specifically, they investigated alternative models for potency estimation; subsequently it was determined that the actual model used had little effect on the values when consistently applied, although the data used could alter PEFs by an order of magnitude. These authors also expanded the list of PAHs for which order-of-magnitude potency estimates were derived. Baars et al (2001) proposed the use of the PEFs developed by Kalberlah et al (1995 cited in WHO, 1998a) for use in the Netherlands.

The PEFs used in existing New Zealand guideline documents (MfE, 1997; 1999) are nominally based on US EPA (1993), although, as can be seen from Table 41, discrepancies exist for benzo(k)fluoranthene and chrysene. As observed in WHO (1998a), the greatest variation in the PEFs shown in Table 41 exists for chrysene, while the values for benzo(k)fluoranthene also vary. The PEFs proposed by Kalberlah et al (1995 cited in WHO, 1998a) are the only ones that cover the range of PAHs considered to be carcinogenic (including those of questionable carcinogenicity) in the most recent evaluation by WHO (1998a) for PAHs that are routinely analysed.

Table 40: Carcinogenicity classifications of selected PAHs by different sources

Polycyclic aromatic hydrocarbon	IARC (1987)[1]	US EPA (1993)[2]	FAO/WHO (2006a)[3]	
			Carcinogenicity	Genotoxicity
Acenapthene	Ne	D	(?)	(?)
Acenapthylene	Ne	D	Ne	(?)
Anthracene	3	D	–	–
Benz(a)anthracene	2A	B2	+	+
Benzo(b)fluoranthene	2B	B2	+	+
Benzo(j)fluoranthene	2B	NA	+	+
Benzo(k)fluoranthene	2B	B2	+	+
Benzo(a)pyrene	2A	B2	+	+
Benzo(g,h,i)perylene	3	D	–	+
Chrysene	3	B2	+	+
Dibenz(a,h)anthracene	2A	B2	+	+
Fluoranthene	3	D	(+)	+
Fluorene	3	D	–	( )
Indeno(1,2,3-c,d)pyrene	2B	B2	+	+
Napthalene	3	D	–	–
Phenanthrene	3	D	(?)	(?)
Pyrene	3	D	(?)	–

1 IARC classification: Ne – not-evaluated; 2A – probably carcinogenic to humans; 2B – possibly carcinogenic to humans; 3 – compound is not classifiable as to its carcinogenicity.

2 US EPA classification: B2 – probably carcinogenic to humans; D – not classifiable as to carcinogenicity; NA – not available.

3 WHO classification: Ne – not-evaluated; + – positive, – – negative; ? – equivocal data; () inadequate database for evaluation.

Table 41: Potency equivalence factors used by various agencies

PAH	New Zealand		US EPA (1993)	Kalberlah et al (1995 cited in WHO, 1998a)	McClure and Schoeny (1995 cited in WHO, 1998a)
	MfE (1999)	MfE (1997)			
Acenapthene	–	–	–	0.001	–
Acenapthylene	–	–	–	0.01	–
Benz(a)anthracene	0.1	0.1	0.1	0.1	0.1
Benzo(b)fluoranthene	0.1	0.1	0.1	0.1	0.1
Benzo(j)fluoranthene	–	–	–	0.1	0.1
Benzo(k)fluoranthene	0.1	0.1	0.01	0.1	0.1
Benzo(a)pyrene	1.0	1.0	1.0	1.0	1.0
Benzo(g,h,i)perylene	–	–	–	–	–
Chrysene	0.01	0.01	0.001	0.01	0.1
Dibenz(a,h)anthracene	1.0	1.0	1.0	1.0	1.0
Fluoranthene	–	–	–	0.01	–
Fluorene	–	–	–	–	–
Indeno(1,2,3-c,d)pyrene	0.1	0.1	0.1	0.1	0.1
Napthalene	–	–	–	–	–
Phenanthrene	–	–	–	<0.001	–
Pyrene	–	–	–	0.001	–

Surrogate approach

This method uses a single compound to characterise the toxicity of the mixture and a single factor to account for the greater toxicity of the mixture. Typically BaP is the "marker" compound. This approach was used by the EU Scientific Committee on Food, who also did not find it appropriate to use the TEF approach for risk assessment of PAHs in food – for several reasons, including that coal-tar mixtures induce tumours in tissues and organs other than those affected by BaP alone; there is evidence that individual PAHs may interact synergistically or antagonistically in mixtures; and, that carcinogenic potency of PAH mixtures is more often underestimated using the TEF approach (EC, 2002). Similarly JECFA (FAO/WHO, 2006a) also endorsed the use of a surrogate approach, because of the availability of data from a study of carcinogenicity of a relevant mixture of PAHs (Culp et al, 1998) and because "the surrogate approach is simpler to apply and is generally as accurate as the TEF approach for most purposes". The EU SCF proposed a conservative estimate that the potency of a mixture of PAHs in food would be 10 times that of BaP alone (EC, 2002). This was based on the observation that the profile of measured carcinogenic PAHs in coal tar and various foods varied within a factor of 2, and the finding that carcinogenic potency of coal-tar mixtures could be up to five times that predicted by their BaP content. JECFA (FAO/WHO, 2006a) did not propose a "potency factor", but rather provided estimates of the $BMDL_{10}$ based on the BaP content of coal-tar mixtures from Culp et al (1998). No further risk estimation, ie, low-dose extrapolation, was undertaken.

More recently the EFSA's (European Food Safety Authority) panel on contaminants in the food chain (CONTAM, 2008) evaluated the use of BaP and additional markers, specifically:

a) BaP and chrysene (PAH2)

b) Benz(a)anthracene, BaP, benzo(b)fluoranthene and chrysene (PAH4)

d) the sum of eight carcinogenic PAHs (benz(a)anthracene, BaP, benzo(b)fluoranthene benzo(k)fluoranthene, benzo(ghi)perylene, dibenz(a,h)anthracene, indeno(1,2,3-cd)pyrene and chrysene (PAH8).

Benchmark dose modelling of the Culp et al (1998) data was undertaken and the lowest $BMDL_{10}$ determined from five models was used to estimate margins of exposure (MOE) for European diets. Based on MOE results, and data on the occurrence of PAHs in food, CONTAM (2008) concluded that PAH4 were better indicators of the occurrence and toxicity of genotoxic and carcinogenic PAHs.

CONTAM (2008) also examined the use of PEFs for risk characterisation; it concluded that this approach was not scientifically valid because of the lack of data from oral carcinogenicity studies for different PAHs, their different modes of action, and evidence of the poor predictability of carcinogenic potency of PAH mixtures based on the current PEFs.

Evaluation

While some agencies (EC, 2002; FAO/WHO 2006a; 2006b; CONTAM, 2008) debate the use and applicability of the PEF approach, other international agencies and researchers consider the PEF approach to be the most robust at this time (eg, US EPA, 1993; Baars et al, 2001; Pufulete et al, 2004; CCME, 2008). Further, there is a lack of consensus on an appropriate surrogate with which to assess carcinogenicity of PAH mixtures. Therefore, it is recommended that the PEF approach remains the preferred approach for assessing the carcinogenic toxicity of PAH mixtures in New Zealand.

2.8.5 Summary of effects

Limited data on the non-carcinogenic effects of BaP are available. Table 42 provides a summary of available effects and is mostly taken from WHO (1998a).

Table 42: Summary of the health effects of benzo(a)pyrene

Dose (mg/kg bw/day	Exposure	Effects
1600	Acute	LD_{50} in mice
120 (diet)	Diet, days 2–10 of gestation	Congenital malformations in mice offspring
133	Diet	No effects of fertility or embryotoxicity in mice
50	Intraperitoneal injection	Embryotoxicity effects (increased numbers of stillborn foetuses, decreased foetal weight, increased congenital anomalies) in mice (intraperitoneal exposure)
0.625	Chronic, dermal exposure 28 days	Immunosuppresion in mice

2.8.6 Weight of evidence

- BaP is considered to be a probable human carcinogen by IARC (1987) and the US EPA (1994).
- Human data specifically linking BaP to a carcinogenic effect are lacking, although lung cancer has been shown to be induced in humans by various mixtures of PAHs known to contain BaP (IARC, 1987; US EPA, 1994).
- Numerous animal studies in many species demonstrate BaP to be carcinogenic following administration by various routes. Repeated BaP administration has been associated with increased incidences of tumours at the site of exposure and, to a lesser extent, tumours at other sites (primarily at high dose levels) (IARC, 1987; US EPA ,1994; WHO, 1998a).
- BaP has produced positive results in numerous genotoxicity assays, and has been demonstrated to act as a direct genotoxin (eg, forms DNA adducts) thus is considered to be a non-threshold contaminant (WHO, 1998a).

2.8.7 Recommendations for toxicological intake values

Benzo(a)pyrene is considered to be a genotoxic carcinogen, and therefore is a non-threshold contaminant. As such, a risk-specific dose is proposed for use. Specifically, use of an oral risk-specific dose of 0.0048 μg/kg bw/day (slope factor of 2.08 per mg/kg bw/day) is recommended (Table 43). This value is the geometric mean of 14 $BMDL_{10}$ estimates from four studies divided by 10,000 and scaled allometrically, maximising the use of available data.

An inhalation intake dose is not recommended as inhalation is expected to be a negligible route of exposure for soil contamination due to the low volatility of BaP.

Dermal absorption of BaP may be expected and a dermal absorption factor of 0.026 (2.6%) based on the geometric mean of estimates for aged soil by Abdel-Rahman et al (2002) is recommended (Table 43). There is some indication that it may be appropriate to develop a dermal-specific soil guideline value for BaP and some international agencies are currently investigating this approach (CCME, 2008). It is recommended to keep a watching brief on any further evaluations of the toxicity of BaP by international regulatory agencies.

To enable an estimate of the potential carcinogenicity of environmental polycyclic aromatic hydrocarbon mixtures, potency equivalence factors have been used previously in New Zealand guidance and are recommended for continuation. It is recommended that a consistent set of PEFs is used to enable assessment of potential carcinogenicity of PAH mixtures through comparison with a BaP-equivalent soil guideline value in New Zealand, and that the range of PAHs routinely analysed is expanded to include additional PAHs considered carcinogenic by FAO/WHO (2006a). It is recommended that the PEFs developed by Kalberlah et al (1995 cited in WHO, 1998a) are used as these follow US EPA (1993), which is currently used in New Zealand guidance documents (MfE, 1997; 1999), but have been developed for a wider range of PAHs. The recommended PEFs are shown in Table 44. These may be used for exposure via both the oral and dermal routes, although it should be noted that these PEFs are largely derived from dermal data; therefore they have debatable relevance to relative potencies of PAH for the oral exposure routes.

A summary of the recommended toxicological criteria for BaP is shown in Table 43, while Table 44 provides the recommended potency equivalency factors for routinely measured PAHs.

Table 43: Recommended toxicological criteria for benzo(a)pyrene

Parameter	Value	Basis
Contaminant status	Non-threshold	See weight of evidence
Oral Risk-specific dose (μg/kg bw/day) Slope factor (per mg/kg bw/day)	 0.0048 2.08	 Geometric mean of 14 risk estimates using 4 datasets with no cross-species scaling.
Inhalation intake	NA	Low-volatility of BaP indicates inhalation exposures are minimal.
Skin absorption factor	0.06 0.026	"Worst-case" – geometric mean of values for dermal absorption values for freshly spiked soil from Wester et al (1990), Abdel-Rahman et al (2002) and Moody et al (2007). "Aged-soil estimate" – geometric mean of dermal absorption from aged soils only, from Abdel-Rahman et al (2002).
Background exposure (μg/kg bw/day)	NA	Exposure to non-threshold contaminants from all sources should be as low as reasonably practicable.

Table 44: Recommended PEFs for use in assessing potential carcinogenicity of PAH mixtures

Polycyclic aromatic hydrocarbon	Potency equivalency factors
Benz(a)anthracene	0.1
Benzo(b)fluoranthene	0.1
Benzo(j)fluoranthene	0.1
Benzo(k)fluoranthene	0.1
Benzo(a)pyrene	1.0
Chrysene	0.01
Dibenz(a,h)anthracene	1.0
Fluoranthene	0.01
Indeno(1,2,3-c,d)pyrene	0.1

2.9 DDT

DDT was used extensively in the past in New Zealand, particularly on pasture to control grass grub, although its use was strictly controlled from the early 1970s by the then Ministry of

Agriculture and its registration was cancelled in 1989 (MfE, 1998). There are still significant residues in soils in many areas, which comprise the breakdown products of DDT: DDD and primarily DDE. Typically, people are not exposed to DDT, DDE, or DDD individually, but rather to a mixture of all three compounds since DDE and DDD are degradation and metabolic products of DDT. In addition, DDT, DDE, and DDD each can exist in three isomeric forms. The most prevalent isomer of DDT, DDE, or DDD in the environment is the *p,p'*-isomer, although the *o,p'* isomers can elicit a different toxicological response.

In a regulatory context, all the breakdown products and structural isomers of DDT are often considered together. The sum of all these compounds (*p,p'*-DDT, *o,p'*-DDT, *p,p'*-DDE, *o,p'*-DDE, *p,p'*-DDD, *o,p'*-DDD) is represented as ∑DDT and referred to as the DDT complex.

The following discussion on the toxicity of DDT and its derivatives summarises various reviews (FAO/WHO, 2000; Baars et al, 2001; ATSDR, 2002). Particular attention is given to studies that have been used in deriving reference health standards. Readers are referred to the original reviews for more details on adverse health effects.

2.9.1 Toxicological status

DDT is an organochlorine pesticide, for which its best known effect is impairment of nerve impulse conduction. As many basic physiological processes, such as respiratory and cardiovascular functions, are controlled by the nervous system, exposure to high amounts of DDT is expected to produce a wide array of symptoms and central and peripheral signs of toxicity. Acute exposure to DDT targets the central and peripheral nervous systems, manifesting as nausea, vomiting, dizziness, confusion, tremors and, in severe cases, convulsions. Chronic exposure of animals to DDT also results in neurological effects such as tremors, loss of equilibrium, and decrease in brain lipids (Baars et al, 2001). DDT acts on the central nervous system by interfering with the movement of ions through neuronal membranes. There appear to be at least four mechanisms by which DDT affects ion movement, including delaying the closing of the sodium ion channel and preventing the full opening of the potassium gates, targeting a specific neuronal adenosine triphosphatase (ATPase) that plays a vital role in neuronal repolarisation and inhibition of the transport of calcium ions in nerves. These actions combine to effectively maintain the depolarisation of the nerve membrane, potentiating the release of transmitters and leading to central nervous system excitation (ATSDR, 2002).

A recent concern about the adverse effects of organochlorine pesticides is their influence on reproductive systems. Thus far, there is no conclusive evidence that exposure to DDT/DDE/DDD at the levels found in the environment has affected reproduction and development in humans, although animal studies indicate the potential for it to do so. The effects on reproduction and development in animals are attributed to hormone-altering actions of DDT isomers and/or derivatives in both *in vitro* and *in vivo* testing (ATSDR, 2002). Of all the DDT-related compounds, the *o,p'*-DDT isomer has the strongest oestrogen-like properties, although it is still several orders of magnitude less potent than the natural hormone, 17β-oestradiol. *p,p'*-DDE, the most environmentally relevant DDT derivative, has anti-androgenic properties and has been shown to alter the development of reproductive organs when administered perinatally to rats (ATSDR, 2002). The anti-androgenic behaviour of *p,p'*-DDE is suggested to occur via three mechanisms: antagonism after binding to the androgen receptor, hydroxylation of testosterone via increases in liver CYP enzyme systems, and conversion of C19 androgens into oestrogens via catalysation of liver enzymes. Thus DDE, like DDT, can have an overall feminising effect on animals by antagonising the androgen receptor at the same time that it increases the concentration of oestrogens.

Although there is no conclusive evidence in the available studies that the human liver is a primary target for DDT toxicity, or that exposure to DDT causes liver toxicity in humans, liver effects were the most sensitive effects observed in animals treated with DDT and its derivatives by relevant routes of exposure (ATSDR, 2002). Effects observed include induction of microsomal enzymes; increased serum transaminase activities of hepatic origin; liver hypertrophy, hyperplasia, and necrosis; and liver cancer (ATSDR, 2002). Induction of microsomal enzymes is important because it can lead to altered metabolism of exogenous and endogenous substrates, including steroid hormones as mentioned above.

Studies in mice and rats have shown that DDT, DDE, and DDD can cause cancer, primarily in the liver. However, studies in monkeys and dogs did not show any increase in liver tumour formation as a result of exposure to DDT (Baars et al, 2001). The possible association between exposure to DDT and various types of cancers in humans has been studied extensively, particularly in regard to breast cancer (Baars et al, 2001; ATSDR, 2002). Thus far, there is no conclusive evidence linking DDT and related compounds to cancer in humans. The IARC (1991) has concluded that, due to evidence of carcinogenicity in experimental animals, DDT is a possible human carcinogen (Group 2B). The US EPA (1991) considers that DDT and its derivatives are probably carcinogenic to humans (Group B).

Possible genotoxic effects in humans have been reported in a few studies, but simultaneous exposure to other chemicals and lack of control for relevant confounders make the results inconclusive (ATSDR, 2002). For the most part, DDT and related compounds are not mutagenic in prokaryotic organisms (FAO/WHO, 2000). Additionally, studies of DDE indicate that genotoxicity is more likely to lead to cell death than to tumour formation (Edelbrock et al, 2004). The data on genotoxicity of DDT and its derivatives is inconclusive, and non-genotoxic mechanisms – specifically, liver microsome induction, interference with nerve impulse conductance, and endocrine disruption or a combination of all three – are suggested to be the mechanisms leading to liver tumour formation (Baars et al, 2001; ATSDR, 2002).

2.9.2 New Zealand classification

DDT and its derivatives have not been classified by ERMA NZ because DDT is no longer registered for use in this country.

2.9.3 Reference health standards

Ingestion

A number of regulatory agencies have developed guideline values for DDT and its isomers (Table 45); most have considered DDT as a threshold contaminant, with total daily intakes ranging from 0.5 to 10 μg/kg bw (Table 49). These TDIs are typically considered to apply to the DDT complex, $\sum$DDT . Only the US EPA has considered DDT and its derivatives DDE and DDD separately (US EPA 1988a; 1988b; 1991; 1996), and as non-threshold contaminants, thus deriving slope factors accordingly (US EPA 1988a; 1988b; 1991) (Table 46). Canadian agencies have not developed a reference health standard for the derivation of soil guideline values for DDT but have based their soil guideline value on ecological receptors, although no indication was given as to whether any initial screening of human health effects was undertaken (Environment Canada, 1999; K. Potter, Environment Canada, pers. comm.).

Most agencies use the study of Laug et al (1950 cited in FAO/WHO, 2000) to derive their TDI (Table 49). US EPA (1996) gives the following reasons for selection of this study: (1) male rats appear to be the most sensitive animals to DDT exposure; (2) the study was of sufficient length to observe toxic effects; and (3) several doses were administered in the diet over the range of the dose-response curve. This study also established a LOAEL and a NOEL, with the LOAEL (0.25 mg/kg bw/day) being the lowest of any observed for this substance.

In contrast, the WHO drinking water guideline (WHO, 2004) is based on the reference health standard established by the JMPR (FAO/WHO, 2000), which in turn is based upon the "lowest relevant" NOAEL for developmental toxicity in rats of 1 mg/kg bw/day nominally sourced from ATSDR (1994 cited in FAO/WHO, 2000). However, it is unclear from the most recent assessment by the ATSDR (2002) what study may have been referred to by FAO/WHO (2000). Thus, it is not possible to comment on the applicability of this value.

Table 45: Summary of oral reference health standards for DDTs as a threshold contaminant, used by different international agencies

Jurisdiction[1]	Compound	Tolerable daily intake (µg/kg bw)	Key study[2]	Critical effect[2]	Basis of value[2]	Reference
New Zealand	∑DDT	0.5	Not stated	Not stated	Not stated (US EPA, 2001)	MfE (2006)
New Zealand drinking water	∑DDT	10	Not stated	Developmental toxicity in rats	NOAEL of 1 mg/kg, and a safety factor of 100	MoH (2005)
Joint FAO/WHO Meeting on Pesticide Residues (JMPR)	∑DDT	10	Not stated	Developmental toxicity in rats	NOAEL of 1 mg/kg, and a safety factor of 100	FAO/WHO (2000)
WHO drinking water	∑DDT	10	Not stated	Developmental toxicity in rats	FAO/WHO (2000)	WHO (2004)
Australia	DDT	20	Not stated	Hepatotoxicity in rats	NHMRC (year unstated)	NEPC (1999)
The Netherlands – current	∑DDT	20	Not stated	Not stated	Vermeire et al (1991). NOAEL of 0.25 mg/kg bw/day from occupational health studies, and application of a UD of 10 for intrahuman variation	Baars et al (2001)
The Netherlands – proposed[3]	∑DDT	0.5	Laug et al (1950)	Hepatotoxicity in rats	NOAEL of 0.05 mg/kg, safety factor of 100 (10 for interspecies variation, 10 for intraspecies variation)	Baars et al (2001)
US ATSDR US EPA	DDT	0.5	Laug et al (1950)	Hepatotoxicity in rats	NOAEL of 0.05 mg/kg, safety factor of 100 (10 for interspecies variation, 10 for intraspecies variation)	ATSDR (2002) US EPA (1996)

1 UK agencies (DEFRA and EA) have not assessed DDT, and the Canadian National Contaminated Sites Remediation Programme considered only the ecological effects of DDT (Environment Canada, 1999).

2 As reported in the reference cited in the reference column.

3 This value is yet to be officially adopted.

Table 46: Summary of oral reference health standards for DDTs, as a non-threshold contaminant, used by the US EPA

Jurisdiction	Compound	Acceptable risk level[1]	Risk-specific dose (μg/kg bw/day)	Cancer slope factor (per mg/kg bw/day)	Key study[2]	Critical effects[2]	Basis of value	Reference
US EPA	DDT	10^{-6} [10^{-5}]	0.00295 [0.0295]	0.34	Terracini et al (1973), Turusov et al (1973), Thorpe and Walker (1973), Tomatis and Turusov (1975), Cabral et al (1982)	Benign and malignant tumours in rats and mice	Linearised multi-stage model. Geometric mean of slope factors from five studies	US EPA (1991)
UK	DDE	10^{-6} [10^{-5}]	0.00295 [0.0295]	0.34	NCI (1978), Tomatis et al (1974), Rossi et al (1983 in US EPA, 2001b)	Liver tumours in mice and neoplastic nodules of the liver in hamsters	Linearised multi-stage model. Geometric mean of slope factors from three studies	US EPA (1988a)
US	DDD	10^{-6} [10^{-5}]	0.0042 [0.042]	0.24	Tomatis et al (1974 in US EPA, 2001c)	Liver tumours in mice	Linearised multi-stage model – note: the slope factor was calculated using tumour incidence data from only one dose	US EPA (1988b)

1 Where the acceptable risk level for a given jurisdiction is not 10^{-5}, the risk-specific dose for a risk of 10^{-5} is shown in square brackets.

2 As reported in the reference cited in the reference column.

Inhalation

Inhalation is anticipated to be a negligible route of exposure as DDT and its derivatives have limited volatility and the amount of dust considered to be inhaled typically represents a very small fraction of exposure (see section 1.1.4), so is not discussed further.

Dermal absorption

Skin absorption is a key contaminant-specific parameter required for the dermal absorption pathway; this is typically used to provide an estimate of "additional" exposure via the oral route. US EPA (2004) recommends a dermal absorption factor of 0.03 (3%), which is based on data from Wester et al (1990). These authors indicate that only 1.0% of DDT from soil penetrated into human skin over a 24-hour period, and none (<0.1%) of this partitioned into human plasma. Additionally, 3.3% of DDT from soil was absorbed percutaneously following *in vivo* exposure of rhesus monkeys. Taking the geometric mean of these values yields an average dermal absorption factor of 0.018 (1.8%).

Other routes of exposure – background exposure

Background exposure is important to take into consideration for threshold contaminants. As DDT has been considered a threshold contaminant by some agencies, background exposure is considered here.

Dietary intake of DDT residues is considered to be the primary source of exposure. Vannoort and Thomson (2005) estimated the dietary intake of ∑DDT was 0.0511 μg/kg bw/day for a toddler (1–3 years, 13 kg), 0.0216 μg/kg bw/day for adult males (25+, 82 kg), and 0.0170 μg/kg bw/day for adult females (25+, 70 kg). The average dietary intake of ∑DDT for an adult is 0.0193 μg/kg bw/day.

New Zealand water quality monitoring data (Davies et al, 2001) indicated that DDT and its derivatives were not detected in any drinking water zones assessed, therefore intake via drinking water is considered to be negligible.

2.9.4 Summary of effects

DDT is an organochlorine pesticide for which its best known effect is impairment of nerve impulse conduction. Effects of DDT on the nervous system have been observed in both humans and animals and can vary from mild altered sensations to tremors and convulsions. Reproductive, developmental and hepatic effects are also commonly reported in animals exposed to DDT, although there is no conclusive evidence of these effects occurring in humans environmentally exposed to the DDT complex.

Table 47 summarises effects observed in animals and humans resulting from exposure to DDT, DDE or DDD (ATSDR, 2002).

Table 47: Summary of the health effects of DDT, DDE, and DDD

Dose (mg DDT/kg/day)	Type of poisoning[1]	Effects
86	Acute	Lowest reported LD_{50} in animals (mice)
10	Intermediate	Lowest dosage reported to cause neurological change (decrease in brain and CNS lipids) in animals (monkeys)
1.9	Intermediate	Lowest dosage reported to cause immunological effects (decreased mast cells) in animals (rats)
1.7	Intermediate	Lowest dosage reported to cause reproductive effects (decreased implanted ova, corpora lutea) in animals (mice)
1.6	Intermediate	Lowest reported NOAEL for developmental effects in animals (mice)
0.75	Chronic	Lowest reported NOAEL for reproductive effects in animals (rats)
0.61	Chronic	No reported neurological effects observed in humans exposed for 12–18 months to technical-grade DDT
0.5	Acute	Lowest dosage reported to cause developmental effects (changes in brain activity) in animals (mice)
0.5	Chronic	No effects on cardiovascular, blood or hepatic system observed in humans exposed for 12–18 months to technical-grade DDT
0.3	Chronic	Lowest dosage reported to cause tumours (liver) in animals (mice)
0.25	Intermediate	Lowest dosage reported to cause hepatic effects (cellular hypertrophy) in animals (rats)
0.05	Intermediate	Lowest reported NOAEL for hepatic effects in animals (rats)

1 Length of exposure: acute (<14 days), intermediate (15–365 days), chronic (>365 days).

2.9.5 Weight of evidence

- DDT is considered to be a possible human carcinogen by the IARC (1991) and a probable human carcinogen by the US EPA (1991).
- Human data specifically linking DDT and DDE to a carcinogenic effect is lacking. DDT has been shown to be carcinogenic in rodents, primarily mice (liver cell tumours) although the responses between studies are markedly different (ATSDR, 2002).
- DDT, DDE and DDD were not mutagenic in bacterial systems, fungi, plant cells and mammalian cells (IARC, 1991; ATSDR, 2002).
- *In vitro* testing for chromosomal aberrations showed conflicting results, some were negative while others were weakly positive (IARC, 1991; ATSDR, 2002).
- DDT and its derivatives enhance liver enzyme production, are weakly hormone disrupting, and act on the central nervous system by interference with the movement of ions through neuronal membranes. All of these mechanisms are suggested to contribute to the tumorigenic potential of DDT and its metabolites (Baars et al, 2001; ATSDR, 2002).
- DDT and its derivatives are considered to be threshold contaminants, given the equivocal data on the genotoxicity of DDT and its metabolites and the potential for tumour formation via non-genotoxic mechanisms.

2.9.6 Recommendations for toxicological intake values

Ideally, toxicological criteria for DDT should be based on data regarding the effects of DDE, because it is the primary metabolite found in the environment. However, insufficient data is available to do so – other than to note that toxicologically the adverse effects of DDE and DDT are similar – hence criteria are set based on the effects of DDT. In line with a number of international agencies, an oral TDI of 0.5 μg/kg bw based on hepatotoxicity in rats (Laug et al, 1950), is recommended for use in New Zealand (Table 48). This study demonstrates the most sensitive toxicity endpoint from existing data.

It is recommended that a dermal absorption of 0.018 (1.8%) be used. This is based on the geometric mean of the results of *in vitro* and *in vivo* skin absorption studies from Wester et al (1990). An inhalation dose is not considered relevant for soil contamination due to the low volatility of ∑DDT. Dietary intake of DDT residues from food is considered to be the primary source of exposure. The dietary intakes of ∑DDT for a child aged 1 –3 years and an average adult are estimated to be 0.0511 μg/kg bw/day and 0.0193 g/kg bw/day, respectively, while intake from drinking water is negligible.

Table 48: Recommended toxicological criteria for ∑DDT

Parameter	Value	Basis
Contaminant status	Threshold	–
Oral (μg/kg bw/day)	0.5	Hepatoxicity in rats, applying a UF of 100 (10 for interspecies variation and 10 for intraspecies variation) to a NOEL of 0.05 mg/kg bw/day from Laug et al (1950)
Inhalation intake	NA	Low volatility of DDT indicates inhalation exposures are minimal
Skin absorption factor	0.018	Wester et al (1990)
Background exposure (μg/kg bw/day)	0.0511 0.0193	Child (1–3 years) Adult Dietary intake of DDT (Vannoort and Thomson, 2005)

2.10 Dieldrin

The following discussion on the toxicity of dieldrin summarises relevant data from various reviews (FAO/WHO 1971; 1977; WHO, 1989; 2004; Baars et al, 2001; ATSDR, 2002). Particular attention is given to those studies that have been used in deriving reference health standards. Readers are referred to the original reviews for more details on adverse health effects.

2.10.1 Toxicological status

The primary site of action of dieldrin in humans and animals is the central nervous system (FAO/WHO, 1967; ATSDR, 2002). CNS stimulation causing convulsions is the cause of death in acute poisoning, and may also occur as a result of chronic exposure. During longer-term exposure other, less serious symptoms of CNS intoxication may be observed including headaches, dizziness, general malaise, nausea, or vomiting. Other toxic effects of chronic exposure to dieldrin in workers exposed to pesticides have not been conclusively established. However, in animal studies other effects include liver and kidney toxicity, immunosuppression, foetal toxicity, neurodevelopmental effects, and decreased reproductive function (ATSDR, 2002). Dieldrin is not mutagenic in *in vitro* and *in vivo* tests.

The liver is the critical target of chronic toxicity in several species, particularly mice, and dieldrin is a powerful inducer of microsomal enzymes. The effects of prolonged enzyme induction include increase in liver weight or size, liver cell enlargement, proliferation of endoplasmic reticulum in the cell, and an increase in microsomal protein (FAO/WHO, 1977; ATSDR, 2002). These changes are fully reversible if exposure to dieldrin is ceased before tumours have developed (FAO/WHO, 1977).

The observation that exposure to dieldrin at low concentrations could lead to the development of liver tumours, particularly in mice, led to further studies on the carcinogenicity and mutagenicity of dieldrin (FAO/WHO, 1977). However, despite reviewing further studies, the IARC (1987) considered that dieldrin (and related compounds aldrin and endrin) was not classifiable as to its carcinogenicity in humans (Group 3), although there was some evidence of carcinogenicity in animals. Furthermore, the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) considered that the effect of dieldrin in mice was likely to be a species-specific effect (FAO/WHO, 1971; 1977). Similarly, ATSDR (2002) considered that mouse carcinogenicity data may not be highly relevant to humans, and that the preponderance of evidence indicates that dieldrin induces a carcinogenic response through non-genotoxic mechanisms. In contrast, the US EPA (1993) classified dieldrin as a probable human carcinogen (class B2) based on the development of liver tumours in mice.

2.10.2 New Zealand classification

Dieldrin has not been classified by ERMA NZ as dieldrin is no longer used in this country.

2.10.3 Toxicological intake values

Ingestion

The majority of international jurisdictions have adopted the total daily intake of 0.1 μg/kg bw determined by JMPR (Table 49). This value was originally established in 1966 (FAO/WHO, 1967), and endorsed at two subsequent meetings (FAO/WHO, 1971; 1977). This intake is stated to be based on no observable effects occurring in the liver of dogs and rats at dietary intakes equivalent to 0.025 mg/kg bw/day, and no information is given regarding the uncertainty factor (250) that must have been applied to obtain the acceptable daily intake. Further, this intake is actually the lowest dose at which effects were observed, ie, a LOAEL.

US authorities have derived a significantly lower reference health standard. ATSDR (2002) and the US EPA (1990) have set an MRL and RfD respectively, of 0.05 μg/kg bw/day. This value is based on liver toxicity in rats observed during a chronic feeding study undertaken by Walker et al (1969). This study was also considered by JMPR in its evaluation in 1970, but no adjustment was made to the ADI it had established in 1966 (FAO/WHO, 1971). Specifically, the US EPA (1990) and ATSDR (2002) both state that they use liver cell changes "characteristic of exposure to organochlorine insecticides" as the toxicological endpoint. However, this aspect is not mentioned in FAO/WHO (1971) in its discussion of this study. ATSDR and the US EPA apply an uncertainty factor of 100 to a stated NOAEL of 0.1 mg/kg in the diet (0.005 mg/kg bw/day) to derive their respective reference health standards. They further state that the LOAEL for the study was 1 mg/kg in the diet (0.05 mg/kg bw/day). However, in the original study (Walker et al, 1969) the authors state: "no changes in liver cell morphology that could be attributed specifically to chlorinated hydrocarbons occurred in rats receiving 1 ppm dieldrin", thus the findings of Fitzhugh et al (1964), who observed that an intake of 0.5 mg/kg in the diet

resulted in enlarged livers and lesions characteristic of those caused by organochlorine insecticides, were not confirmed in their study. Thus it is unclear on what basis the US EPA and ATSDR determined a NOAEL of 0.1 mg/kg in the diet from this study; and it also suggests that the Fitzhugh et al (1964) study does actually provide the most sensitive endpoint for setting a TDI.

US EPA (1993) is the only agency that has derived a slope factor for dieldrin (1 per mg/kg bw/day) (Table 50). This slope factor is the geometric mean of 13 slope factors calculated from liver carcinoma data in both sexes of several strains of mice.

Inhalation

Inhalation is anticipated to be a negligible route of exposure as dieldrin has limited volatility and the amount of dust considered to be inhaled typically represents a very small fraction of exposure (see section 1.1.3), so is not discussed further.

Dermal absorption

The skin absorption factor is the key parameter required to estimate dermal absorption. No data specific to dieldrin were found, hence the default absorption factor of 0.1 specified in US EPA (2004) for semi-volatile contaminants is recommended.

Other routes of exposure – background exposure

Dietary intake of dieldrin is considered to be the primary source of exposure. Vannoort and Thomson (2005) estimated the dietary intake of dieldrin was 0.0036 μg/kg bw/day for a toddler (1–3 years, 13 kg), 0.0015 μg/kg bw/day for adult males (25+, 82 kg), and 0.012 μg/kg bw/day for adult females (25+, 70 kg). The average dietary intake of dieldrin for an adult is 0.0014 μg/kg bw/day.

New Zealand water quality monitoring data (Davies et al, 2001) indicated that dieldrin was detected in only 0.3% of the drinking water zones assessed, and therefore intake via drinking water is considered to be negligible.

2.10.4 Summary of effects

Similar to other organochlorine pesticides, the central nervous system is a target for toxicity for dieldrin. Acute high-level exposure to aldrin or dieldrin in humans results in CNS excitation culminating in convulsions. Longer-term exposure of workers has also been associated with CNS intoxication, although other toxic effects have not been conclusively attributed to exposure to dieldrin. Animal data is consistent with the findings in humans that the CNS is an important target of toxicity, but further shows that other effects may also be associated with exposure to dieldrin, including liver and kidney toxicity, immunosuppression, foetal toxicity and increased postnatal mortality, neurodevelopmental effects, and decreased reproductive function. No studies were located regarding developmental effects in humans, and conflicting results exist in animals (ATSDR, 2002).

Table 51 summarises effects observed in animals and humans resulting from exposure to dieldrin (ATSDR, 2002).

Table 49: Summary of oral reference health standards for dieldrin as a threshold contaminant, used by different international agencies

Jurisdiction[1]	Substance	Tolerable daily intake (μg/kg bw/day)	Key study[2]	Critical effect[2]	Basis of value[2]	Reference
New Zealand	Aldrin/dieldrin or sum	0.1	Not stated	Not stated	(Not stated)	MfE (2006)
New Zealand drinking water	Aldrin/dieldrin or sum	0.1	Not stated	Not stated	FAO/WHO (1977)	MoH (2005)
Joint FAO/WHO Meeting on Pesticide Residues (JMPR)	Aldrin/dieldrin or sum	0–0.1	Fitzhugh et al (1964)	Liver lesions, 2-year rat feeding study	NOEL of 0.025 mg/kg bw/day in rats and dogs	FAO/WHO (1967; 1971; 1977)
WHO drinking water	Aldrin/dieldrin or sum	0.1	Fitzhugh et al (1964)	Liver lesions, 2-year rat feeding study	FAO/WHO (1967)	WHO (2004)
Australia	Aldrin/dieldrin or sum	0.1	Fitzhugh et al (1964)	Liver lesions, 2-year rat feeding study	FAO/WHO (1971; 1977)	DiMarco (1993)
The Netherlands – current	Aldrin/dieldrin or sum	0.1	Fitzhugh et al (1964)	Liver lesions, 2-year rat feeding study	Vermeire et al (1991)	Baars et al (2001)
The Netherlands – proposed[3]	Aldrin/dieldrin or sum	0.1	Fitzhugh et al (1964)	Liver lesions, 2-year rat feeding study	FAO/WHO (1971; 1977)	Baars et al (2001)
US ATSDR – intermediate duration MRL and US EPA	Dieldrin	0.05	Walker et al (1969)	Liver lesions, 2-year rat feeding study	NOEL of 0.1 ppm diet (0.005 mg/kg bw/day, conversion factor 1 ppm = 0.05 mg/kg/day assumed food consumption) and an uncertainty factor of 100 (10 for interspecies variation and 10 for intraspecies variation)	ATSDR (2002) US EPA (1990)

1 UK agencies (DEFRA and EA) did not assess dieldrin, Canadian agencies also have not assessed aldrin/dieldrin for assessment of contaminated land purposes.

2 As reported in the reference cited in the reference column.

3 This value is yet to be officially adopted.

Table 50: Summary of oral reference health standards for dieldrin as a non-threshold contaminant, used by different international agencies

Jurisdiction	Acceptable risk level	Risk-specific dose[1] (μg/kg bw/day)	Cancer slope factor (per mg/kg bw/day)	Key study[2]	Critical effects[2]	Basis of value	Reference
US	10^{-6} [10^{-5}]	0.0000625 [0.000625]	16	Several	Liver tumours in mice	The slope factor is the geometric mean of 13 slope factors calculated from liver carcinoma data in both sexes of several strains of mice	US EPA (1993)

1 Where the acceptable risk level for a given jurisdiction is not 10^{-5}, the risk-specific dose for a risk of 10^{-5} is shown in square brackets.

2 As reported in the reference cited in the reference column.

Table 51: Summary of the health effects of dieldrin in animals and humans

Dose (mg/kg/day)	Type of poisoning[1]	Effects
9 mg/kg	Acute	Lowest reported LD_{50} in animals (rats)
0.33	Intermediate	Lowest dosage reported to cause tumours (liver) in animals (mice)
0.13	Intermediate	Lowest dosage reported to cause immunological effects in animals (mice)
0.125	Chronic	Lowest dosage reported to cause reproductive (decreased litter size) and developmental (increased pup mortality) effects in animals (rat)
0.1	Intermediate	Lowest dosage reported to cause neurological effects (learning deficit) in animals (monkeys)
0.025	Chronic	Lowest dosage reported to cause hepatic effects in animals (rats)[2]
0.003	Chronic	No observed effects on neurological, blood or hepatic systems reported in humans exposed for 18 months

1 Length of exposure: acute (<14 days), intermediate (15–365 days), chronic (>365 days).

2 Excluding the dosage reported for the Walker et al (1969) study for the reasons discussed in section 2.8.3.

2.10.5 Weight of evidence

- Dieldrin is considered to be a probable human carcinogen by the US EPA (2004) but not classifiable as a human carcinogen by the IARC (1987).
- Human data on carcinogenicity is lacking, although dieldrin has been shown to be the cause of liver tumours in mice. This is considered to be a species-specific effect, related to the metabolism of dieldrin (FAO/WHO, 1971; 1977).
- Dieldrin is a powerful inducer of liver microsomal enzymes, which may lead to tumour formation (FAO/WHO, 1971; 1977; ATSDR, 2002).
- *In vitro* and *in vivo* testing has demonstrated that dieldrin is non-mutagenic (FAO/WHO, 1977; IARC, 1987; ATSDR, 2002).
- Given the lack of evidence that dieldrin is genotoxic, dieldrin is considered to be a threshold contaminant.

2.10.6 Recommendations for toxicological intake values

As dieldrin is a threshold contaminant, a tolerable daily intake is proposed for use. The majority of jurisdictions have adopted JMPR's (FAO/WHO, 1977) acceptable daily intake of 0.1 μg/kg bw, while US agencies derived a lower reference health standard of 0.05 μg/kg bw/day. However, it appears that this value is based on a no observable adverse effect level that is 10 times lower than that discussed in the original (Walker et al, 1969) study. Hence it is recommended that the total daily intake of the JMPR, 0.1 μg/kg bw, is adopted for use in New Zealand (Table 52).

There is an absence of dermal absorption data for dieldrin; hence, it is recommended that an absorption factor of 0.1, as specified in US EPA (2004) for semi-volatile contaminants, is used. An inhalation dose is not considered relevant for soil contamination due to the low volatility of dieldrin. Dietary intake is the primary source of background exposure to dieldrin. The dietary intake for a child aged 1–3 years was estimated to be 0.0036 μg/kg bw/day and for an adult, 0.0014 μg/kg bw/day, while intake from drinking water was negligible.

Table 52: Recommended toxicological criteria for dieldrin

Parameter	Value	Basis
Contaminant status	Threshold	–
Oral (μg/kg bw/day)	0.1	ATSDR (2002), US EPA (1990) – Walker et al (1969), liver toxicity in rats; NOAEL of 0.05 mg/kg bw/day and uncertainty factor of 100
Inhalation intake	NA	Low volatility of dieldrin indicates inhalation exposures are minimal
Skin absorption factor	0.1	No data available, hence the default value from US EPA (2004) is used
Background exposure (μg/kg bw/day)	0.0036	Dietary intake for a child 0–6 years
	0.0014	Adult dietary intake (Vannoort and Thomson, 2005)

2.11 Pentachlorophenol (PCP)

Several comprehensive, although mainly older, reviews of the toxicity of pentachlorophenol have been undertaken (CCME, 1997; Goodman et al, 1998; ATSDR, 2001; IPCS 1987). The discussion below summarises relevant data from these reviews. Particular attention is given to those studies that have been used in deriving reference health standards. Readers are referred to the original reviews for more details on adverse health effects.

Review of the toxicity of PCP is complicated by the relatively large database on the toxicity of technical-grade PCP and the comparatively small database on pure PCP. Technical-grade PCP has been shown to contain a large number of impurities, including tetrachlorophenols and, to a much lesser extent, polychloro-dibenzodioxins, polychlorodibenzofurans, polychlorodiphenyl ethers, polychloro-phenoxy phenols and chlorinated hydrocarbons. These impurities, in particular the polychloro-dibenzodioxins and furans, are indicated to be responsible for at least some of the observed toxicity of the technical-grade PCP. While from one perspective the toxicity of the technical-grade mixture is important, as this is what humans are most likely exposed to, the primary impurities suggested to be responsible for some of the observed toxicity – polychloro-dibenzodioxins and polychlorodibenzofurans – are being considered separately in this review process. Thus, it is appropriate to delineate the effects associated with PCP from those associated with the impurities of technical-grade PCP, where possible. The discussion below attempts to focus on effects associated with exposure to PCP, and highlights where impurities are suggested to have the dominant influence.

2.11.1 Toxicological status

Effects arising from acute exposure to PCP are generally suggested to arise from uncoupling of oxidative phosphorylation and inhibition ATPase and several other enzymes, by PCP (Jorens and Schepens, 1993). This leads to excessive heat production and fever. Symptoms of acute poisoning include central nervous system disorders, dyspnoea, and hyperpyrexia, leading to cardiac arrest.

The liver is a target organ for PCP-induced toxicity in animals. The most frequently reported effects are increased liver weight and microscopic changes, and changes in liver enzyme activity. Some studies suggest that impurities in technical-grade PCP influence toxicity, while other studies found no difference between technical-grade and pure PCP (ATSDR, 2001). There are limited and inconsistent data on the effects of PCP on kidneys. The most frequently reported toxic effect seen in kidneys of rodents is increased organ weights and altered enzyme levels; histopathological effects are rarely seen.

Alterations in thyroid hormone concentrations, in particular a decrease in thyroxine, have been observed in rats, minks and sheep exposed to PCP (eg, Jekat et al, 1994; Beard and Rawlings, 1998; Rawlings et al 1998). In young female rats exposed to PCP for eight days, technical-grade PCP and pure PCP tested at 3 mg/kg bw reduced serum concentrations of thyroxine by a similar amount (Jekat et al, 1994). A multi-generational study in mink found decreases in thyroxine and thyroid weight in the offspring of treated females (that were also fed PCP in their diet) associated with exposures of 1 mg/kg bw/day (Beard and Rawlings, 1998). The purity of PCP was not reported in this study, although another study conducted by one of the authors at a similar time suggests pure PCP was used (Rawlings et al, 1998).

Studies of the immunological effects of PCP exposure in mice have reasonably clearly determined that the majority of immunotoxic effects appear to be related to the concentration of impurities. However, pure pentachlorophenol caused effects on the immune system in rats (ATSDR, 2001), thus suggesting the immunotoxic effects of PCP itself could be observed in humans.

A number of studies have examined the reproductive toxicity of PCP, with the available data suggesting that chronic exposure to PCP can reduce fertility, although the mechanism does not appear to be through histological damage to reproductive tissue. No histological alterations were observed in reproductive tissues in male or female rats exposed to 30 mg/kg bw/day pure PCP in the diet for two years (NTP, 1999 cited in ATSDR, 2001). Developmental effects that may occur as a result of gestational exposure to PCP in rats and sheep include foetal/neonatal mortality, malformations/variations, decreased growth, and possible functional deficits (ATSDR, 2001). In many studies decreases in maternal weight gain were observed at the same doses as the developmental effects in rats, although in other studies maternal toxicity occurred at higher doses; this suggests that developmental toxicity can occur in the absence of maternal toxicity.

A number of studies since the 1970s have implicated the group of chemicals including chlorophenols, chlorophenoxy acids, chlorinated dibenzo-*p*-dioxins, and chlorinated dibenzofurans in the causation of cancer, especially soft-tissue sarcoma and non-Hodgkin's lymphoma (IARC, 1991; 1999). WHO (2003) concluded that there is some, although not irrefutable, evidence that chlorophenol preparations, including PCP, may cause cancer in humans. A recent review of epidemiological studies of pentachlorophenol exposure and cancer concluded that there are certain cancers (non-Hodkgin's lymphoma, multiple myeloma, soft-tissue sarcoma) observed with exposure to pentachlorophenol that are not likely due to dioxins or other chlorophenol (in particular tetrachlorophenol) contaminants (Cooper and Jones, 2008).

However, there is limited information on the potential mechanisms of cancer formation. There is, at best, equivocal data on the genotoxicity of PCP: it does not induce gene mutation in bacteria, while gene mutation tests in yeast are largely positive; however, there are questions regarding the quality of data (Goodman et al, 1998). There is weak evidence of PCP causing chromosomal effects, with the most convincing changes occurring only in the presence of rat microsomal protein (S9). The largest question-mark exists around the relative importance of the metabolite tetrochlorohydroquinone (TeHQ) in human metabolism of PCP, and in cancer formation. TeHQ is the primary PCP metabolite formed in rodents and has demonstrated genotoxicity. It has been proposed that TeHQ has a major role in hepatocarcinogeneis in mice (Umemura et al, 1996) although studies have failed to conclusively demonstrate this (Goodman et al, 1998). *In vivo* studies in humans and monkeys do not indicate the formation of TeHQ from PCP, although *in vitro* studies using human cytochrome P-450 enzymes do demonstrate the formation of TeHQ, suggesting that *in vivo* metabolism of PCP to TeHQ may be more quantitatively than qualitatively different to metabolism in rats (Goodman et al, 1998).

While TeHQ is suggested to be the major metabolite of PCP, the majority of PCP, particularly in humans, is excreted unchanged or conjugated. Binding of PCP to plasma proteins is suggested to play a role in this low metabolism, as protein-bound material is not readily distributed to tissues where it may be metabolised. The binding of PCP to plasma proteins also appears to have a role in PCP toxicity. PCP is suggested to exert toxic effects, at least in part, by uncoupling mitochondrial oxidative phosphorylation, thereby causing accelerated aerobic metabolism. Binding of PCP to mitochondrial protein may induce conformational changes in enzymes involved in oxidative phosphorylation. Further, PCP has a greater binding affinity for thyretin, a major thyroxine transport protein in the rat, than for thyroxine itself (den Besten et al, 1991 cited in ATSDR, 2001) and the mechanism of action for anti-thyroid effects is suggested to be competition for serum protein thyroxine-binding sites.

2.11.2 New Zealand classification

The Hazardous Substances and New Organisms Act classification of pentachlorophenol set by ERMA NZ is shown in Table 53. Overall, pentachlorophenol is of high acute toxicity (6.1B) and is a skin and eye irritant (6.3A, 6.4A). Pentachlorophenol also has the following long-term endpoints: it is a suspected human carcinogen (6.7B), causes reproductive/developmental toxicity (6.8B) and is toxic from chronic exposures (6.9B). This classification (Table 53) was carried out at the time of transfer of substances to the HSNO regime. Since PCP was at that time already obsolete, the classification was not exhaustively reviewed before the revocation of the HSNO approval in July 2008 (http://www.ermanz.govt.nz/appfiles/execsumm/pdf/HRC07004-003.pdf).

Table 53: HSNO classification of pentachlorophenol

Hazardous property	HSNO classification
Acute toxicity	6.1B
Skin irritation	6.3A
Eye irritation	6.4A
Sensitiser	–
Mutagenicity	ND
Carcinogenicity	6.7B
Reproductive/developmental toxicity	6.8B
Target organ systemic toxicity	6.9B

ND – not determined; – – not assigned.

2.11.3 Reference health standards

Ingestion

International agencies have variably applied threshold and non-threshold approaches for determining reference health standards for PCP (Tables 54 and 55). Baars et al (2001) considered that PCP did not demonstrate genotoxicity in *in vitro* and *in vivo* systems and occupationally exposed humans, and established a total daily intake of 3 µg/kg bw based on minor changes in thyroid homeostasis in mink (Table 54). This same study was used by ATSDR (2001) to derive a chronic-duration minimal risk level of 1 µg/kg bw/day, although different uncertainty factors were used. Specifically, Baars et al (2001) used an uncertainty factor of 3 to extrapolate from a LOAEL to a NOAEL, as they considered the effects marginal, while the ATSDR (2001) used a factor of 10 to extrapolate from the LOAEL to a NOAEL, even though they considered the effects to be "less-serious". Both studies use additional factors of 10 to

account for inter- and intra-species variation respectively. WHO (1996) also derived a TDI of 3 μg/kg bw but used a different study (the specific study was not stated). In this case the critical endpoint was reproduction in rats, and uncertainty factors of 10 were applied to a NOEL of 3 mg/kg bw/day to account for inter- and intra-species variation respectively, and an additional uncertainty factor of 10 to account for potential carcinogenicity. The same approach was used by CCME (1997) to derive a provisional TDI of 3 μg/kg bw from what appears to be the same study (Schwetz et al, 1978 cited in WHO, 1996). The US EPA (1993) used the same study as CCME (1997) to derive an RfD of 30 μg/kg bw/day, although in this case a 100-fold uncertainty factor was applied to account for inter- and intra-species variation only. A US EPA draft toxicological review on PCP, released in May 2009 for external review, uses a study on beagle dogs to derive an oral reference dose of 5 μg/kg bw/day.

A US study by the National Toxicology Program (NTP 1989 cited in US EPA, 1993) is the basis for all estimates of cancer potency, although different estimates have been derived (Table 55). The US EPA (1993) combined data on three types of tumours using two formulations of PCP and applied multistage model and cross-species scaling to derive a slope factor of 0.12 per mg/kg bw/day. MfE and MoH (1997) considered that PCP should be considered genotoxic and used the US EPA slope factor in the derivation of soil guideline values. The addendum to the second edition of the WHO drinking water guidelines (WHO, 1998) stated that the concentration of PCP associated with a 10^{-5} excess lifetime cancer risk determined using multistage modelling of tumour incidence in the NTP bioassay, without incorporation of a body surface area correction, was similar to the existing drinking water guideline (WHO, 1998; 2003). Thus the existing guideline value of 9 μg/L,[8] which was derived by allocating 10% of the TDI of 3 μg/kg bw to water consumption of 2 L by a 60-kg adult, was maintained. No indication of the degree of similarity was given by WHO (1998), although assuming consumption of 2 L of water at the guideline value by a 70-kg adult yields a risk-specific dose of 0.26 μg/kg bw/day at 1 in 100,000 risk level, which is approximately 10% of the TDI used by WHO (1996) and was used to derive the guideline value. Goodman et al (1998) also used the NTP (1989 cited in US EPA 1993) study, but used only data on haemangiosarcoma (vascular tumours) incidence in female mice exposed to technical-grade PCP to determine a slope factor (95% upper confidence limit of the maximum likelihood estimate) of 0.0245 per mg/kg bw/day, and applied a cross-species scaling factor (6.7, bodyweight to the 3/4 power) to yield a final slope factor of 0.16 per mg/kg bw/day.

No soil guideline values for PCP have been established (and hence no review of tolerable intakes have been undertaken) by UK and Australian agencies.

Inhalation

Inhalation from contaminated soil is likely to be a negligible route of exposure as PCP has limited volatility and the amount of dust considered to be inhaled typically represents a very small fraction of exposure (see section 1.1.4), so is not considered further.

Dermal exposure

Skin absorption is a key contaminant-specific parameter required for the dermal absorption pathway; this is typically used to provide an estimate of "additional" oral exposure, as the amount absorbed is considered to add to the amount ingested and contribute to systemic

[8] The first edition of the WHO drinking guidelines (WHO, 1984) state that a guideline of 10 μg/L is derived by this method; the difference is due to the use of 70-kg bodyweight in WHO (1984).

responses. Pentachlorophenol is rapidly absorbed across the skin, and therefore dermal exposure potentially represents a significant route of exposure. A number of studies investigating dermal absorption of PCP have been undertaken; however, only Wester et al (1993) and Qiau et al (1997) provide data that are readily used. Wester et al (1993) found that *in vivo* absorption in monkeys of PCP in soil was similar to PCP in acetone, with 24% of PCP absorbed over a 24-hour period. This was significantly higher than in *in vitro* tests using human skin, which indicated that only 0.15% of the dose was absorbed. The *in vivo* results were considered more appropriate as *in vitro* absorption was indicated to be limited by the solubility of PCP in the receptor fluid (Wester et al, 1993). A separate study on the *in vivo* absorption of PCP in pigs found a similar amount absorbed (29.1%) but over 17 days (Qiau et al, 1997), which gives rise to an average 24-hour absorption of 1.7%. The Wester et al (1993) study was conducted over a timeframe most relevant to potential exposure on a contaminated site, thus the dermal absorption of PCP from soil from this study is recommended.

Other routes of exposure – background exposure

Limited data is available on background exposure to PCP in New Zealand. A previous study has indicated that the net daily average intake of PCP in eight countries may range from 5 μg to 136 μg and up to 157 μg for people living in PCP-treated timber houses (Reigner et al, 1992). Inhalation exposure is suggested to be a potentially large source of exposure for people living in PCP-treated timber houses. For example, concentrations up to 580 $\mu g/m^3$ were measured in a room panelled with PCP-treated timber shortly after treatment; these concentrations dropped to 4 $\mu g/m^3$ two years after treatment (Jorens and Schepens, 1993 citing Janssens and Schepens, 1984). As PCP was withdrawn from use in 1988, it is considered that any background exposure related to PCP-treated timber in housing will be negligible. In non-occupationally exposed people food (especially fruits, vegetables and grains) has also been suggested to account for 99.8% of a long-term average daily intake of 16 μg/day estimated from an environmental partitioning model (Hattemer-Frey and Travis, 1989). However, daily dietary intake of PCP based on US market basket surveys undertaken over 1965–1970, when PCP was widely used as a pesticide, ranged from 6 μg/day in 1966 to 1–2 μg/day over subsequent years (IPCS, 1987). Environmental partitioning models are likely to overestimate plant uptake of PCP as they do not take into account metabolism of PCP by plants (IPCS, 1987) and disassociation of PCP in the soil environment. Therefore, it is considered that food is unlikely to be a significant route of exposure to PCP although no data on the food intake of PCP in New Zealand is available. PCP was not detected in any drinking water zones in 2001 (Davies et al, 2001). In circumstances where no data is available on background exposure, it was agreed to allocate 5% of TDI to background exposure (see section below).

Table 54: Summary of oral reference health standards for pentachlorophenol as a threshold contaminant, used by different international agencies

Jurisdiction	Tolerable daily intake (µg/kg bw)	Key study[1]	Critical effect[1]	Basis of value[1]	Reference
WHO – drinking water	3	Not stated (presumed to be Schwetz et al, 1978)	Reproduction in rats	NOAEL of 3 mg/kg bw/day and application of 1000-fold uncertainty factor to account for inter- (10) and intra-species (10) variability and 10 for limited evidence of carcinogenicity, reproductive and teratogenic effects	WHO (1984)
The Netherlands – current	30	Not stated	Foetotoxicity in mice	NOAEL of 3 mg/kg bw/day and application of 100-fold uncertainty factor to account for inter- and intra-species variability	Baars et al (2001)
The Netherlands – proposed[2]	3	Not stated	Decreased thyroid hormones – mink	LOAEL of 1 mg/kg bw/day and application of 300-fold uncertainty factor of 3 for a marginal effect and 100 for inter- and intra-species variability	Baars et al (2001)
Canada	3	Schwetz et al (1978)	Subchronic reproductive effects, chronic toxicity	NOAEL of 3 mg/kg bw/day and application of 1000-fold uncertainty factor to account for inter- (10) and intra-species (10) variability and 10 for limited evidence of carcinogenicity, reproductive and teratogenic effects	CCME (1997)
US ATSDR – chronic duration MRL	1	Beard and Rawlings (1998)	Decreased thyroid hormones and thyroid weight – mink	LOAEL of 1 mg/kg bw/day and application of 1000-fold uncertainty factor to account for the use of a LOEL (10) , inter- (10) and intra-species (10) variability	ATSDR (2001)
US EPA	30	Schwetz et al (1978)	Liver and kidney pathology	NOAEL of 3 mg/kg bw/day and application of 100-fold uncertainty factor to account for inter- and intra-species variability	US EPA (1993)

1 As reported in the reference cited in the reference column.

2 This value is yet to be officially adopted.

Table 55: Summary of oral reference health standards for pentachlorophenol as a non-threshold contaminant, used by different international agencies

Jurisdiction	Acceptable risk level[1]	Guideline value (µg/L)[2]	Risk-specific dose (µg/kg bw/day)	Cancer slope factor (per mg/kg bw/day)	Key study[3]	Critical effects[3]	Basis of value[2]	Reference
New Zealand	10^{-5}	–	0.083	0.12	Not stated	Cancer	US EPA (1993)	MfE and MoH (1997)
New Zealand drinking water	10^{-5}	9	0.26	0.039	Not stated	Cancer	WHO (2003)	MoH (2005)
WHO – drinking water	10^{-5}	9	0.26	0.039	NTP, 1989	Cancer	Based on multistage modelling of tumour incidence in the US NTP bioassay, without incorporation of a body surface area correction, although recognising that there are interspecies differences in metabolism, the concentration of PCP associated with a 10^{-5} excess lifetime cancer risk is similar to the current guideline value	WHO (2003)
California EPA	10^{-6} [10^{-5}]	–	0.625 [6.25]	0.016	NTP, 1989	Haemangiosarcomas in female mice	Upper-bound (95% upper confidence limit) estimate of cancer potency determined using linearised multistage model and cross-species scaling for partially purified PCP	Goodman et al (1998)
US EPA – IRIS, R6, R9	10^{-6} [10^{-5}]	–	0.0083 [0.083]	0.12	NTP, 1989	Liver tumours, pheochromocytomas and haemangiosarcomas in female mice	Geometric mean of slope factors (upper bound-estimates) calculated for two PCP formulations using combined data on three types of tumours, multistage model and cross-species scaling	US EPA (1993)

1 Where the acceptable risk level for a given jurisdiction is not 10^{-5}, the risk-specific dose for a risk of 10^{-5} is shown in square brackets.

2 Where a guideline value is provided, the risk-specific dose has been derived assuming consumption of 2 L per day by a 70-kg adult.

3 As reported in the reference cited in the reference column.

2.11.4 Summary of effects

Pentachlorophenol exposure may result in liver and kidney effects, interfere with thyroid homeostasis, and is also suggested to cause cancer. While there is some debate over what effects are associated with PCP and what effects are associated with contaminants present in technical-grade PCP (primarily polychlorinated-*p*-dioxins and furans), Table 56 provides a summary of effects believed to be attributable to PCP only. This data has been primarily sourced from ATSDR (2001).

Table 56: Summary of the health effects of pentachlorophenol

Dose (mg/kg/day	Type of poisoning	Effects
80	Acute	Lowest reported LD_{50} in animals (rats)
18	Chronic	Lowest reported LOAEL for tumours in animals (haemangiosarcomas (vascular tumours) in liver and spleen; no NOAEL reported
3	Chronic	Highest reported NOAEL for hepatic and renal effects in animals (mouse)
1	Chronic	Highest reported NOAEL for reproductive effects in animals (mink) and lowest reported less serious LOAEL for endocrine effects (decreased thyroid hormones and weight) in animals (mink)

2.11.5 Weight of evidence

- PCP binds extensively to plasma proteins, which may be the primary mechanism eliciting its toxicological effects. PCP is indicated to uncouple mitochondrial oxidative phosphorylation, which may occur through conformational changes associated with the binding of PCP to mitochondrial proteins, and may induce changes in thyroid hormones through competitive binding with serum protein thyroxine-binding sites.
- PCP is considered a possible human carcinogen (Class 2B) by the IARC (1999) and a probable human carcinogen (B2) by the US EPA based on insufficient data in humans but adequate data in animals (US EPA, 1993). Recent review of epidemiological studies indicate that specific cancer risks are associated with PCP exposure, and are unlikely to be associated with dioxins or other chlorophenol contaminants (Cooper and Jones, 2008), adding greater weight to carcinogenic effects of PCP in humans.
- The data on the genotoxicity of PCP is equivocal, with the strongest indication of genotoxicity (chromosomal effects) occurring in assays with rat microsomal protein (S9). The primary rodent metabolite, tetrahydrochloroquinone (TeHQ), is unambiguously genotoxic. TeHQ does not appear to be a major metabolite of PCP in humans. Furthermore, the majority of PCP appears to be excreted unchanged (ATSDR, 2001; WHO, 2003).
- The mechanism of cancer formation in rodents and humans is unclear. Given the equivocal data on the genotoxicity of PCP, it seems more likely for non-genotoxic mechanism(s) to be responsible for carcinogenic effects in humans. Thus PCP should be considered a threshold contaminant.

2.11.6 Recommendations for toxicological intake values

As outlined above, there appears to be reasonable evidence of carcinogenic effects in humans arising from exposure to PCP; nevertheless, there is weak evidence of genotoxicity and it seems more plausible for non-genotoxic mechanism(s) to be responsible for carcinogenic effects. As such, it is recommended that PCP be considered a threshold contaminant, and a tolerable daily intake of 0.3 μg/kg bw is recommended. This TDI is based on the application of an additional uncertainty factor of 10, to account for the observed carcinogenicity of PCP, to the TDI derived by Baars et al (2001). This TDI (Baars et al, 2001) is recommended, as it utilises the most sensitive relevant toxicological endpoint from available data (decreased thyroid hormone production); it also uses the more appropriate uncertainty factor (3) in the extrapolation from a LOAEL to NOAEL compared to factor 10 in ATSDR (2001) given that toxicological effect is suggested to be minimal. This TDI is the same as the RSD calculated from the WHO drinking water guideline for a 1 in 100,000 excess risk.

Inhalation exposure is likely to be negligible on contaminated sites due to the low volatility of PCP. However, PCP is indicated to be readily absorbed dermally and an absorption factor of 0.24 based on Wester et al (1993) is recommended.

No data is available on food intake of PCP, and no PCP was detected in drinking water supplies. In circumstances where no data is available on background exposure, it has been agreed to allocate 5% of TDI to background exposure (see section 1.1.3); as such, background exposure is 0.02 μg/kg bw/day.

A summary of the recommended criteria is provided in Table 57.

Table 57: Recommended toxicological criteria for pentachlorophenol

Parameter	Value	Basis
Contaminant status	Threshold	See weight of evidence
Oral intake dose (μg/kg bw/day)	0.3	Application of an additional uncertainty factor of 10 to the TDI derived by Baars et al (2001)
Inhalation intake	NA	Low volatility of PCP indicates that inhalation exposures will be negligible
Skin absorption factor	0.24	Wester et al (1993)
Background exposure (μg/kg bw/day)	0.02	Children and adults, determined from 5% of the TDI

NA – not applicable

These criteria (Table 57) are applicable to exposure to PCP only, and are not necessarily protective of effects associated with the contaminants of technical-grade PCP, such as the polychlorinated dibenzo-*p*-dioxins and polychlorinated dibenzofurans,[9] which should be considered separately.

[9] Tetrachlorophenol (TCP) is also a significant contaminant of technical-grade PCP. However, there is no need to consider TCP either separately or combined with PCP as it has a relatively low toxicity and, within PCP-contaminated soils, is generally present at relatively low concentrations. Research of New Zealand sawmill soils (Tonkin and Taylor and Sphere, 2008) found that the TCP concentration is typically around 8% of the PCP concentration (range 0.8 to 50%). The USEPA RfD for TCP is 30 μg/kg bw/day (US EPA, 1992), only 1% of the proposed RHS for PCP.

2.12 Dioxins and dioxin-like polychlorinated biphenyls (PCBs)

The term "dioxins" encompasses a group of 75 polychlorinated dibenzo-*p*-dioxin (PCDD) and 135 polychlorinated dibenzofuran (PCDF) congeners. Although dioxins are not produced by intention except for research and analytical purposes, these contaminants have a ubiquitous distribution due to their formation as unwanted and often unavoidable by-products in a number of anthropogenic activities. PCDDs and PCDFs are formed during incomplete combustion processes, industrial as well as natural. They occur also as contaminants during various industrial processes, eg, the chemical manufacture of some chlorinated compounds and chlorine bleaching of paper pulp.

The toxicity of individual dioxin congeners differs considerably. The congeners that are of toxicological importance are substituted in each of the 2-, 3-, 7- and 8-positions. Thus, from 210 theoretically possible congeners, only 17 are of toxicological concern. These compounds have a similar toxicological profile to that of the most toxic congener, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD). Other compounds, such as selected polychlorinated biphenyls (PCBs) and polycyclic aromatic hydrocarbons, also exhibit "dioxin-like" toxicity. The current review considers the 17 dioxin congeners of toxicological concern and 12 dioxin-like PCBs; PAHs were considered earlier in this report.

Several comprehensive reviews of the toxicity of dioxins and dioxin-like PCBs have been undertaken (ATSDR, 1998; EC-SCF, 2000; Van Leeuwen and Younes, 2000; FSA, 2001; FAO/WHO, 2002; US EPA, 2003). The discussion below summarises relevant data from these reviews. Particular attention is given to those studies that have been used in deriving reference health standards. Readers are referred to the original reviews for more details on adverse health effects.

2.12.1 Toxicological status

The most widely studied of all the dioxin-like compounds is 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD, or TCDD). It has been shown to affect a wide range of organ systems in many animal species and can induce a wide range of adverse biological responses. The binding of TCDD to the so-called aryl hydrocarbon (Ah) receptor in cells appears to be the first step in a series of events that manifest themselves in biological responses, including changes at the biochemical, cellular and tissue levels. While there is only limited data on the toxic effects of other dioxins and dioxin-like PCBs, it may be inferred 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.

The acute toxicity of TCDD and related compounds can vary widely between and among species. For example in guinea-pigs, an LD_{50} of 0.6 µg/kg bw was recorded after oral administration, as compared with an LD_{50} of > 5000 µg/kg bw in Syrian hamsters. Explanations for this variation include differences in the Ah receptor, such as size, transformation and binding to the dioxin response element, pharmacokinetics (metabolic capacity, tissue distribution), and body fat content (FAO/WHO, 2002).

There is evidence of toxicity in humans as a result of acute high-dose and repeated or long-term exposure to dioxins. The most widely recognised and consistently observed effect following high-dose exposure to TCDD is chloracne. The condition can disappear after termination of exposure or can persist for many years. Other effects on the skin include hyperpigmentation and hirsutism, while other effects of PCDD/Fs and dioxin-like PCBs include elevated levels of liver

enzymes and other disturbances in liver function, increased death rate from non-malignant liver disease, changes in thyroid function, impaired immunological function, effects on the cardiovascular system, influences on reproductive hormones and reproductive outcomes, and in some children, neuro-developmental delays (EC-SCF, 2000; van Leeuwen and Younes, 2000; FAO/WHO, 2002). Of the range of non-cancer health effects evaluated in exposed adult populations, some appear to be transient and were not observed when exposure ceased, whereas other effects persist for some years.

There is agreement amongst expert groups in recent years that the toxicological findings in laboratory animals of most relevance to humans are effects on the immune system, and on reproduction and development (FAO/WHO, 2002). At doses lower than those at which such effects have been observed (body burdens of 3–10 ng/kg bw), TCDD has been found to elicit biochemical or functional actions (eg, inducing liver enzymes), although these are classified as early expression of events that may or may not result in adverse effects (van Leeuwen and Younes, 2000).

Immunotoxic effects of TCDD have been observed in several species at multiple targets in the immune system. The main target of immunotoxicity of TCDD is the thymus, where cellular depletion is observed, with consequent reduced production of T lymphocytes and depression of cell-mediated immunity. Effects of PCDDs and PCDFs on the thyroid appear to be mediated through hormone metabolism, while dioxin-like PCBs may have a direct effect on the thyroid (FAO/WHO, 2002). Cell-mediated and humoral immune responses are also suppressed following TCDD, suggesting the thymus is not the only target within the immune system (EC-SCF, 2000). The severity of TCDD-induced immunotoxic effects varies among species and depends largely on the endpoint investigated (EC-SCF, 2000).

TCDD induces a distinct series of developmental effects, including foetal mortality, structural malformations and postnatal functional alterations, in a variety of species at doses below those associated with maternal toxicity. TCDD can induce significant embryo lethality (early or late resorptions, abortions, stillbirths), which is usually associated with indications of maternal toxicity. The timing of dosing and the age of the embryo or foetus have been shown to be major determinants of TCDD-induced prenatal mortality. Developmental effects that occur at doses not associated with maternal toxicity include induction of cleft palate and hydronephrosis, with the developing urogenital system of rodents, especially in males, being particularly sensitive to perturbation by TCDD and dioxin-like compounds. Effects include reductions in prostate growth and development (rats and mice), decreased testicular and epididymal sperm numbers (rats, mice, hamsters), and decreased numbers of ejaculated sperm (rats and hamsters) (FAO/WHO, 2002).

Endometrial effects in rhesus monkeys arising from exposure to dioxins had been reported (EC-SCF, 2000 citing Rier et al, 1993), but follow-up studies, which included analysis of serum concentrations of dioxins and other chlorinated compounds, have given rise to uncertainties about the relationship between exposure to TCDD and endometriosis (EC-SCF, 2001).

Experimental studies demonstrate that TCDD is carcinogenic in all species and strains of laboratory animals tested, with cancers occurring at many sites. It has been characterised as a multi-site carcinogen. Several short-term assays for genotoxicity with TCDD covering various endpoints gave primarily negative results. Furthermore, TCDD did not bind covalently to mouse liver DNA. This data indicates that TCDD is not an initiator of carcinogenesis. Several studies have shown that TCDD is a potent tumour promoter. Several modes of action have been hypothesised, including increased expression of genes involved in cell growth and differentiation through binding of TCDD to the Ah receptor, induction of specific cytochrome

P-450 (CYP1A1 and CYP1A2) resulting in oxidative stress, and inhibition of apoptosis (EC-SCF, 2000).

In epidemiological studies, the strongest evidence for carcinogenicity of TCDD is associated with an increased risk for all cancers, rather than any specific site (IARC, 1997). Specific cancers associated with dioxin exposure are lung cancer, non-Hodgkin's lymphoma and soft-tissue sarcoma (IARC, 1997). In a 2006 US National Academy of Sciences review of the health effects of Agent Orange, the committee found sufficient evidence of an association with herbicides (2,4-D, 2,4,5-T, picloram and cacodyllic acid) and/or TCDD for four cancers: soft tissue sarcoma, non-Hodgkin's lymphoma, Hodgkin's disease and chronic lymphocytic leukaemia; and limited evidence of an association with laryngeal cancer; cancer of the lung, bronchus, or trachea; prostatic cancer; and multiple myeloma (IOM, 2007). In contrast, other authors have attributed the occurrence of non-Hodgkin's lymphoma, soft-tissue sarcoma and multiple myeloma to exposure to pentachlorophenol and not dioxin contamination (Cooper and Jones, 2008). Further, some authors argue that the evidence for human carcinogenicity is debatable and that TCDD will eventually be recognised as not carcinogenic to humans (Coles et al, 2003).

The biochemical and toxicological effects of PCDDs, PCDFs and coplanar PCBs are directly related to their concentrations in tissues, and not to the daily dose. The body burden, which is strongly correlated with the concentrations in tissue and serum, integrates the differences in half-lives between species. The half-life of TCDD varies considerably between species, with half-lives in mice, rats, and monkeys reported to be 12, 20, and 400 days, respectively; and a representative half-life in humans being 7.5–7.6 years, although a range of 3–16 years has been reported. Thus, rodents require appreciably higher daily doses (100–200-fold) to achieve a body burden at steady state that is equivalent to that recorded in humans exposed to background concentrations. Toxicokinetically, estimates of body burden are considered more appropriate measures of dose for interspecies comparisons than the daily dose.

Equivalence factors

Dioxins and dioxin-like compounds have a common mode of action, notably mediation of toxic effect through binding to the Ah receptor. This enables estimation of the cumulative risk of exposure to dioxins through expression of the toxicity of individual congeners relative to that of 2,3,7,8-TCDD, the most toxic congener. The relative toxicity is expressed as toxic equivalence factors (TEFs), estimated from the weaker toxicity of the respective congener in relation to the most toxic congener 2,3,7,8-TCDD, which is assigned the arbitrary TEF of 1. By multiplying the analytically determined amounts of each congener by the corresponding TEF and summing the contribution from each congener, the total toxic equivalent (TEQ) value of a sample can be obtained using the following equation:

$$TEQ = (PCDD_i \times TEF_i) + (PCDF_i \times TEF_i) + (PCB_i \times TEF_i).$$

Several different TEF schemes have been proposed: the International TEFs (I-TEFs) (NATO/CCMS, 1988 cited in EC-SCF 2000), which provided TEFs for PCDDs and PCDFs, and Ahlborg et al (1994 cited in EC-SCF 2000) for dioxin-like PCBs; the 1998 WHO-TEFs, which were the consensus from an international meeting in 1997 for human, fish and wildlife risk assessment (van den Berg et al, 1998); and most recently evaluated, the 2005 WHO-TEFs, which considered additional data available since the previous evaluation (van den Berg et al, 2006). The primary difference in the 1998 and 2005 WHO evaluations was the use of half order-of-magnitude increments on a logarithmic scale to estimate TEFs. The use of different TEFs (Table 58) will give rise to different TEQ (toxic equivalent) values from the same analytical raw data. These differences have to be taken into account when results calculated

with different TEF models are compared. In food and human samples, dioxin TEQ values based on WHO-TEFs (van den Berg et al, 1998) are approximately 10–20% higher than those obtained by using the I-TEFs (EC-SCF, 2000), and the change in dioxin TEQ values based on 2005 WHO-TEFs (WHO, 2005) being approximately 10–20% lower than those obtained by using the 1998 WHO-TEFs (van den Berg et al, 2006), ie, similar to the TEQs calculated using I-TEFs. Based on dioxin contamination at 13 sawmill sites in New Zealand, TEQ values based on I-TEFs were on average 20% higher (range: 5–60% higher) than those obtained by using TEQ values based on 2005 WHO-TEFs, (pers. comm., A. Bingham, JCL Air and Environment).

Table 58: Comparison of TEFs for dioxins established at various times[1]

Compound	Abbreviation	I-TEF (1988/1994)[2]	WHO (1998)	WHO (2005)
Polychlorinated dibenzodioxins				
2,3,7,8-Tetrachlorodibenzodioxin	TCDD	1	1	1
1,2,3,7,8-Pentachlorodibenzodioxin	1,2,3,7,8-PeCDD	**0.5**	**1**	1
1,2,3,4,7,8-Hexachlorodibenzodioxin	1,2,3,4,7,8-HxCDD	0.1	0.1	0.1
1,2,3,6,7,8-Hexachlorodibenzodioxin	1,2,3,6,7,8-HxCDD	0.1	0.1	0.1
1,2,3,6,7,9-Hexachlorodibenzodioxin	1,2,3,6,7,9-HxCDD	0.1	0.1	0.1
1,2,3,4,6,7,8-Heptachlorodibenzodioxin	1,2,3,4,6,7,8-HpCDD	0.01	0.01	0.01
Octachlorodibenzodioxin	OCDD	**0.001**	**0.0001**	**0.0003**
Polychlorinated dibenzofurans				
2,3,7,8-Tetrachlorodibenzofuran	2,3,7,8-TCDF	0.1	0.1	0.1
1,2,3,7,8-Pentachlorodibenzofuran	1,2,3,7,8-PeCDF	0.05	**0.05**	**0.03**
2,3,4,7,8-Pentachlorodibenzofuran	2,3,4,7,8-PeCDF	0.5	**0.5**	**0.3**
1,2,3,4,7,8-Hexachlorodibenzofuran	1,2,3,4,7,8-HxCDF	0.1	0.1	0.1
1,2,3,6,7,8-Hexachlorodibenzofuran	1,2,3,6,7,8-HxCDF	0.1	0.1	0.1
1,2,3,7,8,9-Hexachlorodibenzofuran	1,2,3,7,8,9-HxCDF	0.1	0.1	0.1
2,3,4,6,7,8-Hexachlorodibenzofuran	2,3,4,6,7,8-HxCDF	0.1	0.1	0.1
1,2,3,4,6,7,8-Heptachlorodibenzofuran	1,2,3,4,6,7,8-HpCDF	0.01	0.01	0.01
1,2,3,4,7,8,9-Heptachlorodibenzofuran	1,2,3,4,7,8,9-HpCDF	0.01	0.01	0.01
Octochlorodibenzofuran	OCDF	0.0001	**0.0001**	**0.0003**
“Non-ortho” polychlorinated biphenyls				
3´,4,4´-Tetrachlorobiphenyl (PCB 77)	3,3´,4,4´-TCB	**0.0005**	**0.0001**	0.0001
3,4,4´,5,-Tetrachlorobiphenyl (PCB 81)	3,4,4´,5-TCB	–	**0.0001**	**0.0003**
3,3´,4,4´,5-Pentachlorobiphenyl (PCB 126)	3,3´,4,4´,5-PeCB	0.1	0.1	0.1
3,3´,4,4´,5,5´-Hexachlorobiphenyl (PCB 169)	3,3´,4,4´,5,5´-HxCB	0.01	**0.01**	**0.03**
“Mono-ortho” polychlorinated biphenyls				
2,3,3´,4,4´-Pentachlorobiphenyl (PCB 105)	2,3,3´,4,4´-PeCB	0.0001	**0.0001**	**0.0003**
2,3,4,4´,5-Pentachlorobiphenyl (PCB 114)	2,3,4,4´,5-PeCB	0.0005	**0.0005**	**0.0003**
2,3´,4,4´,5-Pentachlorobiphenyl (PCB 118)	2,3´,4,4´,5-PeCB	0.0001	**0.0001**	**0.0003**
2,3´,4,4´,5'-Pentachlorobiphenyl (PCB 123)	2,3´,4,4´,5´-PeCB	0.0001	**0.0001**	**0.0003**
2,3,3´,4,4´,5-Hexachlorobiphenyl (PCB 156)	2,3,3´,4,4´,5-HxCB	0.0005	**0.0005**	**0.0003**
2,3,3´,4,4´,5´-Hexachlorobiphenyl (PCB 157)	2,3,3´,4,4´,5´-HxCB	0.0005	**0.0005**	**0.0003**
2,3´,4,4´,5,5´-Hexachlorobiphenyl (PCB 167)	2,3´,4,4´,5,5´-HxCB	0.00001	**0.00001**	**0.0003**
2,3,3´,4,4´,5,5´-Heptachlorobiphenyl (PCB 189)	2,3,3´,4,4´,5,5´-HpCB	0.00001	**0.00001**	**0.0003**

1 Bolding indicates which values have changed from the previous reassessment.

2 TEFs from NATO/CCMS (1988 cited in EC-SCF, 2000) for PCDDs, PCDFs, and Ahlborg et al (1994 cited in EC-SCF, 2000) for PCBs.

2.12.2 New Zealand classification

ERMA NZ has not classified dioxins or furans, as these substances are not deliberately manufactured, and have no known technical use (other than in laboratory standards). They may be present as contaminants in other substances. When this is the case, the concentration of these contaminants and the contribution they make to the hazard of the substance would be taken into account in the approval of the main component in which they are a contaminant.

2.12.3 Reference health standards

Ingestion

Tolerable intakes of dioxins and dioxin-like PCBs have been extensively evaluated over the last 10 years (WHO, 1998; EC-SCF, 2000; 2001; FSA, 2001; FAO/WHO, 2002; US EPA, 2003). With the exception of the US EPA, all agencies have derived tolerable intakes (variably expressed as daily, weekly or monthly intakes) (Table 59) while the US EPA treated cancer as a non-threshold effect and has used benchmark dose modelling to determine cancer potency (US EPA, 2003) (Table 60).

The New Zealand Timber Treatment Guidelines (MfE and MoH, 1997) use a maximum allowable intake of 10 pg/kg bw/day (TEQ) based on the Pentachlorophenol Risk Assessment Pilot Study (NTG, 1992 cited in MfE and MoH 1997) for deriving interim soil guideline values for dioxins. This value was based on the conventional approach of applying uncertainty factors to a relevant NOAEL, which is the approach used by CCME (2000) in their latest evaluation of the toxicity of dioxins, to derive a TDI of 10 pg/kg bw based on reproductive effects in rats. Both of these sources use daily intake as the dose metric, as does the ATSDR (1998) in its derivation of a chronic-duration MRL of 1 pg/kg bw/day (TEQ), based on behavioural study in monkeys. It is notable that EC-SCF (2000) considered that the results of the study used by ATSDR were of doubtful significance for humans.

In contrast, most other agencies have adopted the approach that seems to arise out of the 1997 WHO consultation on dioxins, in which body burden was considered to be the most relevant dose metric (van Leeuwen and Younes, 2000). The rationale for changing to body burden was that, from a pharmaco-kinetic point of view, this was more appropriate for interspecies comparisons given the long half-lives of dioxins in humans and the difference in half-lives between humans and animals (EC-SCF, 2000; van Leeuwen and Younes, 2000). In the 1997 WHO evaluation, an additional uncertainty factor of 10 was applied to the body burdens of animals giving rise to the most sensitive adverse effects, to account for potential differences in susceptibility within the human population, the comparative susceptibility of humans and animals, and the variation in the half-lives of individual components of the dioxin-mix (van Leeuwen and Younes, 2000).

Furthermore, in the evaluation by WHO in 1997 (van Leeuwen and Younes, 2000) and subsequently by EC-SCF (2000), it was considered that there was no scientific basis for selecting any one particular study or effect; thus a range of tolerable intakes were derived. WHO established a TDI range of 1–4 pg TEQ/kg bw, while EC-SCF (2000) considered it more appropriate to express the tolerable intakes on a weekly basis, given the long half-lives in humans, and selected the lower end of the range and established a temporary tolerable weekly intake of 7 pg/kg bw.

In contrast to the 1997 WHO evaluation, EC-SCF (2000) used pharmaco-kinetic principles to convert animal body burdens into equivalent human daily intakes that on a chronic basis would lead to similar body burdens in humans, given by:

$$\text{Body burden at steady state (ng/kg bodyweight)} = \frac{f \times \text{intake (ng/kg bw/day)} \times \text{half-life (days)}}{\ln(2)}$$

where f is the fraction of the dose absorbed, assumed to be 50% from food for humans, and the half-life of TCDD is 2750 (7.5 years: EC-SCF, 2000). This approach was also used by JECFA in their evaluation in 2001, although they used a half-life for TCDD of 2776 (7.6 years, FAO/WHO, 2002). Similarly, the US EPA used this approach in their draft reassessment although they used a half-life of 2593 (7.1 years, US EPA, 2003).

In 2000 data was published that allowed the calculation of the total amount of dioxin in the foetus associated with maternal exposure at steady state (Hurst et al, 2000b cited in EC-SCF, 2001). Based on this information, EC-SCF revised its earlier tolerable intake and established a tolerable weekly intake of 14 pg/kg bw, based on the midpoint of estimates derived from the lowest LOAEL and NOAEL for developmental effects in male rat offspring. JECFA also used this approach to derive a provisional tolerable monthly intake of 70 pg/kg bw, also based on the midpoint of (different) estimates derived from the same studies (FAO/WHO, 2002).

Based on the evaluations of the WHO's European Centre for Environmental Health and International Programme on Chemical Safety, ECEH-IPCS (WHO, 1998), EC-SCF (2001), JECFA (FAO/WHO, 2002), and considering the IARC classification of dioxins as human carcinogens, the Australian NHMRC (2002) established a tolerable monthly intake of 70 pg/kg bw. DEFRA and EA (2002) similarly considered these evaluations in addition to an evaluation by the UK Committee on Toxicity of Chemicals in Food and the Environment (COT) (FSA, 2001), and recommended a tolerable daily intake of 2 pg/kg bw, based on the COT recommendations. In contrast to these agencies, the New Zealand Ministry of Health established an interim monthly maximum intake of 30 pg/kg, based on the lower end of the TDI recommended by WHO of 1–4 pg/kg bw (MoH, 2002). This value was recommended by the Organochlorines Technical Advisory Group, and was adopted by the Ministry as it also endorsed the precautionary approach recommended by Smith and Lopipero (2001) and further recognised the desirability of ongoing reduction in dioxin intake. It is unclear as to whether the EC-SCF (2001) and JECFA (FAO/WHO, 2002) evaluations were considered in this recommendation. This value was considered interim because further research on dioxins is being undertaken, and it was also noted that the margin between current exposures – even in New Zealand, which is low by international standards – and intakes that cause toxic effects in animals is undesirably small.

In contrast to all other agencies, the US EPA has consistently used cancer potency estimates as the primary basis for assessing the toxicity of dioxins and dioxin-like PCBs, with the difference in approach suggested to reflect differences in science policy (US EPA, 2003). The US EPA further considered that there was little point in setting an RfD because it would likely be below current background levels (US EPA, 2003). However, both the EPA's Scientific Advisory Board and the National Academy of Sciences (NAS), in its review of EPA's reassessment (NAS, 2006), recommended the derivation of an RfD. Furthermore, the NAS considered that the EPA reassessment needed substantial work, particularly the risk characterisation including the dose-response modelling for both cancer and non-cancer endpoints (NAS, 2006). Despite the NAS urging the EPA to finalise the reassessment quickly, to date it has not been finalised although a workshop was held in December 2008 to address the NAS concerns (US EPA, 2009).

Toxic equivalents

In all cases the tolerable intake or the potency estimates are considered to apply to the toxic equivalent concentration of dioxins and dioxin-like PCBs. In most cases, the WHO-TEFs (van den Berg et al, 1998) (see earlier) are generally the recommended TEFs, although this is most likely to be the case because the evaluations were undertaken before the WHO (2005) re-evaluation.

Table 59: Summary of oral reference health standards for dioxins and furans (as TEQ) as a threshold contaminant, used by different international agencies

Jurisdiction	Tolerable daily intake[1] (pg/kg bw)	Tolerable weekly intake[1] (pg/kg bw)	Tolerable monthly intake[1] (pg/kg bw)	Key study[2]	Critical effect[2]	Basis of value[2]	Reference
New Zealand	10	70	300	NTP (1991)	Not stated	NTP (1991)	MfE and MoH (1997)
New Zealand Ministry of Health	1	7	30	Not stated	Not stated	Lower end of recommended TDI derived by FAO/WHO (1998) converted to a monthly intake	MoH (2002)
Joint FAO/WHO Expert Committee on Food Additives (JECFA)	2.3	14	70	Faqi et al (1998); Ohsako et al (2001)	Reproductive developmental effects in male offspring of treated females	Midpoint of four estimates of provisional tolerable monthly intake (PTMI) determined by toxicokinetic modelling using a linear model and a power model to determine the maternal body burden after repeated dosing, which would result in the same body burden in foetuses as after administration of a bolus dose on day 15 of gestation at the LOAEL (Faqi et al, 1998) and NOAEL (Ohsako et al, 2001) reported in the studies, conversion to the equivalent human monthly intake, subtraction of the background body burden, and application of uncertainty factor of 3.2 to account for toxicokinetic differences between humans (both studies) and 3 for extrapolation from a marginal LOAEL to a NOAEL (Faqi et al, 1998 only)	FAO/WHO (2002)
European Food Safety Authority (EFSA)	2	14	70	Faqi et al (1998)	Reproductive developmental effects in male offspring of treated females	LOAEL of 20 pg/kg bw (equivalent human dietary intake calculated using pharmaco-kinetics and the foetal body burden), and application of uncertainty factor of 3.2 to account for toxicokinetic differences between humans and 3 for extrapolation from a marginal LOAEL to a NOAEL	EC-SCF (2001)
Australia	2.3	14	70	Evaluation of several previous evaluations	Hormonal, reproductive and/or developmental effects	WHO-ECEH/IPCS (1998) consultation, the EC-SCF (2001) opinion, and the JECFA evaluation (FAO/WHO, 2002)	
UK	2	14	70	Evaluation of several previous evaluations	Reproductive effects	FSA (2001)	DEFRA and EA (2002)
The Netherlands – current	10	70	300	Not stated	Not stated	Janssen et al (1995)	Baars et al (2001)
The Netherlands – proposed[3]	1	7	30	Not stated	Not stated	Lower end of recommended TDI derived by FAO/WHO (van den Berg et al, 1998)	Baars et al (2001)
Canada	10	70	300	Murray et al (1979)	Reproductive effects in rats	NOAEL of 0.001 µg/kg bw/day and application of 100-fold uncertainty factor to account for inter- (10) and intra-species (10) variation	CCME (2000)

Jurisdiction	Tolerable daily intake[1] (pg/kg bw)	Tolerable weekly intake[1] (pg/kg bw)	Tolerable monthly intake[1] (pg/kg bw)	Key study[2]	Critical effect[2]	Basis of value[2]	Reference
US ATSDR – chronic duration MRL – dioxins	1	7	30	Schantz et al (1992)	Altered behaviour in monkeys	LOAEL of 1.2 x 10^{-4} µg/kg bw/day and application of uncertainty factors of 900 comprised of 3 for the use of a minimal LOAEL, 3 for inter-species variation and 10 for human variability	ATSDR (1998)

1 Bold values indicate the reference health standard adopted by the specific agency; the other values are shown for comparative purposes.

2 As reported in the reference cited in the reference column.

3 This value is yet to be officially adopted.

Table 60: Summary of oral reference health standards for dioxins and dioxin-like compounds as non-threshold contaminants, established by the US EPA

Jurisdiction	Acceptable risk level[1]	Risk-specific dose (pg/kg bw/day)	Cancer slope factor (per pg/kg bw/day)	Key study[2]	Critical effects[2]	Basis of value[2]	Reference
US EPA	10^{-6} [10^{-5}]	0.001 [0.01]	0.001	Becher et al (1998)	All cancers	Linear extrapolation of ED_{01} determined using benchmark dose modelling of data on occupationally exposed humans	US EPA (2003) (draft)

1 Where the acceptable risk level for a given jurisdiction is not 10^{-5}, the risk-specific dose for a risk of 10^{-5} is shown in square brackets.

2 As reported in the reference cited in the reference column.

Inhalation

Inhalation will be a negligible route of exposure as dioxins and dioxin-like PCBs have limited volatility and the amount of dust considered to be inhaled typically represents a very small fraction of exposure (see section 1.1.3), so is not considered further.

Dermal absorption

The skin absorption factor is the only contaminant-specific parameter required for the dermal absorption pathway. Dermal absorption of individual dioxins and dioxin-like PCBs will be dependent on the physico-chemical property of the individual substance. Roy et al (2008) estimated that 1.9% of TCDD in a low-organic soil and 0.24% of TCDD in a high-organic soil would be absorbed by human skin. These estimates were based on *in vivo* (rat) and *in vitro* (rat and human) dermal absorption trials. Jackson et al (1993) examined *in vivo* dermal absorption of TCDD, OCDD and a number of furans in rats. These authors report dermal absorption of TCDD in a solvent carrier over 72 hours was 17%, and for OCDD was 4.3%, while absorption of PeDF and TCDF ranged from 25 to 45%. Assuming absorption is linear over the three days, this gives an average 24-hour absorption of 5.6% for TCDD, 1.6% for OCDD, and 8.3–15% for the furans. Given these estimates are for the compounds in a solvent carrier, they likely over-estimate absorption from soil. Further, rat skin is considered to be more permeable than human skin, and was 3–4 times more permeable when dermal absorption of TCDD was examined (Roy et al, 2008). Assuming this is applicable for all PCDDs and PCDFs, revised absorption values from the Jackson et al (1993) study are 1.9% for TCDD, 0.5% OCDD, and 2.8–5% for PeDF and TCDF.

Dermal uptake of PCBs is suggested to be greater than that of PCDDs and PCDFs, and is variable depending on the chlorine content and position (Garner et al, 2006). Roy et al (2009) estimated that 7.4% of PCB77 (3,3,4,4,-tetrachlorobiphenyl) in a low-organic soil would be absorbed by human skin and that 9.6% of PCB77 would be absorbed by rat skin in a high-organic soil – rat skin was estimated to be fourfold to ninefold more permeable than human skin. These estimates were based on *in vivo* (rat) and *in vitro* (rat and human) dermal absorption trials. Wester et al (1993) found that approximately 14% of two PCB mixtures (Aroclor 1242 and 1254) applied to soil (0.9% organic matter) was percutaneously absorbed by rhesus monkeys over a 24-hour period. However, they also indicate that a reduced amount (1.6% to 2.6%) was absorbed into human skin from soil over the same period, although minimal partitioning into human plasma occurred, ie, the PCBs remained bound to the skin. Mayes et al (2002) found that approximately 4% of Aroclor 1260 applied to soil (5–6% organic carbon) was percutaneously absorbed by rhesus monkeys over a 24-hour period.

For the PCDDs, it is recommended that an absorption factor of 0.02 is used – this is based on absorption of TCDD from soil as reported by Roy et al (2008), and provides a conservative estimate of the absorption of higher molecular weight PCDDs. Higher dermal absorption factors are recommended for the furans. In this case, 0.05 is recommended for TCDF based on the adjusted dermal absorption reported in Jackson et al (1993). This is also expected to be a conservative estimate as it is based on dermal absorption from a solvent carrier. For dioxin-like PCBs it is recommended that a dermal absorption factor of 0.07 is used – this is based on the absorption of PCB77 from soil as reported by Roy et al (2009), and provides a conservative estimate of the absorption of higher molecular weight PCBs. In comparison, US EPA (2004) recommends a dermal absorption factor of 0.03 for TCDD and other dioxins, and 0.14 for Aroclors 1242, 1254 and other PCBs.

Other routes of exposure – background exposure

The major route of exposure of humans to dioxins is estimated to be through the diet, primarily meat products (EC-SCF, 2000). There is limited data on the background exposure of New Zealanders to dioxins and dioxin-like PCBs, with Buckland et al (1998) providing the most extensive data. These authors determined the intake of dioxins from simulated diets for an adult male (25–44 years) consuming median energy (10.8 MJ per day) and adolescent males (15–18 years with a high energy intake (21.5 MJ/day) (Table 61). Intakes based on assuming substances not detected were present at half the limit of detection (½ LOD) – which is consistent with the Total Diet Surveys (Vannoort and Thomson, 2005) – are markedly higher than intake based on excluding substances not detected (excluding LOD). However, for consistency with other contaminants the ½ LOD results are used. It should also be noted that the simulated diets used in Buckland et al (1998) are slightly different to those used in the Total Diet Surveys (Vannoort and Thomson, 2005), which have been used to estimate dietary intakes of other contaminants considered in this review. The intakes of dioxins and dioxin-like PCBs were estimated using the I-TEFs, which appear to give dioxin TEQ values approximately 20% higher than those determined using the WHO (2005) TEFs (see earlier) although Smith and Lopipero (2001) recalculated the dietary data using the WHO (van den Berg et al, 1998) TEFs, and obtained a mean dietary intake for an adult male of 0.37 pg/kg bw/day (½ LOD), which is slightly higher than that calculated using the I-TEFs (Table 61). Ideally the intake values would be recalculated using WHO (2005) TEFs.

Smith and Lopipero (2001) also calculated an estimated average lifetime daily exposure (ALDE) of 1.4 pg/kg bw/day for New Zealanders aged 15 and over, based on serum fat concentrations and assuming a half-life of 7.5 years and that the fraction of the dose adsorbed is 90%. The ALDE estimates are higher than estimated dietary intakes as they includes intakes from dietary and non-dietary pathways, and contributions from historical and current exposures, while the dietary intake estimate represents exposure at a single point in time.

Inhalation of dioxins is expected to be a negligible route of exposure. Data from a report on organochlorine concentrations in air indicates that the mean concentrations of PCDD and PCDFs (expressed as I-TEQs) range from 28.1 to 83.9 fg I-TEQ/m^3 in urban areas in New Zealand (Buckland et al, 1999). Assuming a 15-kg child inhales 6.8 m^3/day and a 70-kg adult 13.3 m^3/day (Proffitt and Cavanagh, 2008) of air at the maximum mean dioxin concentration, this gives rise to intakes of 0.038 and 0.015 pg/kg bw/day for a child and adult, respectively.

For the purposes of this work, a dietary intake based on an adult male is used as the best estimate of background exposure, as there are uncertainties in the calculation of ALDE (assumed half-life of TCDD, % absorption), dietary intake is estimated to be the most significant route of exposure, and finally this is most consistent with the approach adopted for other contaminants.

Table 61: Summary of dietary intakes of dioxins and dioxin-like PCBs for an adult male and adolescent male

	Intake of dioxins (I-TEQ pg/kg bw/day)		Intake of dioxins and dioxin-like PCBs (I-TEQ pg/kg bw/day)	
	Including ½ LOD	Excluding LOD	Including ½ LOD	Excluding LOD
Adult male (80 kg)	0.18	0.047	0.33	0.15
Adolescent male (70 kg)	0.44	0.14	0.76	0.34

2.12.4 Summary of effects

Notwithstanding a common mechanism of action as outlined earlier, it is noted that there are considerable species and strain differences in the acute toxicity of dioxins. Adverse effects reported in animals following exposure to dioxins include immunotoxicity, developmental and behavioural effects in offspring of treated rhesus monkeys, and developmental effects in rats. A summary of effects is provided in Table 62. Many of the original toxicity studies report only the doses used, while the WHO (FAO/WHO, 2002) and EC-SCF (2000; 2001) evaluations estimated the body burden associated with toxic effects reported in the original papers. Body burden is considered to be the most appropriate dose metric to assess the health effects of dioxins. Further, all studies were undertaken using TCDD, the most toxic congener, thus Table 62 provides a summary of the health effects associated with TCDD (unless otherwise stated).

Table 62: Summary of the health effects of TCDD

Dose (ng/kg)[1]	Type of poisoning	Body burden[2] (ng/kg bw)	Effects
10 ng/kg/day	Chronic	294 (EC-SCF, 2000)	LOAEL for liver tumour formation in rats
100	Single dose at gestation day 15	60 (EC-SCF, 2000)	LOAEL for delayed hypersensitivity suppression in male offspring from exposed female rats
0.15 ng/kg/day	Chronic	25–37 (EC-SCF, 2000)	Subtle, non-persistent neurobehavioural effects in offspring of exposed female monkeys
5 ng/kg/week	Maintenance of 25 ng/kg bw	25 (FAO/WHO, 2002) 20 (EC-SCF, 2001)	Lowest LOAEL developmental effects of reproductive system of male offspring (decreased sperm production) from exposed female rats
12.5	Single dose at gestation day 15	13 (FAO/WHO, 2002) 10 (EC-SCF, 2001)	NOAEL developmental effects of reproductive system of male offspring (decreased anogenital distance) from exposed female rats

1 Unless otherwise stated.

2 As shown in either FAO/WHO (2002), EC-SCF (2000), or EC-SCF (2001), calculated as the maternal body burden for developmental effects and at gestational day 15 (rats) or maternal body burden at delivery after 16.2 and 36.3 months of exposure (monkeys); or the body burden of the exposed animal (cancer studies).

2.12.5 Weight of evidence

- 2,3,7,8-TCDD is considered a known human carcinogen (Group 1) by the IARC (1997) and a human carcinogen (Class A) by the US EPA (2003), based on soft-tissue cancers in humans, although there is insufficient data to assess the carcinogenicity of all other congeners. Based on animal studies TCDD is considered a multi-site carcinogen and acts as a tumour promoter.
- TCDD is not genotoxic, and mechanistic data suggests a threshold interpretation of TCDD-induced carcinogenicity (EC-SCF, 2001; FAO/WHO, 2002).
- The toxicity of dioxins is mediated through binding to the Ah receptor (EC-SCF, 2000; FAO/WHO, 2002).
- Developmental effects on the reproductive system in male offspring of exposed pregnant females is considered to be the most sensitive toxicity endpoint and is also considered to be protective against carcinogenic effects of dioxins (EC-SCF, 2001; FSA, 2001; FAO/WHO, 2002).
- Body burden is considered to be the most suitable dose measure (EC-SCF, 2001; FAO/WHO, 2002; US EPA, 2003).

2.12.6 Recommendations for toxicological intake values

There is general agreement between the various expert committees that have reviewed dioxins that tolerable intakes are appropriate for use for dioxins and dioxin-like PCBs. The monthly intake value generally adopted is 70 pg/kg bw (also variously expressed as daily (2 pg/kg bw) or weekly (14 pg/kg bw) intakes). Given the long half-lives of dioxins, and thus the likely lack of effect of small excursions of a daily or even weekly intake, it is recommended that a monthly intake toxic-equivalent dose (TEQ) is used.

The Ministry of Health has confirmed it will retain its policy on a maximum monthly intake value of 30 pg/kg bw and therefore this value is recommended (Table 63). This value is based on the lower end of the range of tolerable intakes determined by WHO in 1998 (van den Berg et al, 2000), adopts a precautionary approach, and recognises the desirability of ongoing reduction of dioxin intake.

Table 63: Recommended toxicological criteria for dioxins

Parameter	Value	Basis
Contaminant status	Threshold	See weight of evidence
Oral intake dose (pg TEQ/kg bw/month)	30	MoH (2002)
Inhalation intake	NA	Low volatility of dioxins and dioxin-like PCBs suggests that inhalation exposure is negligible
Skin absorption factor	0.02 (PCDDs) 0.05 (PCDFs) 0.074	Roy et al (2008) Jackson et al (1993) Roy et al (2009)
Background exposure (pg I-TEQ/kg bw/month)	10.0	Daily dietary intake of an adult male determined in Buckland et al (1998) and extrapolated to a month. This value is considered applicable to children in the absence of any other data

NA – not applicable.

Further it is recommended that WHO (2005) TEFs are used to calculate TEQs (Table 64), as these are based on the latest re-evaluation by WHO, and thus are likely to become the international standard.

Table 64: Recommended TEFs for dioxins and dioxin-like PCBs

Compound	Abbreviation	WHO (2005)
Polychlorinated dibenzodioxins		
2,3,7,8-Tetrachlorodibenzodioxin	TCDD	1
1,2,3,7,8-Pentachlorodibenzodioxin	1,2,3,7,8-PeCDD	1
1,2,3,4,7,8-Hexachlorodibenzodioxin	1,2,3,4,7,8-HxCDD	0.1
1,2,3,6,7,8-Hexachlorodibenzodioxin	1,2,3,6,7,8-HxCDD	0.1
1,2,3,6,7,9-Hexachlorodibenzodioxin	1,2,3,6,7,9-HxCDD	0.1
1,2,3,4,6,7,8-Heptachlorodibenzodioxin	1,2,3,4,6,7,8-HpCDD	0.01
Octachlorodibenzodioxin	OCDD	0.0003
Polychlorinated dibenzofurans		
2,3,7,8-Tetrachlorodibenzofuran	2,3,7,8-TCDF	0.1
1,2,3,7,8-Pentachlorodibenzofuran	1,2,3,7,8-PeCDF	0.03
2,3,4,7,8-Pentachlorodibenzofuran	2,3,4,7,8-PeCDF	0.3
1,2,3,4,7,8-Hexachlorodibenzofuran	1,2,3,4,7,8-HxCDF	0.1
1,2,3,6,7,8-Hexachlorodibenzofuran	1,2,3,6,7,8-HxCDF	0.1
1,2,3,7,8,9-Hexachlorodibenzofuran	1,2,3,7,8,9-HxCDF	0.1
2,3,4,6,7,8-Hexachlorodibenzofuran	2,3,4,6,7,8-HxCDF	0.1
1,2,3,4,6,7,8-Heptachlorodibenzofuran	1,2,3,4,6,7,8-HpCDF	0.01
1,2,3,4,7,8,9-Heptachlorodibenzofuran	1,2,3,4,7,8,9-HpCDF	0.01
Octochlorodibenzofuran	OCDF	0.0003
"Non-ortho" Polychlorinated biphenyls		
3´,4,4´-Tetrachlorobiphenyl (PCB 77)	3,3´,4,4´-TCB	0.0001
3,4,4´,5,-Tetrachlorobiphenyl (PCB 81)	3,4,4´,5-TCB	0.0003
3,3´,4,4´,5-Pentachlorobiphenyl (PCB 126)	3,3´,4,4´,5-PeCB	0.1
3,3´,4,4´,5,5´-Hexachlorobiphenyl (PCB 169)	3,3´,4,4´,5,5´-HxCB	0.03
"Mono-ortho" polychlorinated biphenyls		
2,3,3´,4,4´-Pentachlorobiphenyl (PCB 105)	2,3,3´,4,4´-PeCB	0.0003
2,3,4,4´,5-Pentachlorobiphenyl (PCB 114)	2,3,4,4´,5-PeCB	0.0003
2,3´,4,4´,5-Pentachlorobiphenyl (PCB 118)	2,3´,4,4´,5-PeCB	0.0003
2,3´,4,4´,5'-Pentachlorobiphenyl (PCB 123)	2,3´,4,4´,5´-PeCB	0.0003
2,3,3´,4,4´,5-Hexachlorobiphenyl (PCB 156)	2,3,3´,4,4´,5-HxCB	0.0003
2,3,3´,4,4´,5´-Hexachlorobiphenyl (PCB 157)	2,3,3´,4,4´,5´-HxCB	0.0003
2,3´,4,4´,5,5´-Hexachlorobiphenyl (PCB 167)	2,3´,4,4´,5,5´-HxCB	0.0003
2,3,3´,4,4´,5,5´-Heptachlorobiphenyl (PCB 189)	2,3,3´,4,4´,5,5´-HpCB	0.0003

Inhalation exposure to dioxins and dioxin-like PCBs is likely to be negligible on contaminated sites due to their low volatility. Dermal absorption of these compounds is dependent on the physico-chemical properties of the individual congeners. It is recommended that a dermal factor of 0.02 is used as a conservative estimate of dermal absorption of PCDDs, based on dermal absorption of TCDD from soil (Roy et al, 2008). A higher absorption factor of 0.05 is recommended for PCDFs, based on adjustment of dermal absorption estimates from Jackson et al, 1993). For dioxin-like PCBs it is recommended that a dermal absorption factor of 0.07 is used as a is used as a conservative estimate of dermal absorption of PCBs, based on dermal absorption of a tetrachloropbiphenyl from soil Roy et al (2009).

Dietary intake is the primary source of background exposure to dioxins and dioxin-like PCBs and was estimated to be 0.33 pg I-TEQ/kg bw/day or 10.0 pg I-TEQ/kg bw/month for an adult, and is extended to children. Ideally, these intakes should be expressed on the basis of 2005 WHO-TEQs, although it is anticipated it will only make a marginal difference in the estimated intakes.

Appendix

Table A1: CAS numbers and additional details on chemical names for the contaminants considered in this report

Common name	CAS no.	Chemical name (if different from common)
Arsenic	71-43-2	
Benzo(a)pyrene (BaP)	50-32-8	
Boron	7440-42-8	
Cadmium	7440-43-9	
Chromium (III)	16065-83-1	
Chromium (VI)	1840-29-9	
Copper	7440-50-8	
DDT and derivatives	50-29-3	para,para'-dichlorodiphenyltrichloroethane
DDE	72-55-9	p,p'-dichlorodiphenyldichloroethylene
DDD (TDE)	72-54-8	p,p'-dichlorodiphenyl dichloroethane
Dieldrin	60-57-1	
Lead	7439-92-1	
Mercury	7439-97-6	
Pentachlorophenol	87-86-5	PCP
Dioxins and dioxin-like PCBs	–	Polychlorinated-*p*-dioxins, Polychlorinated-*p*-furans and dioxin-like Polychlorinated-biphenyls

Acronyms and Glossary

ADI	Acceptable daily intake – estimated daily amount that can be taken into the body without any detrimental health effects occurring, based on available scientific information – may also be referred to as a reference dose (RfD). Applies to food additives and veterinary drug residues.
Acceptable risk level	Regulatory-defined acceptable level of increased risk associated with exposure to contaminants.
Ah	Aryl-hydrocarbon (receptor)
ALAD	δ-aminolevulinic acid dehydratase
ALDE	Average lifetime daily exposure
AMU	Assessment Methodology Unit (EFSA)
AROI	Acceptable range of oral intake
As	Arsenic
ATSDR	Agency for Toxic Substances and Disease Registry (US)
Background exposure	Exposure to contaminants from background sources including food, water and air.
B	Boron
BaP	Benzo(a)pyrene
BMC	Benchmark concentration – the lowest dose, as estimated from an appropriate model, at which a given excess tumour incidence occurs; used for inhalation exposure data.
BMCL	Benchmark-concentration lower bound – the lower confidence limit of the estimated benchmark concentration (BMC); used for inhalation exposure data.
$BMCL_{adj}$	Adjusted BMCL
BMDx	Benchmark dose – the lowest dose, as estimated from an appropriate model, at which a given (x) excess tumour incidence occurs; used for oral exposure data.
BMDLx	Benchmark-dose lower bound – the lower confidence limit of the estimated benchmark dose (BMD), provides an upper-bound estimate of the slope factor; used for oral exposure data.
BTEX	Benzene, toluene, ethylbenzene, xylene
Carcinogenic potency	Estimates of the potency of non-threshold contaminants, may be expressed as a slope factor (risk per mg/kg bw/day) or risk specific dose (mg/kg bw/day) or similar.
CalEPA	Californian EPA
CCME	Canadian Council of Ministers of the Environment
Cd	Cadmium
CDC	Centre for Disease Control and Prevention (US)
Clastogenic	Microscopically visible damage or changes to chromosomes (eg, breaks in chromosomes, change in chromosome number).

CNS	Central nervous system
CONTAM	Panel on contaminants in the food chain (EFSA)
COT	Committee on Toxicity of Chemicals in Food and the Environment (UK)
Cr	Chromium
Cu	Copper
CSAF	Chemical-specific adjustment factor
CSTEE	Comité Scientifique de Toxicologie, Ecotoxicologie et l'Environnement (EC)
DEFRA	Department for Environment, Food and Rural Affairs (UK)
DWEL	Drinking Water Equivalent Level
EA	Environment Agency (UK)
EAR	Estimated average requirement
EC	Equivalent carbon number
EC	European Commission
EC-SCF	European Commission Scientific Committee on Food
ECEH	European Centre for Environmental Health (WHO)
EFSA	European Food Safety Authority
EPAQS	Expert Panel on Air Quality Standards (UK)
ERMA NZ	Environmental Risk Management Authority New Zealand
ESADDI	Estimated safe and adequate dietary daily intake
FAO	Food and Agriculture Organization (UN)
FPTCDW	Federal-Provincial-Territorial Committee on Drinking Water (Canada)
FSA	Food Standards Agency (UK)
Genotoxic	Direct or indirect damage to the DNA molecule – may lead to mutations or cancer.
HEAST	Health Effects Assessment Summary Table
Hg	Mercury
HSNO	Hazardous Substances and New Organisms Act 1996 (NZ)
IARC	International Agency for Research on Cancer
IEUBK	Integrated Exposure Uptake Biokinetic
Index dose	Estimated daily amount that can be taken into the body without exceeding an acceptable risk level for a non-threshold contaminant based on available scientific information – also referred to as the risk-specific dose.
IOM	Institute of Medicine of National Academy of Sciences (US)
IPCS	International Programme on Chemical Safety (WHO)

IRIS	Integrated Risk Information System (US EPA database)
I-TEQ	International toxic equivalent value
JECFA	Joint FAO/WHO Expert Committee on Food Additives
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
LD_{50}	Lethal dose at which 50% of the exposed population dies
LOAEL	Lowest observable adverse effects level
LOD	Limit of detection
MADEP	Massachusetts Department of Environmental Protection
MAV	Maximum acceptable value
Maximum likelihood estimates	Central point estimate from the distribution of risk (MLE) calculated using a particular risk model and dataset.
MDS	Myelodysplastic syndrome
MfE	Ministry for the Environment (NZ)
MOE	Margin of exposure
MoH	Ministry of Health (NZ)
MRL	Minimal risk level
Mutagen	A substance that can cause changes in DNA sequencing, which may lead to cancer.
NAS	National Academy of Sciences (US)
NCSRP	National Contaminated Sites Remediation Program (Canada)
Neoplasm	Abnormal growth of tissue – may be benign or cancerous.
NEPC	National Environment Protection Council (Australia)
Neoplastic	Pertaining to neoplasm.
NHMRC	National Health and Medical Research Council (Australia)
NICNAS	National Industrial Chemicals, Notification and Assessment Scheme (Australia)
NOAEL	No observable adverse effect level
Non-threshold contaminant	Contaminant for which toxic effects are considered to occur at any level of exposure.
NRC	National Research Council (US)
NRV	Nutrient reference values
NTP	National Toxicology Program (US)
NZDWG	New Zealand Drinking Water Guidelines
NZ PHG	New Zealand Petroleum Hydrocarbon Guidelines

NZTDS	New Zealand Total Diet Survey
NZ-TTG	New Zealand Timber Treatment Guidelines
NZWWA	New Zealand Water and Wastes Association
OIEWG	Oil Industry Environmental Working Group
PAH	Polycyclic aromatic hydrocarbon
Pb	Lead
PbB	Blood lead content
PCB	Polychlorinated biphenyl
PCDD	Polychlorinated dibenzo-*p*-dioxin
PCDF	Polychlorinated dibenzofuran
PCP	Pentachlorophenol
PEF	Potency equivalence factor
PTMI	Provisional tolerable monthly intake
PTWI	Provisional tolerable weekly intake
RfC	Reference concentration – an estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. It can be derived from a NOAEL, LOAEL, or benchmark concentration, with uncertainty factors generally applied to reflect limitations of the data used. Generally used in EPA's non-cancer health assessments.
RfD	Reference dose – an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. It can be derived from a NOAEL, LOAEL, or benchmark concentration, with uncertainty factors generally applied to reflect limitations of the data used. Generally used in EPA's non-cancer health assessments – analogous to the tolerable daily intake (TDI).
RHS	Reference health standard – any value set by a regulatory or advisory body that provides an estimated daily (sometimes weekly or monthly) amount of a substance that can be taken into the body without either any or an unacceptable additional risk of detrimental health effects occurring (based on available scientific information), eg, tolerable daily intake, reference dose, drinking water standard.
RSD	Risk-specific dose – estimated daily amount that can be taken into the body without exceeding an acceptable risk level for a non-threshold contaminant based on available scientific information – also referred to as an index dose.
SCF	Scientific Committee on Food (European Commission)
$SCSs_{(health)}$	Soil contaminant standard protective of human health having regulatory status under the NES
SEGH	Society for Environmental Geochemistry and Health
Slope factor	Plausible upper-bound estimate of the probability of an individual developing cancer as a result of a lifetime of exposure to a particular level of a potential carcinogen.

TDI	Total daily intake
TDS	New Zealand Total Diet Survey
TEF	Toxicity equivalence factor
TeHQ	Tetrochlorohydroquinone
TEQ	Total toxic equivalent value
Threshold contaminant	Contaminant for which toxic effects are considered to occur if exposure exceeds a threshold concentration.
TEX	Toluene, ethylbenzene, xylene
TDI	Tolerable daily intake – estimated daily amount that can be taken into the body without any detrimental health effects occurring based on available scientific information – may also be referred to as a reference dose (RfD).
TIV	Toxicological intake value – estimated daily amount that can be taken into the body without any detrimental health effects occurring based on available scientific information – may also be referred to as a reference dose (RfD), or a tolerable daily intake (TDI). This terminology is specific for values recommended for use in New Zealand.
Toxicological endpoint	The biological response examined in a specific toxicity study.
TPH	Total petroleum hydrocarbons
TPHCWG	Total Petroleum Hydrocarbon Criteria Working Group (US)
TTG	Timber Treatment Guidelines (NZ)
TUL	Tolerable upper limits
UF	Uncertainty factor
UA EPA	United States Environmental Protection Agency
US FDA	United States Food and Drug Administration
US HUD	United States Department of Housing and Urban Development
WHO	World Health Organization

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