

ACC Review

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»» *A distillation of best practice reflecting ACC's current position*

Dioxin – Part 1

- »» The term 'dioxins' is often used to describe a group of structurally similar congeners known as polychlorinated dibenzo-p-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs) and some polychlorinated biphenyls (PCBs)
- »» Dioxins are by-products of some natural events, and industrial processes that involve chlorine. One dioxin, TCDD, was a toxic contaminant of the defoliant Agent Orange and the herbicide 2,4,5-T
- »» Food is the main source of exposure for the general population to background levels in the body
- »» Toxicity is thought to be mediated via the aryl hydrocarbon (Ah) receptor, which is involved in cell growth and differentiation
- »» Dioxins have a long half-life and can accumulate in body fat
- »» Since the late 1980s environmental levels of dioxin have been declining in New Zealand.

Background

Dioxins are highly toxic chemicals that have been associated with a range of adverse health-related effects. They are the by-products of industrial processes that involve chlorine, such as chemical manufacturing, timber treatment, waste incineration, and natural events such as forest fires. The dioxin, 2,3,7,8-tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD), abbreviated as 'TCDD', was the toxic contaminant contained in the herbicide 2,4,5-T that was in the defoliant Agent Orange.

Dioxins can be found in air, soil, sediment and biota. They enter the food chain via deposits on soil and plant surfaces, and subsequent animal consumption, where they accumulate in the fatty tissue.

This review is Part 1 of three and describes dioxins in terms of their action, pharmacokinetics, and exposure. In Parts 2 and 3 the evidence supporting a causal association between human exposure and non-carcinogenic health effects (Part 2), and carcinogenic health effects (Part 3) are summarised.

Chemical properties¹

The term 'dioxins' (plural) is often used to describe a group of structurally similar congeners known as polychlorinated dibenzo-p-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs) and some polychlorinated biphenyls (PCBs). The term dioxin (singular) is usually used to refer to the congener TCDD. These chemicals belong to the class known as organochlorines. In general, these compounds have low water and high fat solubility, low vapour pressure and are resistant to biodegradation under normal environmental conditions.

Relative potency and mode of action

Whilst the precise chain of molecular events associated with human toxicity is not yet fully understood, these compounds share (at least initially) a common mode of action by binding to the aryl hydrocarbon (Ah) receptor. The Ah receptor is a gene regulatory protein that acts as a transcription factor in cell growth and differentiation, and therefore is likely to induce a cascade of biochemical effects. Subtle effects such as expression of specific genes with translation of their protein products and increased activity of cytochrome P450 system may occur, as may effects on the endocrine and immune systems.¹

The potency of dioxin-like compounds with respect to most, if not all, toxic endpoints is determined by the number and position of the chlorine atoms in the molecule.^{1,2} These structural variations affect each compound's ability to bind to the Ah receptor. Humans are thought to be polymorphic with respect to Ah receptor structure and function, and therefore inter-individual susceptibility to dioxin toxicity is likely.^{1,2}

The most toxic and well studied dioxin compound is 2,3,7,8-TCDD. It is assigned a toxicity equivalency factor (TEF) of 1.0 and is the reference against which other less toxic dioxin compounds are assigned relative TEF values 1.^{2,3}

Pharmacokinetics^{1,2}

Dioxins are absorbed through the gastrointestinal tract, skin and lungs. The degree of absorption varies with each congener, the route of absorption and source of exposure.

Animal studies indicate that following oral exposure TCDD is distributed in the blood (mainly via plasma lipids and

lipoproteins), principally to the liver and adipose tissue but also to the skin, muscle and breast milk. Serum TCDD levels are strongly correlated with adipose tissue levels. This relationship holds over a wide concentration range above background levels. TCDD is a poor substrate for the cytochrome P450 enzymes, which oxygenate other lipophilic compounds to inactive derivatives during metabolic processing. Dioxins, therefore, have a long residence time in the body due to a combination of high lipid solubility and widespread distribution coupled with very slow metabolism and rate of elimination.¹ The World Health Organisation estimates the average serum half-life to be around 7.5 years.⁴

Background dioxin levels

Everyone is exposed to small background levels of dioxin-like compounds when they consume food and, to a lesser extent, from the air or contact with dioxin-contaminated materials. About 90% of exposure to the general population is via diet, mainly from foods containing animal fats such as meat, dairy, eggs and fish. Dioxins tend to accumulate in human and animal fatty tissue due to their long half-life and dietary intake.⁵

Dioxin levels in the environment have declined significantly since the late 1980s and evidence in New Zealand (e.g. breast milk studies) suggests that TCDD body burdens are reducing.⁵ In 2000, lipid-adjusted TCDD levels in the USA, Canada, Germany and France were estimated to be approximately 2 pg/g lipid, and are likely to have reduced further.⁶ Dioxin concentrations in New Zealanders tend to be at the lower end of the international range, particularly in younger age groups. This reflects that, on an international scale, environmental concentrations and dietary exposures in New Zealand are lower than those in other industrialised countries where similar studies have been undertaken.⁵

Toxicity assessment

Risk evaluation is complicated by the mix of dioxin compounds usually found in environmental or occupational exposures. The toxic potential of a dioxin depends on the relative concentrations of the various 'dioxins' (e.g. +/-furan) present. Similarly, all dioxins present in the blood contribute to the toxic risk in an individual. In order to estimate toxicity or risk, the relative toxicity of the different dioxins, as reflected by their assigned TEF, need to be taken into account. Thus 'toxic equivalents' (TEQ) are calculated for each dioxin-like compound, by multiplying its concentration by its TEF. The TEQs are added to estimate potential toxicity.³ In individuals, total TEQs will exceed TCDD levels.

References

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