Use of Toxic Equivalency Factors to establish health-based soil criteria for dioxins

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Use of Toxic Equivalency Factors to establish health-based soil criteria for dioxins

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1 INTRODUCTION

Polychlorinated dibenzodioxins (PCDDs) are a group of chlorinated aromatic hydrocarbons best known for the extremely toxic congener 2,3,7,8-tetrachloro dibenzo-*p*-dioxin, commonly termed TCDD. The generic dioxin chemical structure is shown in Figure 1. Much attention has been given to risk assessment of dioxins and to determining acceptable levels in various environmental media (Pohl *et al*., 2002). This attention is due in part to the fact that dioxins are persistent in the environment and bioaccumulate in humans and the food chain. It is also due to the considerable evidence that certain dioxins display carcinogenicity, tumour promotion, immunotoxicity, teratogenicity, endocrine disruption, endometriosis, and acute toxicity such as chloracne (IARC 1997; ATSDR 1998; Birnbaum & Cummings 2002).

The establishment of a health-based soil guideline value for dioxins will require agreement on various issues. One is an estimate of the tolerable intake of dioxins. Another – and the topic to be considered in this paper – is the employment of Toxicity Equivalency Factors (TEFs) to account for dioxin congeners and dioxin-like chemicals which may exist in contaminated soil. This revolves around commonality of molecular mechanism of action.

2 MECHANISMS OF ACTION

Studies on the mechanism of action of dioxins reveal a cell membrane receptor – the *Ah* (aryl hydrocarbon) receptor – that becomes activated through covalent dioxin binding (Poland & Knutson 1982). This activated receptor complex then translocates to the cell nucleus and interacts with specific dioxin-responsive enhancers/elements in the genome. Consequently, specific transcriptional processes are altered which results in the myriad of known toxicological effects.

Elucidating the molecular events of dioxins' mechanism of action has been pivotal in at least three areas – (i) demonstrating that dioxins are nongenotoxic carcinogens, an important consideration in cancer risk assessment of these compounds; (ii) revealing that other persistent chlorinated hydrocarbons operate through the same mechanism; and (iii) establishing a rationale for assigning proportionate toxicity to dioxin congeners and dioxin-like chemicals that may exist as a mixture in contaminated soils. These last two areas will be further explored in this paper.

3 FURANS AND PCBs:- MAJOR DIOXIN-LIKE CHEMICALS

Pyrolysis of organic compounds in the presence of chlorine atoms generates not only dioxins but also polychlorinated dibenzofurans (PCDFs or furans; Fig. 1). Experimental evidence has shown that biologically active furan congeners exert their toxicological effects via the same receptor and genomic response system as the dioxins (IARC 1997).

Furan congeners share several of the toxicological features of dioxins but appear to be less carcinogenic (IARC 1997).

Polychlorinated biphenyls (PCBs) represent a further important class of biopersistent chemicals shown to be active through the *Ah* receptor mechanism (Fig. 1). PCBs have been widely employed in electrical capacitors and transformers, and used as plasticisers, diffusion pump oils and fuel flow improvers. Human, animal and *in vitro* studies have variously demonstrated carcinogenicity, tumour promoter-type effects, endocrine disruption, teratogenicity and possible impairment of psychodevelopment (Walkowiak *et al*., 2001; ATSDR 2000; Swierenga *et al*., 1990).

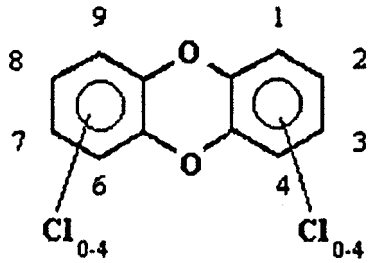
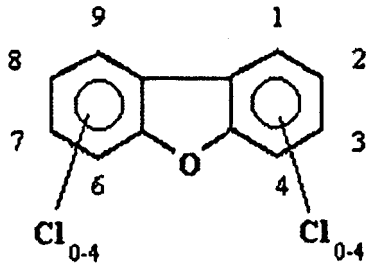
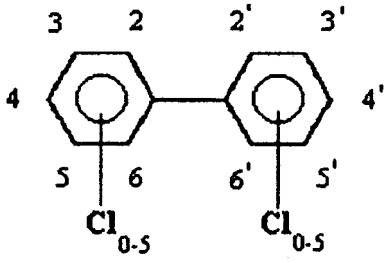
Chemical class	Chemical structure	No. of possible congeners
Polychlorinated dibenzo dioxins		75
Polychlorinated dibenzo furans		135
Polychlorinated biphenyls		209

Figure 1. Structural and congener details of PCDDs, PCDFs and PCBs

4 TOXIC EQUIVALENCY FACTORS (TEFs) FOR DIOXINS, FURANS AND PCBs

Conducting health risk assessment of mixtures in contaminated soils poses major challenges for risk assessors, particularly since the interactions of diverse chemicals at the toxicological level are largely unknown. One approach in dealing with this, and one which has gained broad acceptance, is to assign proportionate toxicity factors to those chemicals known to share a common mechanistic pathway. Thus dioxins, furans and PCBs can be evaluated in this way.

The reference chemical designated for this inter-chemical toxicological comparison is TCDD. This dioxin congener has been extensively studied in a broad range of laboratory experiments and assay systems. For other less-researched dioxin, furan and PCB congeners, dose-response comparisons for at least one of the endpoints studied in common with those of TCDD is often sufficient to estimate relative toxicological activity. Where the endpoint is say receptor binding or cytochrome enzyme induction, then comparative toxicological activity is inferred because of the mechanistic reasoning discussed above. Table 1 lists the endpoints which have been used to derive TEFs for dioxin, furan and PCB congeners.

Table 1. Range of toxicological and biochemical endpoints evaluated for setting TEFs for dioxin, furan and PCB congeners[a,b]

Tumour promotion	Cytochrome P1A1/A2 induction
Immunotoxicity	Toxicokinetics
Organ weights	Hepatic retinol decrease
Ah receptor binding	Thymic atrophy
LD_{50}	QSAR[c]

[a]For details of the endpoints evaluated for each congener, see Van den Berg *et al*. 1998
[b]*In vivo* studies conducted principally in rodents
[c]Quantitative structure-activity relationship

TEF values for these congeners have been recently reviewed by a World Health Organization working group and discussed in detail for application to humans and wildlife exposure circumstances (Van den Berg *et al*., 1998). These values are presented in Table 2.

TEF values are combined with soil test chemical residue data to calculate Toxic Equivalent (TEQ) concentrations according to the equation:-

$$TEQ = \Sigma_{n1}[PCDD_i \times TEF_i] + \Sigma_{n2}[PCDF_i \times TEF_i] + \Sigma_{n3}[PCB_i \times TEF_i]$$

Thus dose additivity – underpinned by mechanistic understanding – is the default assumption in estimating total toxicological potential of these congeners in the absence of any other information on congener interactions in a mixture. A similar approach has been previously presented for dealing with mixtures of polycyclic aromatic hydrocarbons (Fitzgerald 1998).

Table 2. TEFs for dioxin, furan and PCB congeners derived by WHO[a]

Congener	TEF	Congener	TEF
Dioxins		***PCBs***	
2,3,7,8-TetraCDD (TCDD)	1	3,3′,4,4′-TetraCB	0.001
1,2,3,7,8-PentaCDD	1[b]	3,4,4′,5-TetraCB	0.001
1,2,3,4,7,8-HexaCDD	0.1	3,3′,4,4′,5-PentaCB	0.1
1,2,3,6,7,8-HexaCDD	0.1	3,3′,4,4′,5,5′-HexaCB	0.01
1,2,3,7,8,9-HexaCDD	0.1	2,3,3′,4,4′-PentaCB	0.0001
1,2,3,4,6,7,8,-HeptaCDD	0.01	2,3,4,4′,5-PentaCB	0.0005
OctaCDD	0.0001[c]	2,3′,4,4′,5-PentaCB	0.0001
		2′,3,4,4′,5-PentaCB	0.0001
Furans		2,3,3′,4,4′,5-HexaCB	0.0005
		2,3,3′,4,4′,5-HexaCB	0.0005
2,3,7,8-TetraCDF	0.1	2,3′,4,4′,5,5′-HexaCB	0.00001
1,2,3,7,8-PentaCDF	0.05	2,3,3′,4,4′,5,5′-HeptaCB	0.0001
2,3,4,7,8-PentaCDF	0.5		
1,2,3,4,7,8-HexaCDF	0.1		
1,2,3,6,7,8-HexaCDF	0.1		
1,2,3,7,8,9-HexaCDF	0.1		
2,3,4,6,7,8-HexaCDF	0.1		
1,2,3,4,6,7,8-HeptaCDF	0.01		
1,2,3,4,7,8,9-HeptaCDF	0.01		
OctaCDF	0.0001[d]		

[a]Details of rationale given in Van den Berg *et al*., 1998
[b]US-EPA, 0.5 [c]US-EPA, 0.001 [d]US-EPA, 0.001 [b-d]De Rosa *et al*., 1997

Experimental studies with combinations of dioxin and furan congeners have tended to validate the additivity tenet of the TEQ approach (Eadon *et al*., 1986; Van den Berg *et al*., 1998). However, inclusion of PCBs has indicated some nonadditive effects, principally antagonism. Nonetheless it is suggested that use of additivity in the TEF concept is unlikely to result in large errors of TEQ concentration prediction (Van den Berg *et al*.,1998).

5 UNCERTAINTIES WITH THE TEF APPROACH

While the above TEF approach simplifies risk assessment of mixtures of dioxins and dioxin-like compounds, it is important to be aware of the uncertainties associated with this method. For example, for some congeners, there is a lack of parallelism of dose-response across toxicological endpoints and of *Ah* receptor occupancy; this may suggest involvement of other mechanisms of action. In addition, there is inevitable subjectivity in setting one TEF estimate to represent a data base which may contain several studies of the same endpoint and displaying a range of median toxicities (Starr *et al*., 1999).

6 FURTHER STEPS IN DEVELOPMENT OF A SOIL HEALTH-BASED CRITERION

Future development of a health-based criterion for dioxin-TEQs in soil will require agreement on a tolerable intake and on a reasonable proportion of that to be attributed to soil exposure. While beyond the scope of this present discussion, some detail is provided

in Table 3 on acceptable or tolerable dioxin-TEQ intakes proposed by a range of jurisdictions.

Table 3. Some current Acceptable/Tolerable Intakes of dioxin-TEQs

Jurisdiction	Acceptable/Tolerable Intake
WHO 1998	1-4 pg/kg body weight/day
US-ATSDR 1999[a]	1 pg/kg body weight/day
European Commission 2001	14 pg/kg body weight/week
NHMRC Australia 2002	70 pg/kg body weight/month
NHMRC Australia – modified Benchmark dose method	not yet determined

[a]De Rosa *et al*., 1999

Such intake upper limits will need to be seen in the light of actual intake levels. Dietary intakes in Australia are currently not known, but surveys in Europe and New Zealand show average daily dioxin-TEQ intake there of 1.2-3.0 pg/kg body weight and 0.3-0.8 pg/kg body weight, respectively (European Commission 2001; New Zealand 1998). Thus some populations appear to have little or no margin of safety in relation to estimated tolerable intakes.

7 DISCUSSION

Use of Toxic Equivalency Factors for dioxins, furans and PCBs as presented in this paper will assist in risk assessment of soils contaminated with these chemicals. The next major step is to develop a soil guideline level for dioxin-TEQs in Australia. This should progress now with the recent NHMRC proposal of a 70 pg/kg Tolerable Monthly Intake (NHMRC, 2002). In addition, work being undertaken by the NHMRC Expert Working Group on Toxicity Assessment for Carcinogenic Soil Contaminants in applying a modified Benchmark dose method (DiMarco *et al*., 1999) to dioxin cancer and non-cancer dose-response data should further aid the process of soil guideline development.

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