TOXIC EQUIVALENCY FACTORS FOR POLYCHLORINATED DIOXINS, DIBENZOFURANS AND BIPHENYLS PRO'S AND CON'S AND CONSEQUENCES

Ulf G. Ahlborg
Institute of Environmental Medicine, Karolinska Institute, Box 210
S-171 77 Stockholm, Sweden

Polychlorinated dibenzo-*p*-dioxins (PCDDs), dibenzofurans (PCDFs) and biphenyls (PCBs), as well as other related halogenated aromatic compounds, constitute a group of lipophilic, chemically stable environmental contaminants with low volatility which have been identified in fatty tissues of animals and humans. Several PCDDs and PCDFs, as well as a few (dioxin-like) PCBs, have been shown to exert a number of common toxic responses similar to those observed for 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). These include dermal toxicity, immunotoxicity, reproductive deficits, teratogenicity, endocrine toxicity and carcinogenicity/tumour promotion. There is strong evidence suggesting a common mechanism of action of 2,3,7,8-TCDD and related compounds, based on a binding of these compounds to a specific receptor (the Ah-receptor).

Due to the fact that dioxin-like compounds normally exist in environmental and biological samples as complex mixtures of congeners, the concept of toxic equivalents (TEQs) has been introduced to simplify risk assessment and risk management. In applying this concept, relative toxicities of dioxin-like compounds in relation to 2,3,7,8-TCDD (i.e. toxic equivalency factors, TEFs) are determined based on *in vitro* and *in vivo* studies. This approach is based on the evidence that there is a common, receptor-mediated mechanism of action for these compounds, but it has its limitations due to a number of simplifications. The most important limitation is that the combined toxic effects of the components of a given mixture would be additive, neglecting possible synergism or antagonism. Furthermore, pharmacokinetics is not always taken into account.

A number of different TEF-schemes have been developed for PCDDs and PCDFs[1-9], as well as for dioxin-like PCBs[10-12]. Recently, the WHO-European Centre for Environment and Health (WHO-ECEH) and the International Programme on Chemical Safety (IPCS) held a consultation that recommended interim TEFs for selected PCBs[13]. The currently recommended TEFs for PCDD/Fs[8] and PCBs[13] are given in tables 1 and 2.

The criteria for including a compound in a TEF-scheme has previously been discussed [10, 13, 14, 15] and the following criteria should be met for a compound to be considered:

It should show structural relationship to the PCDDs and PCDFs
It should bind to the Ah-receptor
It should elicit dioxin-specific biochemical and toxic responses
It should be persistent and accumulate in the food chain

The concept of TEFs assumes strict additivity. There appears to be a potential for nonadditivity only in very weak agonists or non-Ah-receptor agonists. There is some evidence that there may be nonadditive (in particular antagonistic) interactions between nondioxin-like PCBs and dioxin-like compounds. Such interactions could make the strict assumption of TEF

Table 1. NATO/CCMS I-TEFs for PCDD/Fs[8].

Congener	*TEF*
2,3,7,8-TCDD	1
1,2,3,7,8-PeCDD	0.5
2,3,7,8-subst. HxCDDs	0.1
1,2,3,4,6,7,8-HpCDD	0.01
OCDD	0.00
2,3,7,8-TCDF	0.1
1,2,3,7,8-PeCDF	0.05
2,3,4,7,8-PeCDF	0.5
2,3,7,8-subst. HxCDFs	0.1
2,3,7,8-subst. HpCDF	0.01
OCDF	0.001

Table 2. WHO/IPCS interim TEFs for human intake[13].

Type	Congener		TEF
	IUPAC No.	Structure	
Non-*ortho*	77	3,3',4,4'-TCB	0.0005
	126	3,3',4,4',5-PeCB	0.1
	169	3,3',4,4',5,5'-HxCB	0.01
Mono-*ortho*	105	2,3,3',4,4'-PeCB	0.0001
	114	2,3,4,4',5-PeCB	0.0005[a,b]
	118	2,3',4,4',5-PeCB	0.0001
	123	2',3,4,4',5-PeCB	0.0001
	156	2,3,3',4,4',5-HxCB	0.0005[b]
	157	2,3,3',4,4',5'-HxCB	0.0005[b]
	167	2,3',4,4',5,5'-HxCB	0.00001[a]
	189	2,3,3',4,4',5,5'-HpCB	0.0001[a]
Di-*ortho*	170	2,2',3,3',4,4',5-HpCB	0.0001[a]
	180	2,2',3,4,4',5,5'-HpCB	0.00001[a]

[a] Based on very limited data.
[b] IUPAC 114, 156, and 157 are expected to have similar TEF-values based on similar responses. Although the data is limited, the determination of TEFs for these congeners is supported by their structural similarity.

additivity for complex mixtures highly conservative. Likewise, nondioxin-like PCBs also have their own independent toxicities, which, in certain cases, may be as important as those associated with dioxin-like compounds (e.g., cancer, neurotoxicity). E.g., nondioxin-like PCBs appear to be responsible for most of the tumour promotion associated with higher chlorinated mixtures, e.g., Aroclor 1260 or Clophen A60 and many such PCBs have been demonstrated to be potent tumour promotors[16, 17]. Furthermore, they have also been shown to act additively or may be even synergisticly with PCDD/Fs or dioxin-like PCBs[17, 18, 19]. Effects due to PCB metabolites, e.g. estrogenicity of hydroxylated metabolites or pulmonary toxicity of sulphonated metabolites, may also be critical confounders. The toxicity of nondioxin-like PCB congeners and metabolites should thus be assessed in future studies.

Questions of nonadditivity of complex mixtures must be further investigated since these are environmentally relevant. Additivity, synergism, and antagonism may be effect and species specific [11]. Furthermore, great care will have to be exercised when evaluating effects that can be caused by multiple mechanisms (e.g. increased liver weight, tumour promotion).

The recent WHO/IPCS consultation[13] recognized that the recommended TEFs were developed for use in exposure scenarios, i.e. they are intake TEFs. These values may, or may not, be appropriate for body burden assessments. They may also need to be re-examined for ecotoxicity purposes. There is some data suggesting that TEFs for mammalian systems may not be applicable for fish and birds. TEFs, particularly for PCBs in fish that are based on sac fry mortality in rainbow trout as the endpoint, are significantly different from those proposed for human health risk assessment[20]. E.g., TEFs for non-ortho-substituted PCBs are less than the corresponding human TEF values. Furthermore, mono-ortho-substituted PCBs fail to cause signs of TCDD toxicity during rainbow trout early life stage development, whereas the same congeners cause toxicity in mammals.

The selection of a TEF-value should be driven by the question being addressed. Thus there may be different classes of TEF-values depending upon whether the considerations relate to intake, body burden, or ecological concerns. The ecological concerns may be further subdivided into categories for fish, birds, or other species of wildlife.

REFERENCES

1) Federal Swiss Government (1982) Environmental pollution due to dioxins and furans for chemical rubbish incineration plants. Bern: Ministry of Environment, Federal Swiss Government
2) Danish National Agency of Environmental protection (1984) Formation and emission of dioxins especially in connection with waste incineration. Copenhagen: National Agency of Environmental Protection, Miljøstyrelsen (in Danish)
3) Federal Republic of Germany Office for the Environment (1985) Review of dioxins. Federal Office for the Environment, Report No 5/85, November 1984 (in German). Berlin: Erich Schmidt Verlag, pp 257-266
4) Ontario Ministry of the Environment (1985) Scientific Criteria Document for standard development. Polychlorinated dibenzo-*p*-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs). Report No. 4184. Toronto: Ministry of the Environment Health and Welfare Canada, Great Lakes Health Effects Division (1994), unpublished
5) U.S. EPA (U.S. Environmental Protection Agency) (1987) Interim procedures for estimating risks associated with exposures to mixtures of chlorinated dibenzo-*p*-dioxins and dibenzofurans (CDDs/CDFs). EPA/625/3-87/012, Risk Assessment Forum. Washington, DC
6) U.S. EPA (U.S. Environmental Protection Agency) (1989) Interim procedures for estimating risks associated with exposure to mixtures of chlorinated dibenzo-*p*-dioxins and -dibenzofurans and 1989 update. Risk Assessment Forum. EPA/625/3-89/016. Principal

authors: D Barnes, F Kutz, and D Bottimore. National Technical Information Service, Springfield, VA
7) Ahlborg U.G. (1988): Nordisk dioxinriskbedömning (Nordic risk assessment of dioxins). Stockholm: National Institute of Environmental Medicine (with English summary)
8) NATO/CCMS (North Atlantic Treaty Organization, Committee on the Challenges of Modern Society) (1988) International toxicity equivalency factor (I-TEF) method of risk assessment for complex mixtures of dioxins and related compounds. Report No. 176. Brussels: North Atlantic Treaty Organization
9) van Zorge J.A., J.H. van Wijnen, R.M.C. Theelen, K. Olie, and M. van den Berg (1989): Assessment of the toxicity of mixtures of halogenated dibenzo-*p*-dioxins and dibenzofurans by use of toxicity equivalency factors (TEF). Chemosph. 19, 1881-1895
10) Safe S. (1990): Polychlorinated biphenyls (PCBs), dibenzo-*p*-dioxins (PCDDs), dibenzofurans (PCDFs), and related compounds: Environmental and mechanistic considerations which support the development of toxic equivalency factors. CRC Crit. Rev. Toxicol. 21, 51-88
11) Safe S. (1994): Polychlorinated biphenyls (PCBs): environmental impact, biochemical and toxic responses and implications for risk assessment. CRC Crit. Rev. Toxicol. 24, 1-63
12) Ahlborg U.G., A. Hanberg, and K. Kenne (1992a): Risk assessment of polychlorinated biphenyls. Nordic Council of Ministers, Copenhagen, Nord 1992:26
13) Ahlborg U.G., G.C. Becking, L.S. Birnbaum, A. Brouwer, H.J.G.M. Derks, M. Feeley, G. Golor, A. Hanberg, J.C. Larsen, A.K.D. Liem, S.H. Safe, C. Schlatter, F. Waern, M. Younes, E. Yrjänheikki (1994): Toxic equivalence factors for dioxin-like PCBs. Report on a WHO-ECEH and IPCS consultation, December 1993. Chemosph. 28(6), 1049-1067
14) Barnes D., A. Alford-Stevens, L. Birnbaum, F.W. Kutz, W. Wood, and D. Patton (1991): Toxicity equivalency factors for PCBs? Quality Assurance: Good Practice, Regulation, and Law 1, 70-81
15) Ahlborg U.G., A. Brouwer, M.A. Fingerhut, J.L. Jacobson, S.W. Jacobson, S.W. Kennedy, A.A.F. Kettrup, J.H. Koeman, H. Poiger, C. Rappe, S.H. Safe, R.F. Seegal, J. Tuomisto, and M. van den Berg (1992b): Impact of polychlorinated dibenzo-*p*-dioxins, dibenzofurans and biphenyls on human and environmental health, with special emphasis on application of the toxic equivalency factor concept. Eur. J. Pharmacol. - Environmental Toxicology and Pharmacology Section, 228, 179-199
16) Sargent L., Y.P. Dragan, C. Erickson, C.J. Laufer, and H.C. Pitot (1991): Study of the separate and combined effects of the non-planar 2,5,2',5'- and the planar 3,4,3'4'-tetrachlorobiphenyl in liver and lymphocytes *in vivo*. Carcinogenesis 12(5), 793-800
17) Hemming H., S. Flodström, L. Wärngård, Å. Bergman, T. Kronevi, I. Nordgren, and U.G. Ahlborg (1993): Relative tumour promoting activity of three polychlorinated biphenyls in rat liver. Eur. J. Pharmacol. 248, 163-174
18) Bager Y., H. Hemming, S. Flodström, U.G. Ahlborg, and L. Wärngård. Interaction of 3,4,5,3´,4´-pentachlorobiphenyl and 2,4,5,2´,4´,5´-hexachlorobiphenyl in liver tumour promotion. (Submitted).
19) Hemming H., Y. Bager, S. Flodström, I. Nordgren, T. Kronevi, U.G. Ahlborg, and L. Wärngård. Liver tumour promoting activity of 3,4,5,3´,4-pentachlorobiphenyl and its interaction with 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. (Submitted).
20) Walker M.K., and R.E. Peterson (1991): Potencies of polychlorinated dibenzo-*p*-dioxins, dibenzofurans and biphenyls, relative to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, for producin early life stage mortality in rainbow trout (*Onchorhynchus mykiss*), Aquat. Toxicol. 21, 219-238