Reevaluation of the Toxicity Equivalency Factors for Dioxins and Dibenzofurans

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SUMMARY

In 1986, the Massachusetts Department of Environmental Protection (DEP) instituted the use of toxicity equivalency factors (TEFs) to evaluate the toxicity of complex environmental mixtures containing polychlorinated dibenzo-p-dioxins (PCDDs) and dibenzofurans (PCDFs). TEFs are used to mathematically convert the concentration of PCDDs and PCDFs to an equivalent concentration of 2,3,7,8-tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD). This approach simplifies the risk assessment process.

The current DEP TEFs were selected from a study conducted by the Swiss Government in 1982. The DEP, based on a recommendation from the Office of Research and Standards (ORS), is considering changes in the current TEFs based on a large body of *in vivo* and *in vitro* toxicity data which has become available since 1982.

The recommended changes include increases in the TEFs for the 2,3,7,8-substituted congeners for pentaCDDs, pentaCDFs, heptaCDDs,heptaCDFs, octaCDDs and octaCDFs and decreases in the TEFs for triCDDs, triCDFs and all non-2,3,7,8-substituted congeners relative to the corresponding 2,3,7,8-substituted congener. The proposed DEP TEFs are viewed as conservative estimates of the relative toxicity of the congeners and therefore, affords an adequate margin of safety for the protection of human health.

REGULATORY BACKGROUND

Polychlorinated dibenzo-p-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs) (Figure 1) comprise a family of environmentally ubiquitous chemicals containing 210 specific

monochlorinated and polychlorinated congeners (Table 1). In the spring of 1987, the U.S. Environmental Protection Agency (EPA) formally adopted an interim procedure for estimating risks associated with complex environmental mixtures containing PCDDs and PCDFs (Bellin and Barnes, 1987). The procedure used a set of derived toxicity equivalency factors (TEFs) to convert the concentration of congeners into an equivalent concentration of 2,3,7,8-tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD), the most toxic of the 210 congeners. This approach was adopted to simplify hazard and risk assessments of complex environmental mixtures containing PCDDs and PCDFs. The set of TEFs derived (EPA TEFs/87; Table 2) was based on toxicity information available through 1985 (EPA 1985).

Since 1985, additional data had become available which suggested that modifications in some of the factors were appropriate. In 1988, the EPA initiated a review of the more recent pertinent toxicity studies and published revised TEFs (EPA I-TEFs/89; Table 2) based on data available prior to 1988 (EPA, 1989). The I-TEFs/89 were adopted as international TEFs and are currently being used by more than 20 countries in order to facilitate information exchange and cooperation in reacting to environmental contamination by PCDDs and PCDFs. The EPA plans to initiate a review of their current TEFs in 2-4 years.

In 1986, the Massachusetts Department of Environmental Protection (DEP), then the Department of Environmental Quality Engineering (DEQE), independently instituted the use of toxic equivalency factors to mathematically convert the concentrations of congeners of PCDDs and PDCFs to an equivalent concentration of 2,3,7,8-TCDD. The set of TEFs (current DEP TEFs; Table 3) selected for use by DEP was that delineated by a study conducted by the Swiss Government (1982) utilizing *in vitro* aryl hydrocarbon hydroxylase (AHH) induction as the endpoint. This endpoint is receptor-mediated and therefore may reflect the relative potency of the congeners *in vivo* whose toxicity is also believed to be receptor-mediated.

Much of the experimental evidence used to generate the existing DEP TEFs and EPA I-TEFs/89 is outdated. Numerous studies have been performed since 1988 which provide valuable information concerning the relative toxicity of the PCDD/PCDF congeners. Therefore, at this time, it is reasonable to re-evaluate these factors to determine whether they are still protective of human health based on current experimental knowledge.

TOXICITY BACKGROUND

Of the possible 210 structural congeners of PCDDs and PCDFs, the most toxic is 2,3,7,8-tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD). It is estimated to have an acute oral LD_{50} ranging from 0.06 -2.0 ug/kg. The remaining congeners have been reported to have less toxicity, displayed by oral LD_{50}, values ranging up to more than 4000 ug/kg (Safe, 1990). Several studies have demonstrated that 2,3,7,8-TCDD and its related congeners are all absorbed by various routes of administration and can be detected in body tissues for varying lengths of time post-exposure (Birnbaum and Couture, 1988; Abraham et al., 1989; Brewster et al., 1989; Banks and Birnbaum, 1991). All congeners elicit a number of common toxic responses which include body weight loss, thymic atrophy, impairment of immune responses, hepatotoxicity and porphyria, chloracne and related dermal lesions, tissue-specific hypoplastic and hyperplastic responses, carcinogenesis, teratogenesis and reproductive toxicity (Safe, 1990).

It is widely accepted that many of the toxic effects produced by PCDDs/PCDFs are mediated through binding to the cytosolic Ah receptor. This binding results in the formation of a congener- receptor complex which migrates to the nucleus of the cell. This triggers an alteration of gene expression which leads to the manifestation of toxicity, however, the exact molecular mechanisms of these alterations are currently unknown.

It should be noted that the magnitude of toxic effects are dependent on species, strain, age and sex. The only major difference among the individual congeners is their relative toxic potencies with every congener so far tested displaying a finite toxicity in some experimental system.

There is a strong structure/activity relationship between the members of the PCDD and PCDF families. Congeners in which the lateral 2, 3, 7 and 8 positions are occupied with chlorines (2,3,7,8-substituted congeners) possess more relative toxicity than the other congeners **(**non-2,3,7,8-substituted congeners). It is the relative toxicities of the individual congeners compared to 2,3,7,8-TCDD that is determined and used to derive toxicity equivalency factors. The derived TEFs can be used to convert the concentration of any PCDD/PCDF congener into an equivalent concentration of 2,3,7,8-TCDD. This approach assumes that the toxicity of the individual congeners is mathematically additive, rather than

antagonistic or synergistic, an assumption which is largely substantiated by recent reports (Schrenk et al., 1991; Safe, 1990).

METHODOLOGY EMPLOYED IN THE DEVELOPMENT OF TEFS

The EPA I-TEFs/89 are based on toxicity studies performed in numerous laboratories and *in vitro* and *in vivo* experimental systems. In prioritizing the importance of individual protocols to represent biochemical and toxicological effectiveness, the EPA TEF Subgroup agreed that the most appropriate studies were those which most closely mimic human exposure situations. The most appropriate laboratory studies, therefore, would be those involving chronic bioassays examining carcinogenesis in mammals, since the human health effect of greatest concern is carcinogenesis. However, limited numbers of chronic toxicity studies have been performed. Therefore, other experimental systems are relied upon, including data from subchronic, subacute and acute animals studies or those involving *in vitro* protocols.

Some of the common experimental endpoints used to derive TEFs *in vivo* include acute lethality, body/organ weight data, quantitative histopathology in liver and thymus, the splenic plaque-forming cell response to sheep red blood cells, hepatic microsomal enzyme induction, hepatic I-compound DNA adducts and promotion of rat liver foci. The following is a brief description of the less familiar experimental assay systems.

1. Promotion of rat liver foci

This assay has been determined to be a sensitive *in vivo* short term test to investigate the tumor promoting potential of agents (Oesterle and Deml, 1983). This test reveals the tumorigenic potency of chemicals by the emergence of putative preneoplastic cell populations, identified histochemically by enzyme-alterations including the loss of ATPase activity and the emergence of gamma- glutamyltranspeptidase activity. These preneoplastic cells, when injected into naive animals, have the ability to induce hepatic tumors. Therefore, the promotion of altered enzyme foci is believed to be a prediction of true carcinogenic potency.

2. Hepatic I-compound DNA adducts

Adduct-like DNA modifications have been detected by sensitive ^{32}P-postlabeling methods

(Randerath et al., 1990). These structurally uncharacterized DNA modifications have been designated I (indigenous)-compounds, to contrast them with exogenous carcinogen adducts. I-compounds are absent in newborn animals and increase in frequency with age. Pronounced tissue, sex, strain and species specificities of I-compound profiles suggest that these modifications may play a role in gene expression. Known hepatic carcinogens have been demonstrated to reduce the level of hepatic I-compounds. As normal DNA modifications, I-compounds may play a role in DNA replication and transcription and thus, carcinogen-induced depression of I-compound levels may be associated with cellular dedifferentiation during carcinogenesis. Direct evidence for a role of I-compound depression/loss in carcinogenesis and maintenance of neoplasia is not yet available. However, it is interesting to note that hepatoma cell lines lack detectable I-compounds which are present in non-neoplastic hepatic cell lines.

3. Hepatic microsomal enzyme induction

PCDDs and PCDFs are known to be potent inducers of hepatic microsomal enzymes. It is known that the induction is mediated by binding of the compound to the cytosolic Ah receptor. It is believed that receptor binding is an integral step in the production of toxic manifestation of 2,3,7,8-TCDD and its congeners. The studies examining hepatic enzyme induction monitor a number of different enzyme activities. Those associated with the mixed function oxidase enzyme system include aryl hydrocarbon hydroxylase (AHH) activity, ethoxyresorufin 0-deethylase (EROD) activity and B(a) P hydroxylase activity while those not associated with the mixed function oxidase enzyme system include aminolevulinic acid synthetase activity and glutathione S-transferase activity. Studies utilizing enzyme induction as an endpoint have been criticized since the time-course of induction and the shape of the dose-response curve for this effect are usually not determined.

4. Splenic plaque-forming cell response to sheep red blood cells

The immunotoxic effects of PCDDs and PCDFs have been extensively documented. Exposure to these toxicants results in a significant loss of thymic tissue which is accompanied by the suppression of many cell-mediated immune responses. Several studies provide support for a receptor-mediated mechanism for immunotoxicity. A widely used and highly sensitive *in vivo* assay to detect immunotoxicity is the splenic plaque-forming cell response to sheep red blood cells in mice (Dickerson et al., 1990). Mice are exposed to test agent and immunized with sheep RBCs. A decreased ability of splenic cells isolated from the treated animals to form plaques with murine red blood cells indicates compromised cell-mediated immunity.

In addition to *in vivo* studies, *in vitro* studies have also been employed in the development of TEFs. *In vitro* studies, for the most part, examine enzyme induction (AHH and EROD) in hepatoma cell lines, cell keratinization and Ah receptor-binding. The *in vitro* studies are considered less important for the development of TEFs since they fail to consider the role of absorption, distribution, metabolism and excretion in the production of toxicity.

RECOMMENDATIONS CONCERNING CHANGES IN DEP TEFs

The DEP, based on a recommendation from ORS, is considering changes in the current DEP TEFs based on *in vivo* and *in vitro* toxicity data which have become available since 1982. Such changes would bring the Departmental TEFs more in line with the EPA **I**-TEFs/89, but would also utilize all available scientific literature published since 1988, information not considered by the EPA at the time of their most recent review.

The recommended changes in the current DEP TEFs are as follows and are summarized in Table 4:

1. **A decrease in the TEF for mono-, di- and triCDDs and mono-**, **di- and triCDFs from 0.01 to 0.001**.

Recent *in vivo* and *in vitro* studies by Harris et al. (1990), Zacharewski et al. (1989) and Deml et al. (1989) suggest that the potency of triCDDs and triCDFs is at least a thousand-fold less than that of TCDD. No significant additional information exists concerning mono- and di-CDDs and -CDFs. However, they are grouped with the tri-congeners for analytical reasons.

2. **An increase in the TEF for 2,3,7,8-PeCDDs and 2,3,7,8-PeCDF**s **from 0.1 to 0.5**.

Recent *in vivo* and *in vitro* studies (Davis and Safe, 1988; Brewster and Birnbaum, 1988; Holcomb et al., 1988; Harris et al., 1990; Zacharewski et al., 1989; Brewster et al., 1988a; Randerath et al., 1990; Randerath et al., 1988; Brewster et al., 1988b; Hebert et al., 1990) all support the belief that these isomers are much more toxlc than previously believed. In one study (Davis and Safe, 1988), the toxicity of 2,3,4,7,8-PeCDF was essentially equipotent to that of TCDD when assayed as to its ability to inhibit the splenic plaque-forming cell response *in vivo*. This assay is believed to be a very sensitive indicator of TCDD receptor-mediated toxicity. In a second study (Brewster et al., 1988b), the toxicity of 2,3,4,7,8-PeCDF was assessed in the

Rhesus monkey, an excellent animal model for TCDD effects. This congener was demonstrated to produce the same clinical symptoms in the same dosage range as TCDD. The other 2,3,7,8-isomers seem to possess somewhat less toxicity than the 2,3,4,7,8-isomer. However, the conservative estimate that all 2,3,7,8-substituted PeCDFs are approximately equipotent is most protective.

3. **An increase in the TEF for OCDD and OCDF from 0 to 0.001.**

This recommendation is based on one recent study (Couture et al., 1988) in which OCDD was administered to Fisher 344 rats orally for up to 65 days. Previous studies assessing the toxicity of OCDD and OCDF relied on an acute dosing schedule. In these previous studies, OCDD and OCDF were determined to be inactive. The study of Couture et al. (1988) demonstrated that OCDD accumulates in tissues following subchronic dosing. The animals presented with signs and symptoms similar to those seen following TCDD exposure, however, the dose required to trigger the response was on the order of 1000-fold greater than that required by TCDD. This is the most prevalent of the environmentally detected dioxins, comprising approximately 75% of the total dioxins detected. Therefore, it may be important to factor its contribution into the toxicity of complex environmental mixtures of PCDDs and PCDFs.

4. **An increase in the TEF for 2,3,7,8-HpCDDs and 2,3,7,8-HpCDFs from 0.01 to 0.1.**

This recommendation is based on one recent *in vivo* study (Dickerson, et al., 1990) in which the relative potency of the heptaisomers was determined by immunosuppression and enzyme induction in C57BL/6 mice. The results suggest a TEF of 0.1 for 2,3,7,8-congeners and 0.01 for non-2,3,7,8-congeners.

5. A decrease in the TEFS for non-2,3,7,8-substituted congeners by a factor of 10 relative to their corresponding 2,3,7,8- substituted congeners.

The current DEP TEFS set identical values for specific 2,3,7,8-substituted congeners and non-2,3,7,8-substituted congeners. A decrease in the TEF for non-2,3,7,8-substituted congeners by at least 10-fold may more closely approximate their actual relative toxicities, but still afford an adequate margin of safety for the protection of human health.

The EPA has assigned a TEF of zero to all non-2,3,7,8- substituted congeners. The EPA I-TEFs/89 accompanying document discusses the justification of this assignment. The justification for this is two-fold:

1. As an attempt to simplify the TEF system since this system was to be adopted on an international basis.
2. As a response to recent scientific literature that the non-2,3,7,8-substituted congeners seem to not pose a significant threat since they appear to be either not absorbed or quickly eliminated by biological systems. In contrast, the 2,3,7,8-substituted congeners do appear to be selectively absorbed and/or retained by these same biological systems.

However, there is little scientific basis for assigning a zero value to the non-2,3,7,8-substituted congeners. In certain biological assay systems, a few of these congeners do fail to display any activity. This is seen primarily in the *in vitro* systems including AHH induction and keratinization assays in transformed cell lines. These systems, as stated previously, are generally not considered the most sensitive or most accurate assays to predict the relative toxicity of the PCDDs and PCDFs. In vivo assays mentioned previously have been able to detect and quantitate the toxicity of the non-2,3,7,8-substituted congeners. In all cases, the non-2,3,7,8-substituted congeners have been demonstrated to be less toxic than their respective 2,3,7,8-substituted isomers.

The estimates of relative toxicity of non-2,3,7,8-substituted isomers to their respective 2,3,7,8-substituted isomers range from one to three orders of magnitude less potent (factors of 0.1-0.001 relative to the TEF for the 2,3,7,8-substituted isomer). The proposed 10-fold decrease in the TEF for most non-2,3,7,8-substituted congeners relative to the TEF for the corresponding 2,3,7,8-congeners represents a conservative estimate of relative toxicity, thus affording an adequate margin of safety for the protection of the public. The proposed 100-fold decrease in the TEF for non-2,3,7,8-substituted congeners of TCDD and TCDF relative to 2,3,7,8-TCDD and 2,3,7,8-TCDF reflects available toxicity information directly examining these congeners. In fact, it does not represent a change in the current TEF for non-2,3,7,8- substituted TCDDs. Little congener-specific information exists for the remaining non-2,3,7,8-substituted PCDDs and PCDFs.

CONCLUSIONS

The recommended changes in the current DEP TEFs include proposed increases in the TEFs for the 2,3,7,8-substituted congeners of PeCDDs, PeCDFs, HpCDDs, HpCDFs, OCDD and OCDF and proposed decreases in the TEFs for triCDDs, triCDFs and non-2,3,7,8-substituted congeners relative to the corresponding 2,3,7,8-substituted congener. There is no change recommended for the current TEFs of the 2,3,7,8-substituted hexaCDDs (Hx-CDDs) and hexaCDFs (Hx-CDFs). These recommendations are based on a large number of pertinent *in vivo* and *in vitro* toxicity studies which have been performed since 1982, with major emphasis placed on studies published since 1988, the time of the most current EPA review of the subject. The proposed TEFs are viewed as conservative estimates of the potency of the congeners relative to 2,3,7,8-TCDD and are believed to incorporate an adequate margin of safety for human health protection.

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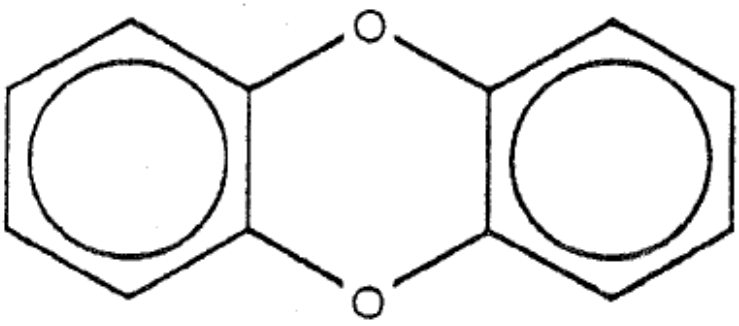
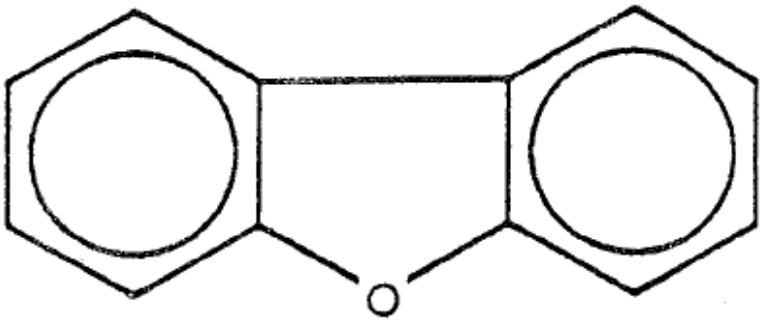


Dibenzo-p-Dioxin



Dibenzofuran

Figure 1. Structure of dibenzo-p-dioxin and dibenzofuran

Table 1. Number of Congeners by Homologue (number of chlorines) and Substitution Type ("2,3,7,8" vs. "non-2,3,7,8")

Type/Homologue	1Cl	2Cl	3Cl	4Cl	5Cl	6Cl	7Cl	8Cl	Total
2,3,7,8-CDDs	0	0	0	1	1	3	1	1	7
Non-2,3,7,8-CDDs	2	10	14	21	13	7	1	0	68
								Subtotal	75
2,3,7,8-CDFs	0	0	0	1	2	4	2	1	10
Non-2,3,7,8-CDFs	4	16	28	37	26	12	2	0	125
								Subtotal	135

Total 2,3,7,8-CDDs/Fs = 17
Total non-2,3,7,8-CDDs/Fs = 193

TABLE 2. TOXICITY EQUIVALENCY FACTORS

Compound	EPA-TEFs/87	I-TEFs/89
Mono-,Di-,and TriCDDs	0	0
2, 3,7,8-TCDD	1	1
Other TCDDs	0.01	0
2,3, 7, 8-PeCDD	0.5	0.5
Other PeCDDs	0.005	0
2378-HxCDDs	0.04	0.1
Other HxCDDs	0.0004	0
2,3,7,8-HpCDD	0.001	0.01
Other HpCDDs	0.00001	0
OCDD	0	0.001
Mono-, Dl-, and TriCDFs	0	0
2,3,7,8-TCDF	0.1	0.1
Other TCDFs	0.001	0
I, 2, 3,7, 8-PeCDF	0.1	0.05
2,3, 4,7, 8-PeCDF	0.1	0.5
Other PeCDFs	0.001	0
2378- HxCDFs	0.01	0.1
Other HxCDFs	0.0001	0
2378-HpCDFs	0.001	0.01
Other HpCDFs	0.00001	0
OCDF	0	0.001

Table 3. Current DEP Toxicity Equivalence Factors

Compound	Current DEP TEFs
Mono-,Di-,and TriCDDs	0.01
2, 3,7,8-TCDD	1
Other TCDDs	0.01
2,3, 7, 8-PeCDDs	0.1
Other PeCDDs	0.1
2,3,7,8-HxCDDs	0.1
Other HxCDDs	0.1
2,3,7,8-HpCDDs	0.01
Other HpCDDs	0.01
OCDD	0
Mono-, Di-, and TriCDFs	0.01
2,3,7,8-TCDF	0.1
Other TCDFs	0.1
2, 3,7, 8-PeCDFs	0.1
Other PeCDFs	0.1
2,3,7,8- HxCDFs	0.1
Other HxCDFs	0.1
2,3,7,8-HpCDFs	0.01
Other HpCDFs	0.01
OCDF	0

Table 4. Summary – Toxicity Equivalency Factors

Compound	EPA/89	Current DEP	Proposed DEP
Mono-, di- and TriCDDs	0	0.01	0.001
2, 3,7,8-TCDD	1	1	1
Other TCDDs	0	0.01	0.01
2,3, 7, 8-PeCDD	0.5	0.1	0.5
Other PeCDDs	0	0.1	0.05
2,3,7,8-HxCDDs	0.1	0.1	0.1
Other HxCDDs	0	0.1	0.01
2,3,7,8-HpCDD	0.01	0.01	0.1
Other HpCDDs	0	0.01	0.01
OCDD	0.001	0	0.001
Mono-, Di-, and TriCDFs	0	0.01	0.001
2,3,7,8-TCDF	0.1	0.1	0.1
Other TCDFs	0	0.1	0.01
I, 2, 3,7, 8-PeCDF	0.05		
2,3, 4,7, 8-PeCDF	0.5		
2,3,7,8-PeCDFs	0	0.1	0.5*
Other PeCDFs	0	0.1	0.05
2,3,7,8- HxCDFs	0.1	0.1	0.1
Other HxCDFs	0	0.1	0.01
2,3,7,8-HpCDFs	0.01	0.01	0.1
Other HpCDFs	0	0.01	0.01
OCDF	0.001	0	0.001

* includes 1,2,3,7,8-PeCDF and 2,3,4,7,8-PeCDF