COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

2005 WHO TOXIC EQUIVALENCY FACTORS FOR DIOXINS AND DIOXIN-LIKE COMPOUNDS

Non-Technical Summary

1. Dioxins and dioxin-like chemicals are pollutants which accumulate in the food chain. It is generally acknowledged that their toxicity is mediated by the same mechanism of action. Hence, it is important that their toxic effects are evaluated together. Since their potency varies greatly, toxic equivalency factors (TEFs) have been developed in order to compare the various chemicals and assess the combined effect of mixtures of dioxins and dioxin-like chemicals. This statement relates to a recent World Health Organisation (WHO) review of the most up to date scientific information that compares the potency of these chemicals. Re-evaluation of the TEF values has resulted in small reductions in the estimated exposure of the UK population to the total activity of dioxins and dioxin-like chemicals. The COT agrees with the scientific rationale for the re-evaluated TEF values and concludes that they should be used in future UK assessments of dietary exposure to dioxins and dioxin-like compounds.

Introduction

2. Dioxins and dioxin-like chemicals are persistent organic pollutants that are resistant to metabolism and subject to bioaccumulation. Most, if not all, of their toxic and biological effects are mediated by the aryl hydrocarbon receptor (AhR). Many different congeners are released into the environment by industrial activity and, since these chemicals share a common mechanism, risk assessment should reflect the mixture rather than the isolated chemical. Experiments using mixtures of congeners are consistent with an additive model and, as a result of this generally accepted additivity, the toxic equivalency concept was developed in the 1980s.

3. The WHO has, on a number of occasions, convened Expert Panels to discuss toxic equivalency factor (TEF) values. This is because the Expert Panel has stated that the TEF concept should be thought of as an interim methodology, which should be subject to periodic review as new scientific information becomes available[1]. The Expert Panel initially set TEF values at a meeting in 1993 and re-evaluated them at a subsequent meeting in 1997. These re-evaluated TEFs were published in 1998 and endorsed by

the COT in the same year[2]. In 2001, the COT undertook an extensive review of dioxins and dioxin-like chemicals[3], which resulted in the adoption of a Tolerable Daily Intake (TDI) of 2 pg WHO-TEQ/kg bw/day †.

4. In 2004 the European Food Safety Authority (EFSA) organised a scientific colloquium to discuss the risk assessment of dioxins and dioxin-like chemicals. This colloquium highlighted some differences in approaches to the risk assessment of these compounds and concluded that it was timely to review the TEF scheme. The WHO-IPCS Expert Panel was reconvened in June 2005 to perform the next periodic re-evaluation of the TEF values and to discuss and develop the TEF concept. A report of this meeting will be published in due course[4].

5. The 2005 WHO-IPCS re-evaluation was based on a recently published relative effect potency (REP) database[1], which was constructed using refined inclusion/exclusion criteria. Of the REP values from the previous database used in the 1997 TEF reassessment, 47% met the more stringent criteria. These 381 REP values were combined with 253 REP values from new studies, forming the 2005 REP database [1]. Unweighted REP values from this database were used as a starting point for the TEF re-evaluation. When the 1997 TEF value for the congener differed from the 75th percentile of the *in vivo* REP distribution in the 2005 database, a more extensive review of the data was performed. During this review, expert judgement was used to assess individual studies and derive an appropriate TEF value based on studies that were most relevant to human exposure.

6. This re-evaluation uses half order of magnitude increments on a logarithmic scale (0.03, 0.1, 0.3 etc). TEF values represent 'order of magnitude estimates', therefore, a degree of uncertainty is implicit. The Expert Panel considered that these increments would be useful in the future so that the uncertainty of TEF values can be better described. Previous evaluations used increments of 0.01, 0.05, 0.1 etc.

Expert Panel Re-Evaluation

7. The re-evaluated TEF values are shown in Table 1. Detailed explanations of how the individual TEF values were determined have been reported by van den Berg et al. [4].

8. The TEF values for OCDD and OCDF were increased from 0.0001 to 0.0003 in light of a new subchronic toxicity study[5,6] and other in vitro data.

9. The TEF value for 1,2,3,7,8-PeCDF was reduced from 0.05 to 0.03 in line with the new half log increments. The rationale for this reduction was explained by van den Berg *et al.* [4]*:*

† The total toxic equivalent (TEQ) is defined as the sum of the products of the concentration of each congener, multiplied by the toxic equivalency factor (TEF).

"The WHO 1998 TEF was set at 0.05 which is within the 50th and 75th percentile of the REP distribution of eight in vivo studies. A new study[5] found a REP of 0.01 for effects on hepatic vitamin A reduction, but another study reported a REP of 0.045 for cleft palate[7]. The majority of the vivo studies report a REP value below 0.1 but many relevant studies have REPs above 0.01. Therefore the Expert Panel decided that the 2005 TEF should become 0.03."

10. The TEF value for 2,3,4,7,8-PeCDF was reduced from 0.5 to 0.3, also to be in line with the new half log increments. Rationale for reduction from van den Berg *et al.* [4] :

    "The WHO 1998 TEF was set at 0.5 which is well above the 75th percentile of the REP distribution of eight in vivo studies. Results from the long term US National Toxicology Programme (NTP) study in female Sprague Dawley rats using many different endpoints had become available. The REPs for neoplastic endpoints from the NTP study are around 0.2 to 0.3, while non-neoplastic endpoints have REPs that range from 0.7 to 1.1 [8] An older subchronic study pointed towards a REP of 0.4 [9]. More recent studies using hepatic vitamin A reduction and immunological effects as endpoints also point toward a TEF below 0.5 [5,10]. In view of this new information the consensus of the Expert Panel was to change the WHO 2005 TEF to 0.3."

11. PCB 81 was increased from 0.0001 to 0.0003 on the basis of *in vitro* studies which indicate that PCB 81 is more potent than PCB 77. However, the Expert Panel expressed a low confidence in this assessment due to the absence of a reliable REP for PCB 81. PCB 169 was increased from 0.01 to 0.03 because the 1998 TEF was close to the median of the *in vivo* REP distribution and it was considered appropriate to raise the TEF to between the 50th and 75th percentile.

12. The 1998 TEF values for the mono-ortho substituted PCBs ranged from 0.00001 to 0.0005. The wide variation in REPs is illustrated in Figure 3 of van den Berg *et al.* [4]. In view of potential contamination of mono-ortho substituted PCB samples with more potent congeners, the Expert Panel expressed low confidence in the higher REP values within this group. The most environmentally relevant mono-ortho PCBs are 27, 105, 118, and 156 and it was decided to use the medians of the REP distribution range of these PCB congeners as a guide. This resulted in a recommended TEF of 0.00003 for these mono-ortho PCBs. A differentiation for all other remaining mono-ortho PCBs was considered unfeasible by the Expert Panel due to the lack of sufficient experimental data. Consequently a TEF of 0.00003 was recommended for all mono-ortho PCBs.

Table 1 Summary of WHO 1998 and WHO 2005 TEF values.		
Compound	**1998 WHO-TEFs**	**2005 WHO-TEFs**
chlorinated dibenzo-p-dioxins		
2,3,7,8-TCDD	1	1
1,2,3,7,8-PeCDD	1	1
1,2,3,4,7,8-HxCDD	0.1	0.1
1,2,3,6,7,8-HxCDD	0.1	0.1
1,2,3,7,8,9-HxCDD	0.1	0.1
1,2,3,4,6,7,8-HpCDD	0.01	0.01
OCDD	0.0001	**0.0003**
chlorinated dibenzofurans		
2,3,7,8-TCDF	0.1	0.1
1,2,3,7,8-PeCDF	0.05	**0.03**
2,3,4,7,8-PeCDF	0.5	**0.3**
1,2,3,4,7,8-HxCDF	0.1	0.1
1,2,3,6,7,8-HxCDF	0.1	0.1
1,2,3,7,8,9-HxCDF	0.1	0.1
2,3,4,6,7,8-HxCDF	0.1	0.1
1,2,3,4,6,7,8-HpCDF	0.01	0.01
1,2,3,6,7,8,9-HpCDF	0.01	0.01
OCDF	0.0001	**0.0003**
non-ortho substituted PCBs		
3,3',4,4'-tetraCB (PCB 77)	0.0001	0.0001
3,4,4',5-tetraCB (PCB 81)	0.0001	**0.0003**
3,3',4,4',5-pentaCB (PCB 126)	0.1	0.1
3,3',4,4',5,5'-hexaCB (PCB 169)	0.01	**0.03**
mono-ortho substituted PCBs		
2,3,3',4,4'-pentaCB (PCB 105)	0.0001	**0.00003**
2,3,4,4',5-pentaCB (PCB 114)	0.0005	**0.00003**
2,3',4,4',5-pentaCB (PCB 118)	0.0001	**0.00003**
2',3,4,4',5-pentaCB (PCB 123)	0.0001	**0.00003**
2,3,3',4,4',5-hexaCB (PCB 156)	0.0005	**0.00003**
2,3,3',4,4',5'-hexaCB (PCB 157)	0.0005	**0.00003**
2,3',4,4',5,5'-hexaCB (PCB 167)	0.00001	**0.00003**
2,3,3',4,4',5,5'-heptaCB (PCB 189)	0.0001	**0.00003**

Bold values indicate a change in TEF value.

Abbreviations: T/Pe/Hx/Hp/OCDD, Tetra / Penta / Hexa / Hepta / Octa chlorodibenzodioxin; T/Pe/Hx/Hp/OCDF, Tetra / Penta / Hexa / Hepta / Octa chlorodibenzofuran; (P)CB, (Poly)chlorinated biphenyl.

Recalculation of Total Dietary Intakes

13. Previously 1998 WHO TEF values were used to estimate the dietary intakes of UK toddlers, school children, adults and senior citizens, and this was reported in the Food Survey Information Sheet (FSIS) 38/03[11]. These dietary intakes have been recalculated using the 2005 TEF values. Table 2 summarises the estimated upper bound dietary intakes of all age groups of dioxins and dioxin-like PCBs in 2001. Recalculation using the 2005 TEF values has resulted in reductions in estimated dietary intakes for the majority of age groups and occasionally no change, when compared to the 1998 TEF values. For comparison, the estimated intakes based on 1998 TEF values have been included in brackets.

Table 2 Summary of estimated upper bound dietary intakes of all age groups of dioxins and dioxin-like PCBs in 2001 calculated using 2005 WHO-TEFs (1998 WHO-TEFs in brackets)

Age group	Average Dietary Intakes (pg WHO-TEQ/kg bw/day)			High Level Dietary Intakes (pg WHO-TEQ/kg bw/day)		
	Dioxins	PCBs	Dioxins +PCBs	Dioxins	PCBs	Dioxins +PCBs
Senior citizens *						
living at home	0.3 (0.3)	0.3 (0.4)	0.6 (0.7)	0.6 (0.7)	0.6 (0.8)	1.1 (1.4)
in old peoples' homes	0.4 (0.4)	0.4 (0.5)	0.7 (0.9)	0.6 (0.8)	0.7 (0.9)	1.3 (1.6)
Adults *	0.3 (0.4)	0.3 (0.5)	0.7 (0.9)	0.6 (0.7)	0.8 (1.0)	1.4 (1.7)
Schoolchildren *						
4-6 years	0.7 (0.9)	0.7 (0.9)	1.4 (1.8)	1.4 (1.7)	1.4 (1.8)	2.8 (3.4)
7-10 years	0.6 (0.7)	0.5 (0.7)	1.1 (1.4)	1.0 (1.2)	1.0 (1.4)	2.0 (2.5)
11-14 years	0.4 (0.4)	0.3 (0.5)	0.7 (0.9)	0.8 (0.9)	0.7 (1.0)	1.5 (1.9)
15-18 years	0.3 (0.3)	0.3 (0.4)	0.6 (0.7)	0.5 (0.6)	0.5 (0.7)	1.0 (1.3)
Toddlers *						
1.5-2.5 years	1.0 (1.1)	0.9 (1.1)	1.9 (2.2)	2.1 (2.5)	2.1 (2.5)	4.2 (4.8)
2.5-3.5 years	0.8 (0.9)	0.7 (1.0)	1.6 (1.9)	1.7 (1.9)	1.7 (2.1)	3.5 (4.0)
3.5-4.5 years	0.8 (0.8)	0.7 (0.9)	1.4 (1.7)	1.5 (1.7)	1.4 (1.8)	2.9 (3.4)
Population average**	0.3 (0.3)	0.2 (0.4)	0.5 (0.7)			

Notes: Combined dietary intakes of dioxins and dioxin-like PCBs may not equal the sum of the separate intakes due to rounding.

* Consumer dietary intakes estimated using food consumption data from the National Diet and Nutrition Survey Programme (NDNS).

** Estimated using food consumption data from the National Food Survey. This method cannot estimate high level intakes.

14. The UK TDI of 2 pg WHO-TEQ/kg bw/day is derived from data relating to 2,3,7,8-TCDD, a potent dioxin congener and point of reference for the TEF values of other congeners. Particularly, this TDI was established based on a study showing effects of 2,3,7,8-TCDD on the developing male reproductive system, mediated via the maternal body burden [12]. Therefore, since the TDI was set based on 2,3,7,8-TCDD which has a TEF of 1, the TDI is unaffected by the re-evaluation of individual TEF values.

15. Table 3, recalculated from Table 7 of FSIS 38/03[11], summarises the percentage of consumers of different age groups who were estimated to exceed the UK TDI for dioxins and dioxin-like PCBs from the whole diet in 2001. Recalculation using the 2005 TEF values resulted in reductions in the percentage of consumers estimated to exceed the TDI. 2,3,4,7,8-PeCDF constituted approximately 10% of the average adult consumer TEQ for dioxins and dioxin-like PCBs. Therefore, reduction of the TEF for this congener from 0.5 to 0.3 was responsible for the majority of the reduction in calculated dietary exposure.

Table 3 Percentage of consumers of different age groups who are estimated to exceed the UK TDI for dioxins and dioxin-like PCBs from the whole diet in 2001

Age group	1998 WHO-TEFs	2005 WHO-TEFs
Senior citizens		
living at home	0.1	0.0
in old peoples' homes	0.0	0.0
Adults	1.1	0.03
Schoolchildren		
4-6 years	35.0	14.0
7-10 years	10.0	3.0
11-14 years	1.7	0.0
15-18 years	0.0	0.0
all children	10.0	3.8
Toddlers		
1.5-2.5 years	48.0	34.0
2.5-3.5 years	35.0	23.0
3.5-4.5 years	28.0	16.0
all toddlers	37.0	25.0

16. These recalculations continue to show that an appreciable number of toddlers exceed the UK TDI, with the highest estimated exposures predominantly in the younger age group. The skewed distribution of intakes of individual toddlers is shown in Figure 1. This graph shows that, whilst there are a few outliers, the majority of toddlers have intakes close to the TDI. The TDI (2 pg WHO-TEQ/kg bw/day) lies on a steep gradient of the toddler distribution curve; hence, a small decrease in calculated TEQ can result in a large reduction in the percentage exceeding the TDI.

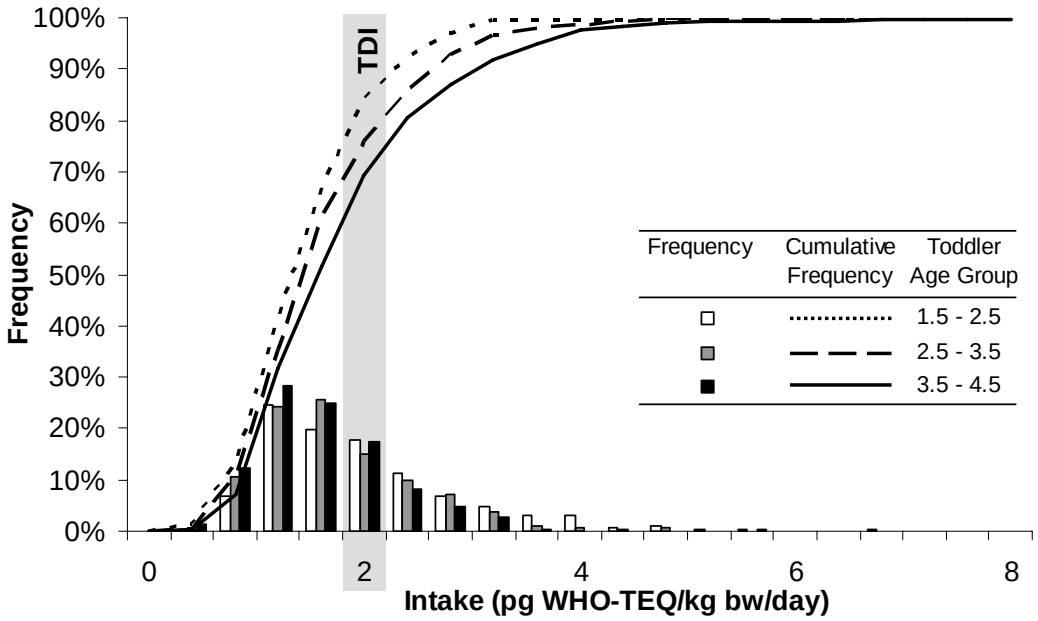

Figure 1 Toddlers' Dietary Intake of Dioxins and Dioxin-like Compounds Calculated using the 2005 TEF values

17. The NDNS programme does not gather consumption data for the 0 – 1.5 year age group; however, several surveys have been conducted by the Food Standards Agency, in order to assess the potential dietary exposure of this group. Surveys analysing infant formula[13] and baby food[14] indicate that these sources are unlikely to result in a dietary intake which exceeds the TDI. However, analysis of a small set of human breast milk samples indicated that infant dietary intakes, when recalculated using 2005 TEF values, are likely to be in the region of 35 pg WHO-TEQ/kg bw/day at 2 months, falling to 8 pg WHO-TEQ/kg bw/day at 10 months[15].

18. The health implications of exceeding the TDI at an early age are not clear. Previously, the Committee considered that, in view of the fact that the TDI was set based on effects on the developing male reproductive system mediated by maternal body burden, there was uncertainty with respect to whether similar effects would arise from post-natal exposure. However, the Committee concluded that there was no basis for assuming that the young infant is at increased risk[15]. Furthermore, recent publications suggest that the half lives of dioxin and certain other furan congeners in young children are considerably shorter than in adults[16,17]. Estimated exposures for all age groups have substantially declined since 1982 [11] and

it is anticipated that exposures will continue to decline in the future, due to the environmental controls already in place and those planned.

Development of the TEF Concept

19. The WHO Expert Panel noted that recent *in vivo* mixtures studies continue to demonstrate additivity, a tenet of the TEF concept. The Panel stated that PCB 126 could be used as a reference compound in rat studies with a REP of 0.1, but that further work is required to confirm that PCB 126 is suitable for use as a reference compound in mouse studies. It was considered that more research was also required for REP values in human systems to establish whether TEFs based on rodent species are also valid for humans.

20. The 'Ideal REP study design' was discussed and general guidelines suggested for both *in vivo* and *in vitro* studies. These are reported in van den Berg *et al.* [4]. The Panel recognised that criteria for weighted REP values, based on study type (*in vivo* versus *in vitro*, chronic versus acute, etc.), would be of value to future assessments.

21. The Panel noted that the current approach does not describe the range of REP values, and may reflect a bias in the judgement of the Expert Panel. Probabilistic methodology would require weighting factors to be applied to REPs determined in different types of study. Distribution of REPs would be expressed in terms of maximum and minimum values and would better describe the level of uncertainty. However, the Panel was concerned that varying degrees of conservatism might alter how these ranges are interpreted by national authorities.

22. Emerging evidence suggests that relative potency of several dioxins and dioxin-like compounds may differ when calculated based on administered dose versus tissue concentration (body burden). The possibility of using 'systemic TEFs', based on body burden, was raised by the Expert Panel. It was considered that, whilst from a biological and toxicological point of view, the use of systemic TEFs is recommended, at present the data are insufficient to develop this concept. The need to determine whether *in vitro* TEFs can be used as surrogates for systemic TEFs was highlighted. The Panel envisaged using systemic TEFs alongside intake TEFs for ingestion situations.

23. Concern was also expressed at the use of TEF values for abiotic matrices since TEF values have been developed primarily for calculating dietary exposure, with the greatest weight being placed on data from oral intake studies. The Expert Panel emphasised that, whilst calculating TEQ values may be useful for comparing abiotic matrices, factors such as fate, transport and bioavailability from each matrix should be specifically considered as part of the risk assessment.

Other Compounds for Potential Inclusion in the TEF Scheme

24. The Expert Panel considered the polybrominated dibenzo-p-dioxins (PBDDs) and dibenzofurans (PBDFs) should be given high priority for inclusion in the TEF scheme. A better human exposure analysis and more REP studies are required. Based on the AhR mechanism of action, inclusion of certain congeners of polybrominated biphenyls (PBBs) was also considered appropriate. However, further human exposure analysis should identify the possible relevance of PBBs to the total TEQ.

25. To address this exposure data requirement the FSA has surveyed samples from the 2003 and 2004 Total Diet Studies and related them to food consumption data[18]. In this analysis, TEF values for the chlorinated congeners were applied to brominated congeners based on advice provided by the committee[19]. This assumes equivalent potency and a similar structure activity relationship. This study estimated a dietary intake of <0.4 pg TEQ/kg bw/day for brominated dioxins and dioxin-like PBBs. On the basis of this information, the COT considered this intake did not raise additional toxicological concerns [20].

26. The Expert Panel noted that early *in vitro* studies suggest the mixed halogenated dibenzo-p-dioxins (PXCDDs) and dibenzofurans (PXCDFs) follow the same structure-activity rules as the PCDDs and PCDFs. It was felt that these should definitely be considered for inclusion in the scheme.

27. The possibility of contamination with more potent congeners requires attention before polychlorinated and brominated naphthalenes (PCNs and PBNs) can be considered for inclusion in the TEF scheme. Similar contamination issues also affect hexachlorobenzene (HCB). In addition confirmation of the dioxin-like properties of HCB are required before this compound can be considered for inclusion.

28. There is a need for more *in vivo* and *in vitro* information on PCB 37 (3,4,4'-TCB) in order to consider inclusion in the TEF scheme.

29. The Expert Panel considered that pure polybrominated diphenylethers (PBDEs) do not have AhR agonist properties and should not be included in the TEF scheme.

30. It was noted that non dioxin-like AhR ligands may modulate the effect of dioxin congeners and the potential impact of these compounds on the risk of toxicity posed by exposure to a particular level of TEQs should be further investigated.

Committee Discussion

31. Members reiterated that, in some instances, TEF values for individual congeners are based on a limited dataset. Where more data are available for an individual congener, there is commonly a large spread of REP values, which are based on a range of different toxicological endpoints. Owing to this inherent variability, the TEF values are, at best, order of magnitude estimates. It was also considered necessary to stress that, whilst TEFs are generally calculated based on administered dose, the toxicological endpoint used to derive the TDI was based upon maternal TCDD body burden. The TDI is expressed in terms of amount of TCDD (and hence TEQ) that would need to be ingested to achieve the 'tolerable body burden'. However, the amount of TEQ ingested on a daily basis is unlikely to directly reflect the total body burden of dioxins and dioxin-like compounds due to differences in the bioavailability and biological half-life of the various congeners.

32. Members highlighted that the TEF principle assumes that the toxicity of these compounds is mediated by a common aryl hydrocarbon receptor (AhR) mediated mechanism. It was noted that the possibility of non-AhR mediated toxicity should be considered if TEF values were substantially lowered.

33. Concern was expressed that an appreciable number of toddlers exceed the TDI and that exposure is likely to be higher in breast fed babies. Previously, the COT noted that intake is highest during breast feeding and that concentrations of dioxins in breast milk have decreased in recent years, in line with decreases in dietary exposure. Continuing controls on emissions to the environment are expected to further reduce dietary intake in the future.

Conclusions

34. We agree with the scientific rationale for the re-evaluated TEF values; although we concur with the opinion of the WHO Expert Panel, that this should be thought of as an 'interim' methodology, until a more suitable method of estimating risk from dioxins and dioxin-like compounds can be found.

35. We conclude that the revision of the TEFs does not raise additional concerns regarding exposure to dioxins and dioxin-like compounds, and that they should be used in future UK assessments of dietary exposure.

COT
December 2006

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