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

COT STATEMENT ON OCCURRENCE OF MIXED HALOGENATED DIOXINS AND BIPHENYLS IN UK FOOD

Introduction

1. The Food Standards Agency (FSA) has recently completed a study that analysed 19 mixed halogenated (chlorinated and brominated) dibenzo-*p*-dioxins (PXDDs), dibenzofurans (PXDFs) and biphenyls (PXBs) in samples of fish, shellfish, meat and eggs consumed in the UK. This was the first study to measure levels of PXDDs, PXDFs and PXBs in food. The research report will be published on foodbase (http://foodbase.org.uk/), the Food Standards Agency's open access repository.

2. The Committee was asked by FSA to consider the results and to advise on whether the measured levels of these PXDDs, PXDFs and PXBs indicated a health concern. Data on the concentrations of PXDDs, PXDFs and PXBs in food consumed in the UK have not been available previously. The Committee was also provided with data on levels of polychlorinated dibenzo-*p*-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), dioxin-like polychlorinated biphenyls (PCBs), polybrominated dibenzo-*p*-dioxins (PBDDs), polybrominated dibenzofurans (PBDFs) and dioxin-like polybrominated biphenyls (PBBs) measured in the same food samples.

Dioxins and dioxin-like organic contaminants

3. Dioxins, a group of 75 PCDD and 135 PCDF congeners, are persistent organochlorine compounds that are widely dispersed environmental contaminants and accumulate in fatty foods. Dioxins can be formed as a result of thermal reactions and as trace contaminants in the synthesis of some chemicals and some industrial processes. PBDDs and PBDFs are closely related in structure to PCDDs and PCDFs, having bromine instead of chlorine substitutions in the hydrocarbon rings. They are not intentionally produced (except for scientific purposes) but, like dioxins, are generated as undesired by-products in various processes. In experimental animal models, exposure to PBDDs or PBDFs is reported to result in many of the

effects typically produced by PCDDs and PCDFs. Figure 1 illustrates the dioxin and furan structure and substituent positions.

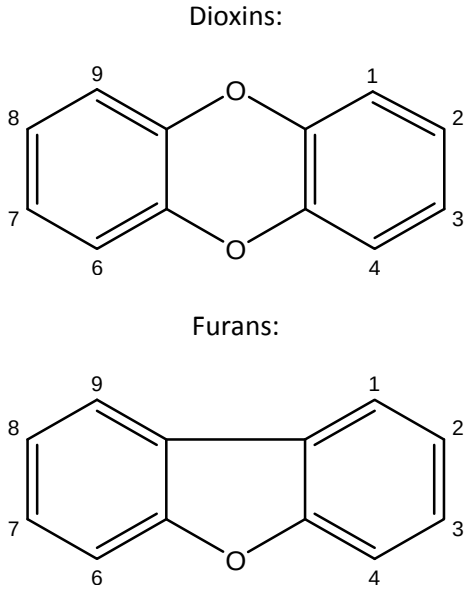

Figure 1. Chemical structures of dioxin (above) and furan (below) rings indicating substituent positions.

4. PCBs are persistent organochlorine chemicals that are no longer manufactured, but which may be released to the environment during disposal of obsolete electrical equipment and other materials. Twelve non-*ortho* and mono-*ortho* PCBs, of the 209 theoretically possible PCB congeners, exhibit biological activity similar to that of dioxins and are, therefore, referred to as dioxin-like PCBs. PBBs are analogous to PCBs but having bromine instead of chlorine substitutions in the hydrocarbon rings, and were formerly used as additive flame retardants.

5. Exposure of the general population to dioxins and dioxin-like compounds is primarily from food[1,2]. Exposures for all age groups estimated from the UK Total Diet Study declined substantially over the 2 decades from 1980 [2]. Environmental levels of dioxins have continued to decline[9].

6. PXDDs, PXDFs and PXBs are structurally similar to PCDDs/PCDFs/PCBs and PBDDs/PBDFs/PBBs but with mixed bromine and chlorine substitutions in the hydrocarbon rings rather than solely chlorine or bromine respectively. Theoretically 4600 individual PXDDs and PXDFs and 9180 PXBs are possible. Except for some PXBs produced for research purposes, mixed halogenated dioxins, furans and biphenyls have never been produced commercially.

Previous COT evaluations of dioxins and dioxin-like biphenyls.

7. The COT has considered dioxins on multiple occasions. Notably in 2001, COT set a tolerable daily intake (TDI) of 2 pg WHO-TEQ/kg bw/day† to protect against the most sensitive effect of dioxins. This was considered to be impaired development of the fetal male reproductive system leading to decreased sperm quality, caused by fetal exposure *in utero* and correlated with the maternal body burden of dioxins[2]. In 2006 the Committee endorsed the revised WHO-TEFs (2005 WHO-TEFs) proposed following a WHO-IPCS re-evaluation of TEF values based on a recently published relative effect potency (REP) database[3,4,5]. However the TDI was numerically unchanged as it was based on data on TCDD. In 2007 COT considered the results of a FSA funded developmental toxicity study which aimed to address some of the limitations identified by the Committee in the studies used for setting the TDI in 2001. The Committee concluded that this study was valuable in clarifying some of the uncertainties in their 2001 risk assessment. In the new study, the most sensitive effect of dioxin was a delay in puberty, rather than altered sperm quality. However, this was observed at levels of dioxin exposure that were similar to those used as the basis for the 2001 TDI. Thus, the Committee concluded that the study provided additional evidence that the existing TDI of 2 pg/kg bw/day was protective [6].

8. In December 2005 COT discussed key toxicological data for the PBDDs/PBDFs and dioxin-like PBBs and concluded that TEFs developed for the chlorinated dioxins could be used as an indication of the dioxin-like activity of the PBDDs, PBDFs and dioxin-like PBBs (see paras 12-16 below). Moreover combining the TEQs of the chlorinated and brominated compounds to provide an indication of the total dioxin-like activity would be more protective of public health than performing risk assessments for either chlorinated or brominated compounds separately. [7].

FSA funded study on mixed halogenated dioxins, furans and biphenyls.

Selection of mixed halogenated dioxins, furans and biphenyls for analysis.

9. The PXDDs, PXDFs and dioxin–like PXBs in the FSA funded study were selected for analysis based on chemical configuration, type and degree of halogenation, and limited knowledge of their toxicological properties and levels of environmental occurrence. In particular compounds containing 2,3,7,8 substitutions were targeted because chlorinated and brominated congeners with these substitutions generally have higher TEFs. However, the final selection of 19 compounds for analysis in food (6 dioxins, 7 furans and 6 biphenyls (table 1)) was also determined by practical considerations such as the availability of standards and ability to synthesize such standards within the time frame of the project.

† Toxicity Equivalency Factors (TEFs) allow concentrations of the less toxic dioxin-like compounds (16 PCDDs/PCDFs and 12 PCBs) to be expressed as a concentration equivalent to the most toxic dioxin 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). These toxicity-weighted concentrations are then summed to give a single value, which is expressed as a Toxic Equivalent (TEQ). The system of TEFs used in the UK and a number of other countries is that set by the World Health Organisation (WHO), and the resulting overall concentrations are referred to as WHO-TEQs.

Table 1. Congeners measured

Analyte	Configuration	Degree of halogenation	Equivalent chlorinated congener	2005-WHO TEF of chlorinated congener
Dioxins	2-Br-7,8-Cl-DD	Tri		
	2-Br-3,7,8-Cl-DD	Tetra	2,3,7,8-TCDD	1
	2,3-Br-7,8-Cl-DD	**Tetra**	2,3,7,8-TCDD	1
	1-Br-2,3,7,8-Cl-DD	**Penta**	1,2,3,7,8-PCDD	1
	2-Br-1,3,7,8-Cl-DD	Penta	1,2,3,7,8-PCDD	1
	2-Br-3,6,7,8,9-Cl-DD	Hexa	1,2,3,4,7,8-HCDD	0.1
Furans	**2-Br-7,8-Cl-DF**	**Tri**	2,7,8-TCDF	-
	2-Br-6,7,8-Cl-DF	Tetra	2,6,7,8-TCDF	-
	3-Br-2,7,8-Cl-DF	**Tetra**	2,3,7,8-TCDF	0.1
	2,3-Br-7,8-Cl-DF	Tetra	2,3,7,8-TCDF	0.1
	1-Br-2,3,7,8-Cl-DF	Penta	1,2,3,7,8-PCDF	0.03
	4-Br-2,3,7,8-Cl-DF	**Penta**	2,3,4,7,8-PCDF	0.3
	1,3-Br-2,7,8-Cl-DF	Penta	1,2,3,7,8-PCDF	0.03
Biphenyls	**4'-Br-3,3',4,5-Cl-B**	**Penta**	PCB 126	0.1
	3,4-Br-3',4',5'-Cl-B	Penta	PCB 126	0.1
	3',4',5-Br-3,4-Cl-B	Penta	PCB 126	0.1
	4'-B-2,3,3',4-C	**Penta**	PCB 105	0.00003
	4'-B-2,3',4,5-CB	Penta	PCB 118	0.00003
	4'-B-2,3,3',4,5-CB	Penta	PCB 156	0.00003

Bold type indicates congeners for which ^{13}C-labelled standards were available

Analytical methodology and levels in food.

10. Analytical methods for the measurement of PXDDs, PXDFs and PXBs were developed based on high resolution mass spectrometry. The method was validated and used to measure concentrations of PXDDs, PXDFs and PXBs in around 100 food samples. The limits of detection that were achieved were similar to those in earlier analyses for chlorinated dioxins and biphenyls and ranged from 0.005 to 0.02 ng/kg fat depending on the congener and type of food.

11. PXDDs, PXDFs and PXBs were detected in common items of retail food. Whilst the frequency of detection and measured concentrations varied according to the type of food, levels generally followed the order – biphenyls > furans > dioxins. The mono-brominated PXDDs, PXDFs and PXBs (i.e. those with one bromine substituent and chlorine substituents elsewhere) were observed in food samples more frequently than di- or tri-brominated PXDDs, PXDFs and PXBs (i.e. those with two or three bromine substituents and chlorine substituents elsewhere). Whilst most of the foods analysed contained at least some of the PXDDs, PXDFs and PXBs, detection rates and concentrations were higher for samples of shellfish, fish and liver.

Applicability of the TEFs for chlorinated congeners to the brominated and mixed halogenated dioxins, furans and biphenyls.

12. In experimental animal models, PBDDs and PBDFs are reported as producing "the classic effects demonstrated for PCDDs and PCDFs, and TCDD-like responses have also been measured *in vitro*"[7]. Additionally, limited toxicokinetic data for the PBDDs and PBDFs indicate that the half-lives in rats are similar to those of PCDDs and PCDFs. The vast majority of data are for the 2,3,7,8-tetrabrominated dioxins and furans, which, like TCDD and TCDF, are considered to be the most toxic. PBDDs/PBDFs are believed to share a common mechanism of action with PCDDs/PCDFs, the first step of which involves binding to the aryl hydrocarbon receptor (AhR). Results from *in vitro* studies to assess activation of the AhR and estimate the relative potency of several PBDD/PBDFs indicate that at the receptor level the activity of PBDDs, PBDFs and dioxin-like PBBs are broadly comparable to their chlorinated congeners. The majority of PBDDs and PBDFs had similar or lower relative potencies than the corresponding PCDD/PCDFs.

13. In 1997, a WHO working group concluded that 'at present, insufficient environmental and toxicological data are available to establish a TEF value' for these compounds[8]. However, the WHO[4] report on PBDDs and PBDFs discussed the concept of using TEFs for the assessment of these chemicals and suggested that preliminary use of the same TEF values for the brominated congeners as are used for the corresponding chlorinated analogues appeared to be justified.

14. On the basis of the available data, COT concluded that TEFs developed for PCDDs, PCDFs and dioxin-like PCBs could be used as an indication of the dioxin-like activity of the PBDDs, PBDFs and dioxin-like PBBs. However, the Committee highlighted that this was tentative advice due to uncertainties in the available data on comparative toxicokinetics in rodents and humans, and a lack of chronic dosing studies with these compounds

15. The toxicological database for PXDDs, PXDFs and dioxin-like PXBs in experimental animals and *in vitro* is even more limited than for PBDDs, PBDFs and dioxin-like PBBs. However the limited data available are consistent with the effects observed with PCDDs, PCDFs and dioxin-like PCBs. The majority of PXDDs, PXDFs and PXBs tested had comparable or lower relative potencies than the corresponding PCDD, PCDFs and dioxin-like PCBs[7,10.11,12,13]. Although unable to establish TEF values for PXDDs, PXDFs and dioxin-like PXBs due to insufficient environmental and toxicological data, the WHO considered that the concept of using TEFs for the assessment of PXDDs, PXDFs and dioxin-like PXBs was valid.

16. The Committee concluded that the arguments described above for applying the TEFs for PCDDs, PCDFs and dioxin-like PCBs to the PBDDs, PBDFs and dioxin-like PBBs would also apply to PXDDs, PXDFs and dioxin-like PXBs. However, as the toxicological database for PXDDs, PXDFs and dioxin-like PXBs was even more limited, the uncertainty associated with the approach would be greater than for the PBDDs, PBDFs and dioxin-like PBBs. The Committee considered that the evidence overall suggested that PCDD, PCDFs and dioxin-like PCBs have higher relative potencies than either PBDDs, PBDFs and dioxin-like PBBs or PXDDs, PXDFs and dioxin-like PXBs.

Estimated exposures to mixed halogenated, chlorinated and brominated dioxins, furans and biphenyls in fish, meat, offal and eggs.

17. The limited number of foods surveyed was not adequate for assessment of total dietary exposure to PXDDs, PXDFs and PXBs. However, it was possible to compare levels of PXDDs, PXDFs and PXBs with PCDDs/PCDFs/PCBs and PBDDs/PBDFs/PBBs measured in the same food samples, albeit estimates for these PCDDs/PCDFs and PBDDs/PBDFs also included contributions from the hexa, hepta and octa-substituted congeners. For this purpose, exposures were estimated on a pg TEQ/kg bodyweight (b.w.) basis for a single portion of fish, offal and meat or a single egg applying the TEFs for PCDDs/PCDFs/PCBs to the corresponding PBDDs/PBDFs/PBBs and PXDDs, PXDFs and PXBs. The estimates are summarised in tables 2-5. Estimation of total dietary exposure would need to take into account the amounts of these foods consumed as well as exposure from other foods.

Table 2. Estimates of exposure to mixed halogenated dioxin and biphenyl congeners, expressed as pg TEQ/kg b.w., from consumption of one portion of fish.

Fish	**Mixed halogenated dioxins pg TEQ/kg b.w.**	**Polybrominated dioxins pg TEQ/kg b.w.**	**Polychlorinated dioxins pg TEQ/kg b.w.**
Oily fish	0.01 – 0.14	0.04 - 0.19	2.0 – 9.1
Shellfish	0.005 – 0.02	0.024 – 0.22	0.046 – 2.1
Eel	0.01 – 0.03	0.02 – 1.5	0.79 – 4.5
Smoked oily fish	0.02 – 0.05	0.07 – 3.0	1.1 – 3.0

n.m. – not measured
Portion size of 140g or 70g, depending on type of fish as described previously[7] ; based on 60kg b.w. person

Table 3. Estimates of exposure to mixed halogenated dioxin and biphenyl congeners, expressed as pg TEQ/kg b.w., from consumption of one portion of offal.

Offal		**Mixed halogenated dioxins pg TEQ/kg b.w.**	**Polybrominated dioxins pg TEQ/kg b.w.**	**Polychlorinated dioxins pg TEQ/kg b.w.**
Liver	Deer	0.05- 0.8	0.18	5.8 - 6.02
	Ox	0.01	0.12	0.18
	Lamb	0.01 - 0.02	0.2597	0.63 – 1.785
	Pork	0.06*	0.12	0.32
	Chicken	0.02 – 0.04	0.03 – 0.06	0.03
Kidney	Ox	0.005	0.02	0.1
	Lamb	0.004	0.05	0.12

Portion size of 100g; based on 60kg b.w. person
* Results from more than one sample

Table 4. Estimates of exposure to mixed halogenated, brominated and chlorinated dioxin and biphenyl congeners expressed as pg TEQ/kg b.w., from consumption of one portion of meat.

Meat	Mixed halogenated dioxins pg TEQ/kg b.w.	Polybrominated dioxins pg TEQ/kg b.w.	Polychlorinated dioxins pg TEQ/kg b.w.
Beef joint	0.008 – 0.012	0.034	0.12 – 0.42
Beef processed	0.09 – 0.013	0.034 – 0.052	0.25 – 0.30
Lamb joint	0.007 – 0.022	0.044	0.18 – 0.63
Lamb mince	0.013 – 0.015	0.044	0.58 – 0.65
Mutton	0.007	n.m.	0.27
Chicken	0.005 – 0.006	0.06	0.12 – 0.15
Duck	0.06	n.m.	2.8

n.m. – not measured
Portion size of 100g; based on 60kg b.w. person

Table 5. Estimates of exposure to mixed halogenated dioxin and biphenyl congeners expressed as pg TEQ/kg b.w., from consumption of one egg

Eggs	Mixed halogenated dioxins pg TEQ/kg b.w.	Polybrominated dioxins pg TEQ/kg b.w.	Polychlorinated dioxins pg TEQ/kg b.w.
Organic free range hen eggs	0.002	0.026	0.15
farmhouse hen eggs	0.004	0.018	0.042
Organic hen eggs,	0.008	0.026	0.66
Omega 3 free range hen eggs	0.002	0.026	0.04
Duck eggs	0.009	0.06	0.83
Gull eggs	0.15	n.m.	5.7

n.m. – not measured
Portion size of one egg; based on 60kg b.w. person

18. The effect of the contribution from the hexa, hepta and octa-substituted congeners was estimated for PCDDs, PCDFs and dioxin-like PCBs. The percentage contribution for fish and meat was around 10% whilst for eggs and offal it was around 20-25%. After taking this contribution into account there remained two orders of magnitude difference in the contribution to the TEQ from PCDDs, PCDFs and dioxin-like PCBs compared to PXDDs, PXDFs and dioxin-like PXBs.

Dietary exposure to mixed halogenated dioxin and biphenyl congeners.

19. Dietary exposure to the chlorinated dioxins has been estimated using upper bound data for concentrations of PCDDs, PCDFs and dioxin-like PCBs in food groups from the 2001 Total Diet Study (expressed in terms of 2005 WHO-TEFs), combined with information on the distribution of individuals' food consumption patterns from the National Diet and Nutrition Survey (NDNS)[5]. High level (97.5th percentile) dietary exposure of adult consumers in the UK was estimated to be 1.4 pg WHO-TEQ/kg bw/day. The upper bound approach assumes that all undetected congeners were present at the reporting limit and is thus likely to overestimate actual exposure.

20. Although it was not possible to produce reliable dietary estimates for the PXDDs, PXDFs and dioxin-like PXBs, estimates of the contribution of the measured PXDDs, PXDFs and dioxin-like PXBs and of the corresponding PBDDs, PBDFs and dioxin-like PBBs relative to the corresponding PCDDs, PCDFs and dioxin-like PCBs were made for those food samples for which levels of all three had been measured. The TEQs for the PBDDs, PBDFs and dioxin-like PBBs were generally 1 or more orders of magnitude lower than the TEQs for PCDDs, PCDFs and dioxin-like PCBs in these samples, whilst the PXDDs, PXDFs and dioxin-like PXBs were generally 2 or more orders of magnitude lower than the TEQs for PCDDs, PCDFs and dioxin-like PCBs. Thus, assuming the relative concentrations in these food samples were representative of those in other foods, the PBDDs, PBDFs and dioxin-like PBBs would be expected to contribute 10% or less to the overall TEQ intake and the measured PXDDs, PXDFs and dioxin-like PXBs 1% or less.

21. The 19 PXDDs, PXDFs and dioxin-like PXBs measured in the samples were only a minority of possible PXDD, PXDF and dioxin-like PXB congeners. However, they included a higher proportion of the congeners which would be expected to have high TEFs (i.e. 10% of those possible with a 2,3,7,8 configuration) than of congeners which would be expected to have low or zero TEFs. Therefore, additional allowance for other PXDDs, PXDFs and dioxin-like PXBs would not be expected to increase materially the contribution to the overall TEQ intake for combined dioxin exposure.

22. The measured PXDDs, PXDFs and dioxin-like PXBs would be expected to contribute 1% or less to the overall TEQ intake when the TEFs for the PCDDs, PCDFs and dioxin-like PCBs are used for the corresponding PXDDs, PXDFs and dioxin-like PXBs. The study measured 10% of the possible congeners containing four or more halogen atoms that include a 2,3,7,8 configuration. If we assume that there are similar prevalences of the remaining PXDDs and PXDFs with these structural elements, the total expected contribution would be 10% or less of the overall TEQ intake. The relative potencies of the PXDDs and PXDFs containing four or more halogen atoms, including a 2,3,7,8 configuration would need to be at least four-fold greater than those of the corresponding PCDDs, PCDFs and dioxin-like PCBs before the combined total TEQ for high level adult consumers was greater than the TDI. However, as noted in paragraph 16, the evidence overall suggests that PCDD, PCDFs and dioxin-like PCBs have higher relative potencies than PXDDs, PXDFs and dioxin-like PXBs.

Conclusions.

23. The new data demonstrated that mixed halogenated dioxins, furans and biphenyls are detectable in a range of food samples that also contained chlorinated and brominated dioxins, furans and biphenyls.

24. The TEFs developed for the PCDDs, PCDFs and dioxin-like PCBs were used as an indication of the dioxin-like activity of the corresponding PXDDs, PXDFs and dioxin-like PXBs congeners. This approach is consistent with the Committee's previous conclusions on PBDDs, PBDFs and dioxin-like PBBs in 2006. However, as the toxicological database for PXDDs, PXDFs and dioxin-like PXBs was even more limited, the uncertainty associated with the approach is greater than for the PBDDs, PBDFs and dioxin-like PBBs. By combining the TEQs for the PXDDs, PXDFs and dioxin-like PXBs contaminants with the TEQs for the PCDDs, PCDFs and dioxin-like PCBs and PBDDs, PBDFs and dioxin-like PBBs, it was possible to obtain an indication of the combined toxic potential of dietary exposure to chemicals with dioxin-like properties, that would be more protective of public health than assessing the individual chemicals separately. This approach is conservative as the evidence overall suggests that PCDDs, PCDFs and dioxin-like PCBs have higher relative potencies and lower clearances than either PBDDs, PBDFs and dioxin-like PBBs or PXDDs, PXDFs and dioxin-like PXBs.

25. Based on the levels estimated per portion of the foods surveyed, the PCDDs, PCDFs and dioxin-like PCBs are likely to be the major contributors to the total TEQ. Assuming that the measured congeners were representative, PXDDs, PXDFs and dioxin-like PXBs are likely to be a minor contributor to the total TEQ. The estimated high level adult dietary exposure to PCDDs, PCDFs and dioxin-like PCBs was 1.4 pg/kg bw/day[5], which is only 70% of the TDI of 2 pg/kg bw/day. Thus, the measured levels of PXDDs, PXDFs and dioxin-like PXBs do not indicate a health concern.

26. Levels of PCDD, PCDFs and dioxin-like PCBs in food and the environment have decreased substantially since the 1980s. Since PXDDs, PXDFs and dioxin-like PXBs are not intentionally manufactured and would be generated in the environment by similar mechanisms to other dioxins, it is probable that controls on PCDD, PCDFs and dioxin-like PCBs would also limit environmental levels of PXDDs, PXDFs and dioxin-like PXBs.

27. The most important uncertainty in this risk assessment was the lack of toxic equivalency factors for the mixed halogenated dioxins, furans and biphenyls, and the consequent reliance on toxic equivalency factors for the corresponding PCDDs, PCDFs and dioxin-like PCBs. However, even if the TEFs for PXDDs, PXDFs and dioxin-like PXBs were up to four fold higher than assumed, their contribution to the total TEQ in the diet would still be small. Thus, further research on PXDDs, PXDFs and dioxin-like PXBs is not considered a priority.

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Abbreviations.

b.w.	bodyweight
FSA	Food Standards Agency
PBDDs	polybrominated dibenzo-*p*-dioxins
PBDFs	polybrominated dibenzofurans
PBBs	dioxin-like polybrominated biphenyls
PCDDs	polychlorinated dibenzo-*p*-dioxins
PCDFs	polychlorinated dibenzofurans
PCBs	dioxin-like polychlorinated biphenyls
PXDDs	mixed halogenated (chlorine and bromine) dibenzo-*p*-dioxins
PXDFs	mixed halogenated (chlorine and bromine) dibenzofurans
PXBs	mixed halogenated (chlorine and bromine) biphenyls
REP	relative effect potency
TCDD	2,3,7,8-tetrachlorodibenzo-*p*-dioxin
TDI	tolerable daily intake
TEFs	Toxicity Equivalency Factors
TEQ	Toxic Equivalents
WHO	World Health Organisation
WHO-TEFs	World Health Organisation Toxicity Equivalency Factors
WHO-TEQs	World Health Organisation Toxic Equivalents