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

STATEMENT ON ORGANIC CHLORINATED AND BROMINATED CONTAMINANTS IN SHELLFISH, FARMED AND WILD FISH

Introduction

1. The Food Standards Agency has recently completed two surveys that analysed 47 species of farmed and wild fish and shellfish consumed in the UK to determine the concentrations of a number of organic contaminants:

   i) Polychlorinated dibenzo-*p*-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs) and polychlorinated biphenyls (PCBs); and

   ii) Brominated flame retardants (BFRs), i.e. polybrominated biphenyls (PBBs), polybrominated diphenyl ethers (PBDEs), hexabromocyclododecane (HBCD) and tetrabromobisphenol A (TBBPA) as well as polybrominated dibenzo-*p*-dioxins (PBDDs) and polybrominated dibenzofurans (PBDFs) which occur as contaminants in brominated organic chemicals.

2. The Committee was invited to consider the data and advise on whether they form a basis for the Food Standards Agency to amend its advice on fish consumption. The Agency's current advice on fish consumption is based upon the report of the Scientific Advisory Committee on Nutrition (SACN) and the COT review 'Advice on fish consumption: benefits and risk', published in 2004 [1]. Data on the concentrations of PBDDs, PBDFs and PBBs in fish consumed in the UK have not been available for consideration previously.

Dioxins and dioxin-like organic contaminants

Polychlorinated dibenzo-p-*dioxins, dibenzofurans and dioxin-like PCBs,*

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.

4. PCBs are persistent organochlorine chemicals that are no longer manufactured, but may be released to the environment during disposal of materials and obsolete electronic equipment. Twelve non-*ortho* or mono-*ortho*

PCBs, of the 209 theoretically possible PCB congeners, exhibit similar biological activity to dioxins and are, therefore, referred to as dioxin-like PCBs.

5. Exposure of the general population to dioxins and dioxin-like PCBs is primarily from food [2,3]. The estimated exposures from the UK Total Diet Study samples for all age groups have declined substantially over the past 2 decades [3]. Based on occurrence and consumption in 2000/1, the most recent estimates of dietary exposure were in the region of 0.8 and 1.6 pg WHO-TEQ/kg bw/day for average and 97.5th percentile consumers [1].

Previous COT evaluations

6. In 2001, COT set a TDI of 2 pg WHO-TEQ/kg bw/day[†] to protect against the most sensitive effect of dioxins. This is considered to be impaired development of the fetal male reproductive system, caused by fetal exposure *in utero* and correlated with the maternal body burden of dioxins [3].

7. SACN/COT [1] considered risks and benefits of consuming more oily fish than the recommended "at least two portions of fish per week, one of which should be oily." They recommended that in considering fish consumption the TDI of 2 pg WHO-TEQ/kg bw/day should be applied to women of reproductive age and girls, the most susceptible subgroup, by virtue of exposure of fetuses that they might bear. Other populations, particularly women past child-bearing age and men, are not at risk of the developmental effects and are likely to be less susceptible to dioxin toxicity. The most sensitive and relevant non-developmental effect was considered to be increased cancer risk. An alternative safety guideline level of 8 pg WHO-TEQ/kg bw/day was proposed for these groups to be used to indicate a long term average intake that would not be expected to be associated with an increase in cancer risk.

8. Together with the nutritional advice the guideline ranges for oily fish consumption were:

- Women of reproductive age and girls should aim to consume within the range of one to two portions of oily fish a week, based on maintaining consumption of dioxins and dioxin-like PCBs below the tolerable daily intake (TDI) of 2 pg WHO-TEQ/kg bodyweight per day.
- Women past reproductive age, boys and men should aim to consume within the range of one to four portions of oily fish a week, based on maintaining consumption of dioxins and dioxin-like PCBs below the guideline value of 8 pg WHO-TEQ/kg bodyweight per day.

[†] 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.

9. In order to avoid providing over-complicated instructions that could be a deterrent to fish consumption as a whole, the general guidelines on fish consumption were based on an overview of the concentrations of contaminants previously detected in a range of commonly consumed fish [4,5,6].

Non-dioxin-like PCBs

10. A recent EFSA evaluation concluded that the simultaneous exposure to non-dioxin-like PCBs and dioxin-like compounds hampers the interpretation of the results of the toxicological and epidemiological studies. The data were insufficient to set tolerable intake levels and it was recommended that continued effort to lower the levels of non-dioxin-like PCBs in food is warranted (http://www.efsa.eu.int/science/contam/contam_opinions/1229_en.html).

Polybrominated dibenzo*-p-*dioxins, polybrominated dibenzofurans and dioxin-like polybrominated biphenyls

11. A group of substances that have been found as contaminants in brominated organic chemicals, in particular BFRs, are the PBDDs and PBDFs. PBDDs/PBDFs are structurally closely related to chlorinated dioxins and furans. They are not intentionally produced (except for scientific purposes) but, as with dioxins, are generated as undesired by-products in various processes. They can be formed by chemical, photochemical, or thermal reactions from precursors. In experimental animal models, exposure to PBDDs or PBDFs is reported to result in many of the effects typical for the chlorinated dioxins.

12. Theoretically, 75 PBDDs and 135 PBDF congeners are possible, and as with the chlorinated analogues the most toxic congeners are reported to be those substituted at the 2, 3, 7, and 8 positions [7]. In experimental animal models, PBDDs and PBDFs are reported as producing the classic effects demonstrated for the chlorinated dioxins and furans. These include lethality, wasting, thymic atrophy, teratogenesis, reproductive effects, chloracne, immunotoxicity, enzyme induction, decreases in T4 and vitamin A, and increased hepatic porphyrins. TCDD-like responses have also been measured *in vitro*, including enzyme induction, anti-estrogenic activity in human breast cancer cells, and transformation of mouse macrophages into tumour cells [7].

13. Additionally, limited toxicokinetic data for the brominated dioxins and furans indicate that the half-lives in rats are similar to those of their chlorinated analogues [8,9,10]. The vast majority of data are for the 2,3,7,8-tetrabrominated dioxin and furan, which are considered to be the most toxic. Golor and colleagues compared the kinetics of three pairs of corresponding polychlorinated and polybrominated dioxins and furans in Wistar rats monitored for ninety five days following a single dose (subcutaneous injection) [9]. Elimination rates from the liver and adipose tissue of both the 2,3,4,5,8-penta-chloro- and bromo-dibenzofuran congeners were similar, and the same was also the case for the 1,2,3,7,8-penta-chloro- and bromo-dibenzo-*p*-dioxin congeners. However, in the case of the 2,3,7,8-tetrahalogenated dibenzofurans,

the chlorinated congener was rapidly eliminated from liver and adipose tissue in the rat, whereas the brominated congener was much more slowly eliminated from both tissues.

14. Both 2,3,7,8-TBDD and 2,3,7,8-TBDF are developmental toxicants in mice at subcutaneous and oral doses that do not produce maternal toxicity or fetal mortality. The LOAELs (in µg/kg bw) for hydronephrosis and cleft palate after a single oral dose to pregnant mice on gestation day 10 were, respectively, 3 and 48 for TBDD, 25 and 200 for TBDF, 400 and 2400 for 2,3,4,7,8-PeBDF and 500 and 3000-4000 for 1,2,3,7,8-PeBDF [11]. The dose-response curves for the induction of cleft palate by the four brominated compounds were parallel to that of TCDD, supporting a common mechanism of action involving the AhR. The results indicated that bromination decreased the teratogenic activity of TBDD relative to TCDD and of both PeBDFs relative to the chlorinated analogues. However, substitution of bromines for chlorines increased by two-fold the teratogenic potency of TBDF relative to TCDF.

15. 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). A number of recent *in vitro* studies have used the ethoxyresorufin-O-deethylase (EROD) assay [12,13] or the chemical-activated luciferase gene expression (CALUX) assay [14,15] to assess activation of the AhR and estimating the relative potency of several PBDD/PBDFs. Results from these studies indicate that at the receptor level the activity of brominated dibenzo-*p*-dioxins, dibenzofurans and biphenyls are broadly comparable to their chlorinated congeners. The majority of PBDDs and PBDFs had comparable or lower relative potencies than the PCDD/PCDFs.

16. Polybrominated biphenyls (PBBs) are brominated hydrocarbons formerly used as additive flame retardants. As such these substances were added, rather than chemically bound, to plastics used in a variety of consumer products, such as computer monitors, television, textiles and plastic foams, and were able to leave the plastic and enter the environment. They are structurally similar compounds in which 2-10 bromine atoms are attached to the biphenyl molecular structure. In total, as with the structurally similar PCBs, 209 different PBB congeners are possible.

17. Individual PBB congeners vary in their pattern of toxicity. PBBs have been categorised on a similar structural basis as the PCBs, with category I comprising congeners lacking *ortho* substituents (coplanar PBBs). Coplanar PCBs are dioxin-like with regards to their toxicity and are included in the toxicity equivalency factor (TEF) concept. A number of PBB effects are dioxin-like and consistent with the AhR-mediated mechanism of action, including altered vitamin A homeostasis, thymic atrophy, dermal and ocular effects (e.g. chloracne and inflammation of eyelids), and body weight changes (wasting syndrome). This is determined by the magnitude of the response that is initiated by binding with the AhR. The binding affinity, in turn, is determined by the substitution pattern of the congener, many of the most toxic congeners resemble the structural configuration of 2,3,7,8-TCDD. The dioxin-like coplanar PBB-169 (3,3',4,4',5,5'-hexaBB) has been found to be the most toxic congener

in several test systems [16]. However, this congener was present at low concentrations in commercial PBB mixtures and may not contribute significantly to the exposure profile for PBB congeners.

18. Category II comprises mono-*ortho* substituted derivatives and other PBBs, mainly those with two or more *ortho* bromines, are in category III. These congeners are not considered to have dioxin-like properties [17].

Preliminary advice from COT on combination of brominated dioxins, furans and biphenyls

19. In December 2005 COT discussed the key toxicological data for the PBDDs/PBDFs and dioxin-like PBBs. The limited data available supported the conclusion that these compounds share a common mechanism of action with their chlorinated analogues. Therefore, TEFs used in the assessment of chlorinated dioxins and dioxin-like PCBs, might have potential application to the assessment of PBDDs/PBDFs. 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 [18]. However, the WHO [7] report on PBDDs and PBDFs discusses the concept of using TEFs for the assessment of these chemicals and suggests that the preliminary use of the same TEF values for the brominated congeners as described for the chlorinated analogues appears to be justified.

20. On the basis of the available data COT 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. The TEQs for the brominated contaminants could be combined with the TEQs for the chlorinated dioxins to provide an indication of the total intake of chemicals with dioxin-like properties as this would be more protective of public health than to view the chemicals separately. However, the Committee highlighted that this was tentative advice. The uncertainties in the available data with regards to the comparative toxicokinetics in rodents and humans, and lack of chronic dosing studies with these compounds indicated the need for maintaining a watching brief. It was acknowledged that the use of TEFs assigned to chlorinated congeners for the brominated analogues was likely to be over-precautionary. Given the current state of the science this is a prudent science position as long as the uncertainties in the combined chlorinated and brominated TEQs are fully acknowledged. However, further data should be sought to support the use of the TEF concept for the brominated compounds.

Non-dioxin-like polybrominated biphenyls

21. PBB congeners that exhibit AhR-mediated responses constitute only a fraction of the components in commercial PBB mixtures. Therefore, it is presumed that congeners that act by other mechanisms (category II and III PBBs) also contribute to the toxicity of PBB mixtures. The mechanism(s) of toxicity for non-dioxin-like PBB congeners is less clearly elucidated, but also may involve receptors (e.g. the estrogen receptor), or the involvement of

reactive intermediates (e.g., arene oxides) that can form potentially toxic covalently bound substrate-macromolecular adducts. The non-dioxin-like PBBs are considered to be less toxic that the coplanar PBB congeners.

22. WHO (1994) proposed a TDI for PBBs, based on a 2-year NTP carcinogenicity study that showed liver tumour formation in rats [19]. In the NTP study, the lowest dose of PBBs (FireMaster FF-1) tested that produced carcinogenic effects was 0.5 mg/kg bw/day. A dose of 0.15 mg/kg bw/day together with prenatal and perinatal exposure of the dam to 0.05 mg/kg bw/day did not result in any adverse effects, indicating a NOAEL of 0.15 mg/kg bw/day.

23. Assays for mutagenicity and genotoxicity have not shown positive effects with commercial mixtures or individual PBB congeners [20,21]. It was concluded that PBBs probably induce cancer by a non-genotoxic mechanism, and an uncertainty factor of 1000 was applied to the NOAEL to obtain a TDI of 0.15 µg/kg bw/day. However, analogy to the discussion above of non-dioxin-like PCBs indicates that the derivation of this proposed TDI may not be appropriate since simultaneous exposure to dioxin-like PBBs cannot be excluded.

Polybrominated diphenyl ethers

24. There are 209 individual PBDE congeners. Three commercial PBDE flame retardants have been available in the UK: pentabromodiphenyl ether (pentaBDE), octabromodiphenyl ether (octaBDE) and decabromodiphenyl ether (decaBDE). These commercial PBDEs are not pure products, but a mixture of various diphenyl ethers with varying degrees of bromination.

25. The European Union directive to restrict hazardous substances from electrical and electronic equipment will ban penta- and octaBDE from the production of electrical and electronic equipment from 1 July 2006. However, a voluntary ban on pentaBDE in Europe was formalised in July 2003.

COT statement 2003/04

26. The COT considered PBDEs in 2003 and issued a statement [22], in response to a survey of brominated flame retardants in brown trout and eels from the Skerne-Tees river system. The Committee noted that toxicity data are unavailable for many of the individual congeners. The concentrations of the individual congeners were therefore summed for comparison with the toxicity data on the commercial PBDE mixtures.

27. Studies on the commercial PBDEs indicate that pentaBDE is the most toxic. The COT therefore compared the estimated intakes of the sum of the measured PBDE congeners with the reported effect levels for pentaBDE. This was described as a precautionary approach, as some of the congeners are expected to be less toxic than pentaBDE.

28. Noting inadequacies in the toxicological database and the absence of identifiable no-effect levels, the COT felt it was not possible to determine a TDI.

The Committee therefore decided to take a Margin of Exposure (MoE) approach and set a target MoE of 1000 for liver toxicity of pentaBDE. Above this MoE, risks to health would not be expected. The MoE was calculated by dividing the NOAEL for liver effects of pentaBDE in rats (450 µg/kg bw/day) by the estimated dietary exposure.

JECFA Evaluation – 64th Meeting, February 2005

29. JECFA published an opinion on PBDEs last year [23]. It noted that, although PBDEs are non-genotoxic substances, the available data on PBDEs were not adequate to allocate a provisional maximum tolerable daily intake (PMTDI) or provisional tolerable weekly intake (PTWI) because:

- PBDEs represent a complex group of related chemicals and the pattern of PBDE congeners in food is not clearly defined by a single commercial mixture
- Data are inadequate to establish a common mechanism of action that would allow a single congener to be used as a surrogate for total exposure or, alternatively, as the basis for establishing toxic equivalency factors
- There is no systematic database on toxicity including long-term studies on the main congeners present in the diet, using standardised testing protocols that could be used to define a NOEL for individual PBDEs of importance
- Several of the reported effects are biological outcomes for which the toxicological significance remains unclear
- Studies with purified PBDE congeners *in vitro* have shown a lack of Ah receptor activation; however, many of the adverse effects reported are similar to those found with dioxin-like contaminants, suggesting that some toxicity data may be confounded by the presence of traces of impurities that are potent Ah receptor agonists

30. It was noted that, for the most toxic PBDE congeners, adverse effects would be unlikely to occur in rodents at doses of less than approximately 100 µg/kg bw/day, and this figure was used as the basis for a MoE assessment. JECFA used dietary intake estimates of 0.004 µg/kg bw/day (for North American regions) and 0.1 µg/kg bw/day for breastfeeding infants. These would give MoEs of 25,000 and 1,000, respectively. These values were viewed as giving reassurance that intakes of PBDEs are not likely to be a significant health concern.

Hexabromocyclododecane (HBCD)

31. HBCD is a non-aromatic, brominated cyclic alkane used primarily as an additive flame retardant in materials such as styrene resins. The commercial product consists of three diastereoisomers α-, β-, and γ-HBCD. Although the technical HBCD typically consists primarily of γ-HBCD, the relative proportions of the isomers varies depending on product application.

32. Studies in laboratory animals have shown that, following oral administration, HBCD can be detected in adipose tissue, liver and muscle. Longer-term exposure shows HBCD has the potential to bioaccumulate. Following oral administration, the majority of HBCD was detected unchanged in the faeces, although it is unclear how much of this was unabsorbed material [24].

COT statement 2003/04

33. The COT also considered HBCD in 2003 in relation to levels in fish in the Skerne-Tees river system [22] using toxicological data from a draft EU risk assessment. The COT used a margin of exposure (MoE) approach in their risk assessment and set a target MoE of 3,000-10,000.

Tetrabromobisphenol A

34. Worldwide, TBBPA is the most widely used BFR and approximately 90% of TBBPA is used as a reactive intermediate in the manufacture of epoxy and polycarbonate resins. In this case it is covalently bound to the polymer and is unlikely to escape into the environment. The remaining 10% is used as an additive flame retardant, where it does not react chemically with the other components of the polymer and may therefore leach out of the matrix.

COT statement 2004/02

35. The COT considered TBBPA in 2004 [25], primarily using data from the EU risk assessment. From the data available, the COT concluded that TBBPA did not raise specific toxicological concerns. In a 90-day study and a two-generation reproductive toxicity study, no clear adverse effects were observed at doses up to 1000 mg/kg bw/day. This dose was used as the basis for the TDI. An uncertainty factor of 100 was used to allow for inter- and intra- species variation and an additional factor of 10 was required because of the lack of chronic toxicity studies. The COT therefore recommended a TDI of 1 mg/kg bw/day.

Exposure data

36. Composite samples of 47 species of farmed and wild fish and shellfish consumed in the UK were analysed for 17 dioxins, 12 dioxin-like PCBs, 11 PBDDs/PBDFs, 3 dioxin-like PBBs, 7 non-dioxin-like PBBs, 17 PBDEs, HBCD and TBBPA. A total of 24 species of fresh wild fish, 7 of fresh farmed fish, 7 of fresh shellfish and 10 of canned or processed fish or shellfish were sampled between 2002 and 2004. Full details of the survey methodology are available in the Food Survey Information Sheets (FSIS) at http://www.food.gov.uk/science/surveillance/.

37. Estimates of total dietary exposure were derived from concentrations in samples from the 2003 and 2004 Total Diet Studies combined with consumption

data from the 2000/1 National Diet and Nutrition Survey (NDNS) [26]. Single composite food group samples were formed by homogenising individual food groups (excluding beverages) from 24 locations. These composite samples were analysed for the same range of organic chlorinated and brominated contaminants as the fish survey.

Occurrence and consumption data

Polyhalogenated dioxins and dioxin-like polyhalogenated biphenyls

38. The concentrations of chlorinated dioxins and dioxin-like PCBs (ng WHO-TEQ/kg fresh weight) in composite fish and shellfish samples are presented in Tables 1 (oily fish) and 3 (non-oily fish). Time trend data for a limited number of species indicate that, for all but one species, concentrations of dioxins and dioxin-like PCBs are the same or have decreased since last surveyed [5,6]. All results refer to edible portions of the fish. The results from the composite samples show these to be a good representation of the range of results seen for the individual analyses.

39. Tables 1 and 3 also show estimates of average upper bound adult daily intake for 1-4 portions of fish per week taking into account intakes from the rest of the diet based on analysis of the 2001 TDS, the approach taken in the SACN/COT report [1]. These values are based on the total concentrations found in the composite samples and, based on published data, assume portion sizes of 140 g for most fresh fish, 70 g for fresh sardines/pilchards, whitebait, rollmops, most canned fish and all shellfish species, and 30g for fish paste, canned anchovy and surimi [26].

40. The concentrations of brominated dioxins and biphenyls found in sampled fish were on average lower than those of the chlorinated analogues. Total TEQ[†] concentrations (upper bound) for the PBDDs and PBDFs were in the range 0.02 – 0.26 ng TEQ/kg freshweight, and for the *non-ortho* PBBs were in the range 0 – 0.01 ng TEQ/kg freshweight. The total combined concentrations of polyhalogenated dioxins and dioxin-like polyhalogenated biphenyls (ng TEQ/kg freshweight) in composite fish and shellfish samples are presented in Tables 2 (oily fish) and 4 (non-oily fish).

41. It was estimated from the 2003 TDS that the average upper bound adult dietary intake of brominated dioxins and dioxin-like PBBs from the non-fish part of the diet is 0.4 pg TEQ/kg bw/day. These surveys analysed an incomplete brominated dioxin congener set (11 PBDDs/PBDFs and 3 dioxin-like PBBs), and the total upper bound intakes may be higher. However, comparison with the lower bound intake (0.08 pg TEQ/kg bw/day) demonstrates the uncertainty in these exposure estimates. Upper bound concentrations assume that all individual congeners that are present at concentrations below the reporting limit (limit of detection) are present at the reporting limit, and therefore could be an

[†] The WHO-set TEFs for the chlorinated analogues have been used to give toxicity-weighted concentrations for the brominated dioxin-like congeners, these have been summed to give a single value expressed as a TEQ. As the TEFs have not been set by the WHO for brominated congeners the resulting overall concentrations are referred to simply as TEQs.

overestimate of the true concentrations. By contrast, lower bound concentrations assume that all individual congeners that are present at concentrations below the limit of detection are absent, and will therefore be an underestimate of the true concentrations. The true concentrations will lie somewhere between the upper and lower bounds.

42. Tables 2 and 4 also present estimated daily intakes of chlorinated and brominated dioxins and dioxin-like PCBs and PBBs from the whole diet (on the basis of analysis of the 2003 TDS samples) including one to four portions of oily or non-oily fish per week.

43. The combined chlorinated and brominated dioxins data (Table 2) indicate that consuming an average of two weekly portions of a range of oily fish could result in intakes in the region of the TDI of 2 pg TEQ/kg bw/day, when the rest of the diet is taken into account. Consuming an average of four weekly portions of a range of oily fish will result in intakes within the guideline value of 8 pg TEQ/kg bw/day, when the rest of the diet is taken into account.

44. It can be seen from Tables 1 and 2 that the inclusion of the brominated substances in the TEQ has a minor impact on the estimates of total exposure, particular taking into account the uncertainty in the estimated intake of the brominated dioxins from the non-fish part of the diet.

45. Tables 3 and 4 demonstrate that whereas most non-oily fish species contribute little to total dietary intake of chlorinated and brominated dioxins some species contain concentrations similar to those found in oily fish, and could make a relatively substantial contribution to total intake if eaten regularly. This particularly applies to wild sea bass, farmed sea bass, farmed halibut, turbot (Greenland), wild turbot (UK) sea bream, dogfish, and crab (brown/white).

Table 1. Estimated upper bound average daily dioxins and dioxin-like PCBs dietary exposure for a 60 kg adult consuming 1-4 portions of oily fish per week.

Species	Concentration in fish (ng WHO-TEQ/ kg fresh weight)	Portion size (g)	Fat content (%)	Total daily dietary intake [a] (pg WHO-TEQ/kg bodyweight/day) Number of portions of fish consumed per week			
				One portion	Two portions	Three portions	Four portions
Oily fish							
Sprat	4.29	140	9.1	2.1	3.5	4.9	6.4
Herring	3.47	140	19.3	1.8	3.0	4.2	5.4
Farmed salmon	2.51	140	14.1	1.5	2.4	3.2	4.1
Wild salmon	1.51	140	13.5	1.2	1.7	2.3	2.8
Mackerel	2.22	140	16.2	1.3	1.9	2.5	3.2
Sea Trout	1.42	140	9.9	1.1	1.6	2.1	2.6
Farmed Trout	1.02	140	8.8	1.0	1.3	1.6	2.0
Swordfish	0.72	140	6.1	0.9	1.1	1.4	1.6
Salmon (Alaska wild)	0.25	140	3.9	0.7	0.8	0.9	1.0
Tuna (Fresh)	0.07	140	0.7	0.7	0.7	0.7	0.7
Sardine/Pilchard	5.96	70	12.7	1.7	2.6	3.6	4.6
Whitebait	3.13	70	4.5	1.2	1.7	2.2	2.7
Canned sardines	2.34	70	11.3	1.0	1.4	1.8	2.2
Herring (Rollmops)	1.67	70	10.9	0.9	1.2	1.5	1.8
Eel	1.31	70	22.1	0.9	1.1	1.3	1.5
Canned mackerel	1.28	70	14.8	0.9	1.1	1.3	1.5
Canned pilchards	1.25	70	10.5	0.9	1.1	1.3	1.5
Canned salmon	0.65	70	9.7	0.8	0.9	1.0	1.1

[a] Assuming a 60 kg adult with a 0.7 pg WHO-TEQ/kg bw/day dietary intake from non-fish part of diet.

Exceeds TDI by upto 2-fold Exceeds TDI by 2- to 4-fold

Table 2. Estimated upper bound average daily dioxins, dioxin-like PCBs, brominated dioxins and dioxin-like PBBs dietary exposure for a 60 kg adult consuming 1-4 portions of oily fish per week.

Species	Concentration in fish (ng TEQ/kg fresh weight)	Portion size (g)	Fat content (%)	Total daily dietary intake [a] (pg -TEQ/kg bodyweight/day) Number of portions of fish consumed per week			
				One portion	Two portions	Three portions	Four portions
Oily fish							
Sprat	4.31	140	9.1	2.5	3.9	5.4	6.8
Herring	3.69	140	19.3	2.3	3.5	4.8	6.0
Farmed salmon	2.63	140	14.1	1.9	2.8	3.7	4.6
Wild salmon	1.66	140	13.5	1.6	2.2	2.7	3.3
Mackerel	1.96	140	16.2	1.7	2.4	3.0	3.7
Sea Trout	1.45	140	9.9	1.5	2.0	2.5	3.0
Farmed Trout	1.02	140	8.8	1.4	1.7	2.1	2.4
Swordfish	0.74	140	6.1	1.3	1.6	1.8	2.1
Salmon (Alaska wild)	0.28	140	3.9	1.2	1.3	1.3	1.4
Tuna (Fresh)	0.09	140	0.7	1.1	1.1	1.2	1.2
Sardine/Pilchard	5.99	70	12.7	2.1	3.1	4.1	5.1
Whitebait	3.16	70	4.5	1.6	2.1	2.6	3.2
Canned sardines	2.37	70	11.3	1.5	1.9	2.2	2.6
Herring (Rollmops)	1.70	70	10.9	1.3	1.6	1.9	2.2
Eel	1.34	70	22.1	1.3	1.5	1.7	2.0
Canned mackerel	1.33	70	14.8	1.3	1.5	1.7	2.0
Canned pilchards	1.28	70	10.5	1.3	1.5	1.7	1.9
Canned salmon	0.68	70	9.7	1.2	1.3	1.4	1.5

[a] Assuming a 60 kg adult with a 1.1 pg TEQ/kg bw/day dietary intake from non-fish part of diet made up of 0.7 pg WHO-TEQ/kg bw/day for chlorinated dioxins and DL-PCBs and 0.4 pg TEQ/kg bw/day (range of lower to upper bound 0.08 - 0.4 pg TEQ/kg bw/day) for brominated dioxins and DL-PBBs

Exceeds TDI by upto 2-fold Exceeds TDI by 2- to 4-fold

Table 3. Estimated upper bound average daily dioxins and dioxin-like PCBs dietary exposure for a 60 kg adult consuming 1-4 portions of non-oily fish per week.

Species	Concentration in fish (ng WHO-TEQ/ kg fresh weight)	Portion size (g)	Fat content (%)	Total daily dietary intake [a] (pg WHO-TEQ/kg bodyweight/day) Number of portions of fish consumed per week: One portion	Two portions	Three portions	Four portions
Non-oily fish							
Wild Sea Bass	3.71	140	6.8	1.9	3.1	4.4	5.6
Farmed Sea Bass	1.46	140	8.5	1.1	1.6	2.1	2.6
Farmed Halibut	2.43	140	4.2	1.5	2.3	3.1	3.9
Wild Halibut	1.09	140	4.5	1.0	1.4	1.7	2.1
Turbot (Greenland)	2.33	140	10.4	1.4	2.2	3.0	3.8
Dogfish	2.15	140	7.3	1.4	2.1	2.8	3.5
Wild Turbot (UK)	1.54	140	1.5	1.2	1.7	2.2	2.7
Farmed turbot	1.01	140	9.6	1.0	1.3	1.7	2.0
Sea Bream	1.48	140	1.5	1.2	1.6	2.1	2.6
Plaice	0.70	140	2.3	0.9	1.1	1.4	1.6
Hake	0.59	140	2.4	0.9	1.1	1.2	1.4
Lemon Sole	0.43	140	1.1	0.8	0.9	1.1	1.2
Coley	0.16	140	1.9	0.7	0.8	0.8	0.9
Shark	0.13	140	1.2	0.7	0.7	0.8	0.8
Red snapper	0.12	140	1.9	0.7	0.7	0.8	0.8
Cod	0.10	140	0.4	0.7	0.7	0.8	0.8
Whiting	0.09	140	0.7	0.7	0.7	0.8	0.8
Haddock	0.07	140	0.9	0.7	0.7	0.7	0.7
Crab (brown/white)	3.59	70	6.0	1.3	1.9	2.5	3.1
Oysters	0.45	70	2.0	0.7	0.8	0.9	1.0
Mussels	0.28	70	2.8	0.7	0.8	0.8	0.8
Scampi	0.24	70	1.1	0.7	0.7	0.8	0.8
Canned crab (white)	0.15	70	1.1	0.7	0.7	0.7	0.8
Prawns cold	0.10	70	1.7	0.7	0.7	0.7	0.7
Scallops	0.07	70	1.5	0.7	0.7	0.7	0.7
Prawns warm	0.07	70	1.5	0.7	0.7	0.7	0.7
Canned tuna	0.02	70	2.3	0.7	0.7	0.7	0.7
Fish paste	2.40	30	10.1	0.8	1.0	1.2	1.3
Canned anchovy	0.58	30	13.7	0.7	0.7	0.8	0.8
Surimi	0.02	30	1.3	0.7	0.7	0.7	0.7

[a] Assuming a 60 kg adult with a 0.7 pg WHO-TEQ/kg bw/day dietary intake from non-fish part of diet.

Exceeds TDI by upto 2-fold Exceeds TDI by 2- to 4-fold

Table 4. Estimated upper bound average daily dioxins, dioxin-like PCBs, brominated dioxins and dioxin-like PBBs dietary exposure for a 60 kg adult consuming 1-4 portions of non-oily fish per week.

Species	Concentration in fish (ng TEQ/ kg fresh weight)	Portion size (g)	Fat content (%)	Total daily dietary intake [a] (pg TEQ/kg bodyweight/day) Number of portions of fish consumed per week			
				One portion	Two portions	Three portions	Four portions
Non-oily fish							
Wild Sea Bass	3.73	140	6.8	2.3	3.6	4.8	6.0
Farmed Sea Bass	1.49	140	8.5	1.6	2.1	2.6	3.1
Farmed Halibut	2.45	140	4.2	1.9	2.7	3.5	4.3
Wild Halibut	1.13	140	4.5	1.4	1.8	2.2	2.5
Turbot (Greenland)	2.35	140	10.4	1.8	2.6	3.4	4.2
Dogfish	2.17	140	7.3	1.8	2.5	3.2	3.9
Wild Turbot (UK)	1.56	140	1.5	1.6	2.1	2.6	3.1
Farmed turbot	1.03	140	9.6	1.4	1.8	2.1	2.4
Sea Bream	1.51	140	1.5	1.6	2.1	2.6	3.0
Plaice	0.72	140	2.3	1.3	1.5	1.8	2.0
Hake	0.61	140	2.4	1.3	1.5	1.7	1.9
Lemon Sole	0.45	140	1.1	1.2	1.4	1.5	1.6
Coley	0.18	140	1.9	1.1	1.2	1.2	1.3
Shark	0.15	140	1.2	1.1	1.2	1.2	1.2
Red snapper	0.14	140	1.9	1.1	1.1	1.2	1.2
Cod	0.12	140	0.4	1.1	1.1	1.2	1.2
Whiting	0.11	140	0.7	1.1	1.1	1.2	1.2
Haddock	0.10	140	0.9	1.1	1.1	1.1	1.2
Crab (brown/white)	3.63	70	6.0	1.7	2.3	2.9	3.5
Oysters	0.71	70	2.0	1.1	1.2	1.3	1.4
Mussels	0.42	70	2.8	1.1	1.2	1.3	1.3
Scampi	0.26	70	1.1	1.1	1.2	1.2	1.2
Canned crab (white)	0.17	70	1.1	1.1	1.1	1.1	1.2
Prawns cold	0.12	70	1.7	1.1	1.1	1.1	1.1
Scallops	0.10	70	1.5	1.1	1.1	1.1	1.1
Prawns warm	0.09	70	1.5	1.1	1.1	1.1	1.1
Canned tuna	0.04	70	2.3	1.1	1.1	1.1	1.1
Fish paste	2.44	30	10.1	1.2	1.4	1.6	1.8
Canned anchovy	0.62	30	13.7	1.1	1.2	1.2	1.2
Surimi	0.04	30	1.3	1.1	1.1	1.1	1.1

[a] Assuming a 60 kg adult with a 1.1 pg TEQ/kg bw/day dietary intake from non-fish part of diet made up of 0.7 pg WHO-TEQ/kg bw/day for chlorinated dioxins and DL-PCBs and 0.4 pg TEQ/kg bw/day (range lower to upper bound 0.08 - 0.4 pg TEQ/kg bw/day) for brominated dioxins and DL-PBBs.

Exceeds TDI by upto 2-fold Exceeds TDI by 2- to 4-fold

Tribrominated dioxin and furan

46. The concentrations of 2,3,7-triBDD and 2,3,8-triBDF are also reported in these surveys. The trichlorinated congeners, have short half-lives, and therefore do not have TEFs. There are no data on the half-lives for the brominated compounds and they have not been included in the combined TEQ.

47. Analysis of the 2003 TDS samples estimated the upper bound adult dietary intake for an average consumer of 2,3,7-triBDD from the non-fish part of the diet to be 0.09 pg/kg bw/day (lower bound 0 ng/kg bw/day). Consumption of only four species of shell fish, crab (white and brown), canned crab (white), mussels and oysters would increase the dietary intake. The maximum concentration detected in oysters was 6.7 µg/kg freshweight. Assuming that a 60 kg person consumes a weekly portion of 70 g of oysters containing this concentration of 2,3,7-triBDD, the total dietary intake from the oysters and the rest of the diet would be 1.1 pg/kg bw/day.

48. For the tribrominated dibenzofuran, 2,3,8-triBDF, the non-fish part of the diet would contribute an estimated upper bound adult dietary intake for an average consumer of 0.25 pg/kg bw/day (lower bound 0.13 pg/kg bw/day). Concentrations detected in surveyed fish ranged from 0.001 – 0.078 µg/kg freshweight, with oysters having the highest concentrations. Consumption of four portions of oysters containing 0.078 µg/kg freshweight per week could increase the total dietary intake of 2,3,8-TriBDF by 0.05 pg/kg bw/day for a 60 kg person.

Ortho*-polybrominated biphenyls*

49. The concentrations of the seven *ortho*-PBBs detected in all species were similar, with PBB-52 being detected at the highest concentration of 0.05 µg/kg freshweight in sprats. Sprats also showed the highest concentration of PBBs when all seven congeners were summed (0.1 µg/kg freshweight).

50. Assuming that a 60 kg person consumes a weekly portion (140g) of sprats with a total PBB concentration of 0.1 µg/kg freshweight the total dietary intake including the non-fish part of the diet would be approximately 0.4 ng/kg bw/day, which is considerably lower than the TDI of 0.15 µg/kg bw/day proposed by WHO [17]. Estimated lower bound intakes from the non-fish part of the diet for the *ortho*-PBBs were <0.001 ng/kg bw/day for PBBs 49, 52, 80, 101, and 153, 0.002 ng/kg bw/day for PBB 15 and 0.18 ng/kg bw/day for PBB 209.

Polybrominated diphenyl ethers

51. In total 17 PBDE congeners were analysed in fish and the 2003 TDS samples, consisting of 2 triBDEs, 5 tetraBDEs, 5 pentaBDEs, 3 hexaBDEs, 1 heptaBDE and decaBDE.

52. The congeners present at the highest levels in the sampled fish were, in order of decreasing concentrations, PBDE-47 (2,2',4,4'-tetraBDE), PBDE-209

(decaBDE), PBDE-100 (2,2',4,4',6-pentaBDE), and PBDE-49 (2,2',4,5-tetraBDE).

53. Fish with the highest concentrations of the sum of the measured PBDEs were dogfish (8.71 µg/kg freshweight) and eel (5.4 µg/kg freshweight). Farmed salmon, herring, sprat and whitebait had concentrations ranging from 4.0 to 4.5 µg/kg freshweight.

54. Estimated upper bound adult dietary exposure to the sum of the measured PBDEs from the non-fish part of the diet is 5.6 ng/kg bw/day (lower bound 5.5 ng/kg bw/day). Assuming a 60 kg person consumes one weekly portion of dogfish containing the highest total PBDE concentration detected, the total intake from the diet would be 8.5 ng/kg bw/day.

55. COT set a target MoE of 1000 for liver toxicity of pentaBDE on the basis of the NOAEL for liver effects in rats (450 µg/kg bw/day). Above this MoE, risks to health would not be expected. The MoE for the intake levels described above is approximately 53,000. JECFA proposed using a reference dose at which adverse effects were not expected, 100 µg/kg bw/day, on which to base the MoE (2005). In this case, consumption of one weekly portion of dogfish will result in a MoE of approximately 11,000.

Hexabromocyclododecane

56. Eels had the highest maximum concentration of HBCD detected, the α-HBCD concentration was 5.1 µg/kg freshweight, with the sum of all three isomers being 5.3 µg/kg freshweight. This level is significantly lower than the maximum concentration of 9432 µg/kg freshweight detected in eels from the Skerne-Tees river system in 2003 [22].

57. For the non-fish part of the diet, the upper bound concentration of HBCD (sum of all diastereoisomers) in the 2004 TDS samples was 5.8 ng/kg bw/day (lower bound 1.9 ng/kg bw/day). Assuming that a 60 kg person consumes a weekly portion (70 g) of eel containing 5.3 µg/kg freshweight of HBCD, the intake would be 6.6 ng/kg bw/day.

58. COT has previously used a margin of exposure approach in the risk assessment of HBCD, using a LOAEL of 100 mg/kg bw/day as the basis for the calculation. The uncertainty factors of 100 to allow for inter and intra-species differences, 10 to allow for gaps in the data and 3-10 for extrapolation from the LOAEL to a NOAEL produce a target MoE of 3,000-10,000. Applying the MoE approach to the most recent intake data for HBCD produces MoEs of approximately 15,000,000.

Tetrabromobisphenol A

59. Mackerel was identified as having the highest concentrations of TBBPA (0.21 µg/kg freshweight). The average concentration for all species of fish was 0.04 µg/kg freshweight (range 0.03 – 0.21). On the basis of the 2004 TDS samples, intake of TBBPA from the non-fish part of the diet is 1.5 ng/kg bw/day.

Assuming that a 60 kg person consumes a weekly portion (140 g) of mackerel containing 0.21 µg/kg freshweight, the daily dietary intake of TBBPA would be 1.6 ng/kg bw/day.

60. In 2004 COT recommended a TDI of 1 mg/kg bw/day for TBBPA [25]. The estimated dietary intake from the total diet including one weekly portion of mackerel is considerably below the TDI.

COT Evaluation

61. The COT reviewed the new information in the light of previous COT conclusions and paid particular attention to possible combined effects of the different contaminants.

62. The COT noted that where comparison is possible concentrations of chlorinated dioxins and dioxin-like PCBs in fish from the most recent survey are generally lower than detected in fish sampled in 1994 to 1996. In the case of some species of oily fish (herring, mackerel and farmed salmon) the decreases were particularly marked (for herring, up to 50% lower).

63. There is increasing evidence that the brominated dioxins, furans and coplanar and mono-*ortho* polybrominated biphenyls are dioxin-like in respect to their effects in *in vitro* and *in vivo* mammalian test systems. However, there still remains some significant data gaps for a number of the congeners, in particular in terms of repeat-dose studies and the toxicokinetics of these compounds in man. The available data indicates that the brominated congeners are equally or less toxic compared to the chlorinated dioxins, and in rodents the few tested congeners have similar half-lives to the chlorinated congeners.

64. The Committee agreed that in light of this evidence, and the absence of an alternative approach, it would be prudent to apply the TEFs assigned to the chlorinated dioxins to the brominated congeners. The TEQs for the brominated contaminants should be combined with the WHO-TEQs for the chlorinated dioxins to provide an indication of the total intake of chemicals with dioxin-like properties.

65. Including the brominated congeners in the TEQs for intake from fish and the rest of the diet did not raise additional toxicological concerns. As there are no new toxicity data giving rise to new concerns, it was considered unnecessary to alter the COT's previous advice on oily fish consumption.

66. The data for the *ortho*-PBBs, PBDEs, HBCD and TBBPA were considered separately from the dioxin-like compounds as they were considered to have different modes of action. The Committee agreed that the concentrations of these contaminants in the sampled fish did not raise toxicological concerns. In the cases of the *ortho*-PBBs and TBBPA the estimated dietary intake from the total diet including a portion of the species of fish with the highest concentration of the respective contaminant were considerably below the TDIs (WHO-proposed TDI for the PBBs). For the

PBDEs and HBCDs the MoE for the intake levels described earlier in this statement were above the target MoE set previously by COT.

Conclusions

67. We consider that the concentrations of PBDEs, HBCD and TBBPA detected in these surveys do not raise toxicological concerns.

68. We conclude that concentrations of dioxin-like compounds detected in these surveys are not a concern for the health of the majority of UK consumers, who do not eat fish frequently. For those who choose to eat more than two portions of fish per week, the data reconfirm the previous SACN/COT guidance on upper levels of oily fish consumption.

69. The concentrations of dioxin-like compounds in some species of non-oily fish (sea bass, sea bream, halibut, turbot, dogfish and crab) are similar to those commonly found in some oily fish. Frequent consumption of these species of fish in addition to the recommended amounts of oily fish could result in exceedance of the intake guidelines for dioxin-like compounds.

70. We welcome the decrease in concentrations of chlorinated dioxin-like compounds in most fish species for which comparative data are available. Concentrations in wild fish can be reduced only in the long term by control of emissions to the environment. Controls on contaminant levels in feed for farmed fish are important for reducing dietary exposure of people who eat fish frequently.

71. We consider that the new survey data do not indicate a need for a change in the Food Standards Agency's current advice on consumption of oily fish.

72. There are considerable uncertainties in the data which indicate that this assessment might be over-precautionary. The risk assessment could be improved by refinement both of exposure assessment and of the toxicological basis for the TEFs, using probabilistic approaches. Modelling the available information may help to determine where the greatest uncertainty lies, in order to prioritise future research.

COT statement 2006/06
April 2006

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