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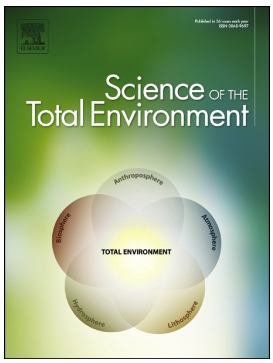

Polybrominated dibenzo-p-dioxins and furans (PBDD/Fs): Contamination in food, humans and dietary exposure

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Polybrominated dibenzo-*p*-dioxins and furans (PBDD/Fs): Contamination in food, humans and dietary exposure

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Abstract

Polybrominated dibenzo-*p*-dioxins and dibenzofurans (PBDD/Fs) have been recognised as environmental pollutants for decades but their occurrence in food has only recently been reported. They elicit the same type of toxic response as analogous polychlorinated dibenzo-*p*-dioxins and dibenzofurans (PCDD/Fs) with similar potencies and effects, and share similar origins - inadvertent production during combustion and occurrence as by-products in industrial chemicals. Surprisingly, PBDD/Fs have received considerably less attention than PCDD/Fs, perhaps because determination requires a higher degree of analytical competence, a result of the higher adsorptivity and lability associated with carbon-bromine bonding. For most populations, the principal exposure pathway is dietary intake. The PBDD/F toxicity arising from occurrence in foods has often been expressed as toxic equivalents (TEQs) using the same scheme developed for PCDD/Fs. This approach is convenient, but resulting TEQ estimates are more uncertain, given the known differences in response for some analogous congeners and also the different patterns of PBDD/F occurrence confirmed by the newer data. Further studies to consolidate potency factors would help to refine TEQ estimates. Characteristically, most foods and human tissues show more frequent and higher PBDF concentrations relative to PBDDs, reflecting major source patterns. Occurrence in food ranges from < 0.01 to several thousand pg/g (or up to 0.3 pg TEQ/g whole weight) which is comparable to PCDD/F occurrence (ΣPBDD/F TEQs are underestimated as not all relevant congeners are included). Plant based foods show higher PBDD/F: PCDD/F TEQ ratios. Reported PBDD/F dietary intakes suggest that some population groups, particularly young children, may exceed the revised tolerable weekly intake for dioxin-like contaminants (2 pg TEQ/kg bw/week), even for mean consumption estimated with lower bound data. It is evident that the omission of PBDD/Fs from the TEQ scheme results in a significant underestimation of the cumulative toxicity and associated risk arising from this mode of action.

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1.0 Introduction

Polybrominated dibenzo-*p*-dioxins and dibenzofurans (PBDD/Fs) are diaromatic molecules with two bromine substituted benzene rings that are linked by a diether (dioxin) or furan bridge (Figure 1). These polybrominated structures are analogues of the polychlorinated dibenzo-*p*-dioxins and dibenzofurans (PCDD/Fs) - a widely recognised and well-studied group of environmental and food contaminants. When laterally halogenated (positions 2,3,7 and 8), these molecules elicit a range of pleiotropic responses in animal cells, a process that is initiated by binding to the cellular aryl hydrocarbon receptor (AhR). In addition to promoting tumours, both classes of contaminants also elicit other effects such as immunosuppression and endocrine disruption, and PCDDs have been shown to be frankly toxic (Viluksela et al., 1998; Bell et al., 2007) in rodents at microgram quantities. These properties have been the subject of numerous studies on PCDD/Fs over the last half a century or so and latterly, have resulted in regulation of their release to environmental compartments such as air, soil and water, as well as control of their occurrence in food (MEJ, 1999; European Commission, 2011). It is therefore surprising that, despite sharing a similar timeline on occurrence, to the PCDD/Fs, there is relatively little information on PBDD/Fs.

Insert Figure 1

Although closely related to PCDD/Fs, data on the physical and chemical properties of PBDD/Fs is scarce with much of the knowledge being derived from model calculations or extrapolated and inferred from PCDD/F data and behaviour. Comparatively, PBDD/Fs have higher molecular weights, melting point, octanol-water partition coefficients, lower aqueous solubility, vapour pressure, and demonstrate surficial particulate adsorption (Ballschmiter and Bacher, 1996; WHO, 1998). As described earlier (Fernandes et al., 2020), much of the high

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molecular stability derives from the halogenated aromaticity and the strength of the C-Br bonding (bond energy 276 kJ/mol – Zumdahl and Zumdahl, 2000) in PBDD/Fs. Values for formation enthalphy are smaller for the lower brominated compounds and vary depending on the substitution positions, suggesting the influence of both, the degree of bromination as well as configuration, on the stability of PBDD/Fs (Li et al., 2003). The octanol-water partition coefficients (K_{OW}) are relatively high, in the range of 5 to 10, and estimated octanol-air and air-water partition co-efficients (ranging from 7 to 15 and -6.3 to -2.6 respectively) are similar to PCDD/Fs (Puzyn et al., 2008). These properties suggest a physical stability that results in environmental persistence, although they are also more photo-labile in ambient air than PCDD/Fs. On the other hand, the relatively higher K_{OW} values and low water solubility (Birnbaum et al., 2003) of PBDD/Fs indicate a higher degree of lipophilicity, evidenced by their strong solubility in most organic solvents including fats and oils. This lipophilicity results in bioaccumulation in food webs and animal tissues, particularly in fat reserves, but protein (e.g. CYP1A2) associated segregation is also observed in organs such as the liver (Kedderis et al., 1993). In common with other persistent lipophilic contaminants, chronic intake of PBDD/Fs through the diet is widely recognised as being the main exposure pathway, unless there is specific occupational exposure such as that arising from electronic waste recycling (Xiao et al., 2016; Dai et al., 2020).

The last two decades have seen an increasing amount of evidence that reveals occurrence in biological matrices and perhaps most relevantly, in food and in human tissues. This paper explores the origins, toxicity, metrology, food and human tissue occurrence of PBDD/Fs and discusses our evolving understanding of the resulting human exposure to this significant component of dioxin-like toxicity.

2.0 Sources of PBDD/Fs

PBDD/Fs have never had any industrial utility and they have never been intentionally produced. The PBDD/Fs that occur in environmental matrices, biota, food and human tissues are the products of inadvertent formation through three principal routes. The most abundant source is by-production during the manufacture of brominated industrial chemicals such as brominated flame retardants (BFRs). They are also formed during controlled (or improperly controlled) thermodynamic processes during combustion and incineration, in much the same way that PCDD/Fs are formed (Söderström and Marklund, 2002; Weber and Kuch, 2003). Biogenic formation in aquatic, particularly marine environments is mediated by marine fauna such as sponges, acting on bromophenol precursors and leads to the formation of mostly lower (one to four Br) brominated PBDD/Fs (Malmvärn et al., 2005, 2008)

Other inadvertent formation pathway are also known, but it is difficult to estimate the magnitude of formation. The action of sunlight on atmospheric and exposed water and soil-bound polybrominated diphenylethers (PBDEs) can result in photolytically mediated rearrangement to yield PBDD/F congeners, and more recently, reports have emerged of PBDD/F formation during the recycling of electronic waste by open-burning (Bruce-Vanderpuije et al., 2019; Tue et al., 2019). The most relevant source types along with indications of by-production levels or emissions of PBDD/Fs, have been summarised in Table 2.

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2.1 By-production in industrial chemicals

The formation of PBDD/Fs as by-products during the manufacture of brominated organic chemicals is well recognised. In particular, the industrial production of BFRs such as PBDEs, tetrabromobisphenol A, bromophenols, 1,2-bis(tribromophenoxy)ethane and bromine containing agricultural chemicals such as bromoxynil, bromophos, profonofos etc. also yields small

quantities of PBDD/Fs (WHO, 1998; Hanari et al., 2006; Ren et al., 2011) but apart from some studies on BFRs, these potential sources have not been fully investigated.

As one of the largest volume produced flame retardants, PBDEs have been studied more frequently than other BFRs, including those for PBDD/F content (Hanari et al., 2006; Öberg et al., 2010; Ren et al., 2011; Sindiku et al., 2015). Commercial PBDE mixtures such as PentaBDE, OctaBDE, and DecaBDE commonly referred to as "Penta", "Octa" and Deca" were manufactured globally under a number of trade names e.g. Bromkal Series 70-5-DE, 79-8-DE, 82-0-DE; Great Lakes DE-79 and DE-83 Dow FR-1208 HM and Dow FR-300BA, Saytex 102E, etc. A number of these mixtures were shown to contain significant amounts of PBDD/Fs, particularly PBDFs. The PBDF contents ranged from 0.36 mg/kg in PentaBDE, 10 to 19 mg/kg in Octa and 31 to 50 mg/kg in DecaBDE (Hanari et al., 2006). PBDD occurrence in these mixtures were orders of magnitude lower, typically ranging from < 0.1, to 0.2 pg/g. This suggests that in addition to the main reaction (a Friedel–Kraft catalysed bromination of diphenylether) that is used for commercial PBDE manufacture, side reactions also occur with kinetics that favour protonation of nascent PBDE molecules, followed by HBr loss to form furan linkages. Diether linkages that would yield PBDDs are thought to be less likely, an outcome that was also observed during combustion processes (Dumler et al., 1990; Luijk and Govers. 1992). A later study (Ren et al., 2011) investigating PBDD/F impurities in commercial Deca mixtures produced in China and the US, similarly identified PBDFs as the main by-products. Twelve laterally substituted tetra- to octa-BDD/F congeners, dominated by OBDF and 1,2,3,4,6,7,8-HpBDF, occurred in the range of 3.4 to 13.6 µg/g, averagely accounting for 99% of the total PBDD/Fs in the products (Ren et al., 2011). However Octa-BDD also occurred in significant amounts ranging from 1.9 ng/g in the US mixture to 139 ng/g in one of the Chinese products. The total concentration of planar PBDD/Fs measured ranged from 3400 to 13600 ng/g (mean 7800 ng/g).

PBDEs were manufactured in many countries around the world and recent reports suggests that this continues in China (Wang et al., 2019). During peak production periods, these mixtures would provide a major source of PBDD/Fs. It was estimated that a single years production of Penta and Octa would yield 2.3 tons of mostly PBDFs (Hanari et al., 2006) while the production of Deca would yield 0.43 (range: 0.21-0.78) tons (Ren et al., 2011). The total inadvertent by-production of PBDD/Fs during PBDE manufacture was estimated to be at least a thousand tons (after Sindiku et al., 2015), a relatively high value in comparison to existing inventories on PCDD/Fs (Horii et al., 2011; Cheruiyot et al., 2016).

2.2 Combustion related sources

Prior to the widespread use of BFRs and the introduction of emission controls in many countries, combustion processes such as the incineration of domestic and clinical waste were one of the major sources of PBDD/Fs. Both, precursor governed pathways, as well as *de novo* synthesis (molecular rearrangement from the basic elements) were known formation mechanisms (Söderström 2003; Weber and Kuch, 2003; Söderström and Marklund, 2004). In recent decades however emission monitoring and control measures combined with efficient combustion conditions and effective scrubbing of emission gasses have reduced PBDD/F emissions from these traditional combustion sources. Levels are usually lower than the simultaneous emissions of PCDD/Fs (Wang and Chang- Chien, 2007; Du et al., 2010; Wyrzykowska et al., 2008). However, as precursor governed formation appears to be the more dominant pathway to PBDD/F formation (Weber and Kuch 2003), certain types of incineration processes with precursor rich feed stocks may be more important sources. Thus incineration of chemical and industrial waste with a high proportion of bromine and in particular, incinerators used in metallurgical and metal reclamation (Du et al., 2010; Wang et al., 2010) show reported

emissions of PBDD/Fs at 0.02 - 3.0 and 0.56 - 5.8 ng sum PBDD/F/Nm^3 in Taiwan and China respectively. The precursors are most likely to be high volume BFRs used in industrial and electrical applications (e.g. plastic wire coatings) and although PBDEs are the most commonly reported precursors, (Dumler et al., 1990; Luijk and Govers, 1992), formation from other BFRs such as hexabromocyclododecane (HBCDD) and tetrabromobisphenol A (TBBPA) have also been reported (Barontini et al., 2001; Ortuño et al. 2014; Takigami et al. 2014).

The (often) uncontrolled open-burning of BFR containing e-waste products to recycle valuable metals, is another combustion related pathway that results in the inadvertent by-production of PBDD/Fs. The original products were generally flame proofed during manufacture and the lower temperatures and slow rates of combustion during open burning lead to substantial discharges of many toxic compounds including PBDD/Fs (Li et al., 2007; Wang and Chang-Chien, 2007; Wang et al., 2010; Wyrzykowska-Ceradini et al., 2011; Zhang et al 2012; Ni et al., 2016; Tue et al., 2019). An experimental study (Duan et al., 2011) showed that maximum formation occurred between 250 and 400 °C. At 325 °C, using a feedstock with high bromine content, the sum of PBDD/Fs congeners in solid, liquid, and gaseous fractions measured 19, 000, 160, 000, and 57 ng TEQ/kg respectively, occurring at substantially greater (orders of magnitude) concentrations than PCDD/Fs.

Similarly PBDD/Fs can also be formed during industrial, commercial and residential fires (Litten et al., 2003; Söderström, 2003; Lundstedt et al., 2011) and during firefighting, as seen in experiments on accidental fires (in domestic settings such as a residential apartment) using different firefighting methods (Bjurlid et al., 2017). PBDD/Fs were generated in both, the gas (4020–18,700 pg m^3) and the soot (76–4092 pg m^2) phase. The predominant PBDF congener in the gas and soot phases was 1,2,3,4,6,7,8-HpBDF. A potential but thus far, un-investigated source of PBDD/Fs is the casual, uncontrolled incineration (open burning) of plastic containing

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domestic refuse and other waste materials (containing bromine/BFRs) which occurs worldwide and has been experimentally shown to emit PBDEs and HBCDD (Ni et al., 2016).

Although combustion sources give rise to both PBDDs and PBDFs, the mechanisms governing formation influence the relative yield. As precursor driven mechanisms are reported to dominate thermodynamic formation (Weber and Kuch, 2003), the chemical configuration of the precursor molecules determines the product. Under these conditions, the cyclisation driven mechanism dominates and for PBDEs, the existing ether linkage readily yields PBDFs, but formation of the second ether link for PBDD formation appears to be much less favoured. This reflects the kinetically governed patterns that influence by-product formation as observed in section 2.1. It is also reflected in atmospheric environments where the most dominant congeners in air are often PBDFs, - 2,3,7,8-TBDF, 1,2,3,7,8-PeBDF and 2,3,4,7,8-PeBDF (Li et al., 2011), and similarly in soils where PBDDs are considerably less abundant than PBDFs (Ramu et al., 2008).

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2.3 Photolytic formation

The formation of PBDD/Fs through the photolytic degradation of BFRs has been reported in a number of experimental studies, but there is a very strong potential for this process to occur in the environment on a continual basis when BFR containing material is exposed to sunlight. e.g., discarded plastic products, sewage sludge, etc. This photo-mediated pathway has been observed in laboratory conditions at different wavelengths and in different matrices, but mainly with PBDEs as the precursor (Watanabe and Tatsukawa, 1987; Hua et al., 2003; Söderström et al., 2004; Hagberg et al., 2006). The process is likely to proceed initially via *ortho* de-bromination of PBDEs (Wang et al., 2018) and subsequent cyclisation to yield mostly PBDFs (Eriksson et al., 2004; Hagberg et al., 2006). Photolytic de-bromination readily occurs in the photo-labile

PBDEs, but also in PBDD/Fs and PXDD/Fs (Chatkittikunwong and Creaser, 1994; Wang et al., 2018), resulting in relatively short half-lives (of the order of 100 to 1000 h) under these conditions. These reaction proceed much faster under laboratory conditions where clean and clear solvent solutions are used but in real environmental situations where mixed or solid matrices are involved, the process would be expected to proceed at much slower rates and mainly at exposed surfaces (Soderstrom et al., 2004). This was seen in tests with PBDD/Fs adsorbed on fixed phases and soils that yielded significantly higher half-lives (WHO, 1998). This process has also been recorded for indoor environments where household goods and furnishings containing PBDEs, yield PBDFs through the action of solar radiation (Kajiwara et al., 2008, 2013).

Among the (mostly) PBDFs that are formed a wide range of congeners has been recorded (Hagberg et al., 2006). The most abundant compounds appear to be higher brominated compounds such as the PeBDFs and HxBDFs, although the study did not include HpBDF. In environmental media such as sediments and sewage sludge, HpBDF (usually 1,2,3,4,6,7,8-HpBDF) occurs to the highest extent among other PBDFs and appears to correlate well with the much higher concentrations of co-occurring deca-BDE (Goto et al., 2017; Fernandes et al., 2019) suggesting commercial Deca-BDE as the likely source.

2.4 Biogenic sources

Although the anthropogenic sources discussed in the previous sections contribute to the bulk of existing PBDD/Fs, biogenic formation of mostly lower brominated PBDD/Fs has been documented (Haglund et al., 2007, 2010; Malmvärn et al., 2008; Unger et al., 2009; Goto et al., 2017). The formation of these PBDD/Fs is thought to be enzymatically mediated by the action of bromoperoxidases on naturally occurring precursors such as bromophenols and hydroxy-

PBDEs. Bromophenols are abundantly produced by a number of marine species such as cyanobacteria (*Aphanizomenon flos-aquae*), algae (*Ceramium tenuicorne, Sargassum sp*.), lower order biota such as marine sponges, *Ephydatia fluciatilis, Nodularia sprumigentia*, and bivalves such as *Mytilus edulis, Mytilus galloprovincialis* and *Perna viridis.* (Flodin and Whitfield, 1999; Haglund et al., 2007, 2010; Malmvärn et al., 2008; Unger et al., 2009; Goto et al., 2017). The more effective bromophenols precursors are likely to be those that are substituted in the more reactive *para* and *ortho* positions, i.e. 2,4-DiBP, 2,4,6-TrBP and 2,3,4,6-TBP. Hydroxylated PBDEs are also known to be produced naturally in marine organisms (Carte and Faulkner, 1982; Kelly et al., 2008, Löfstrand et al., 2011), but commercial PBDE congeners present in sewage can undergo hydroxylation (Ueno et al., 2008; Stapleton et al., 2009) followed by discharge to marine waters.

Unlike the anthropogenic formation routes which yield mostly PBDFs, the biogenic routes lead to a number of di-, tri- and tetra-BDDs, prominent among which are 1,3,7-TrBDD and 1,3,8-TrBDD; 1,3,6,8-, 1,3,7,9-, 1,2,3,8-, 1,2,4,7-, 1,2,3,7- and 1,2,4,8-TBDD (Haglund, 2010). Tri-BDDs account for more than 90% of the sum of the observed compounds in common mussels (*Mytilus edulis*) with 1,3,8-TrBDD dominating the occurrence followed by 1,3,7-TrBDD. A study on shellfish contamination (Fernandes et al., 2009A) showed that the laterally substituted 2,3,7-TrBDD was also found to occur at a level of 0.06 – 14 pg/g fresh weight in native oysters (*Ostrea edulis*) although the chromatographic profiles suggested that this was a minor constituent among the other non-planar TrBDD congeners. 2,3,8-TrBDF also occurred but at much lower concentrations.

2.5 Other sources

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PBDD/Fs are also inadvertently formed when BFRs are incorporated in materials during industrial high temperature processes such as polymer extrusion and moulding that are used to manufacture plastics (Ebert and Bahadir, 2003; Weber and Kuch, 2003). These are formative processes that do not use very high temperatures, so are only relevant when precursors such as PBDEs are used. These processes also generally give rise to PBDFs via the precursor dominated pathways involving HBr elimination followed by formation of the furan linkage.

In recent decades the emphasis on sustainability of resources has led to the rise of another source – recycling processes. These often involve the recycling of flame retarded materials and goods such as plastics, end of life motorised vehicles, electrical and electronic goods, (Ma et al., 2009; Takahashi et al., 2017; Dai et al., 2020), leading to high levels of PBDD/F contamination of workspaces and the surrounding environment. There are reports of floor dust and the surrounding soil from electronic waste recycling facilities containing total PBDD/F concentrations of up to 143 µg/kg dry weight (dw) in floor dust and 800 µg/kg dw in surrounding soil, amongst other similar contaminants such as PBDEs, PCBs and PCDD/Fs. The associated toxicity from PBDD/Fs was greater than that of PCDD/Fs, with PBDF concentrations exceeding PCDDs by several orders of magnitude (Ma et al., 2009). The process of recycling plastics that are used in electronic equipment such as computer monitors, televisions and other plastic housings, also gives rise to PBDD/Fs, with reported concentrations between 1 and 35 µg/kg (Schlummer et al., 2004). The PBDD/Fs present in recycled materials (e.g. plastics) are likely to be a cumulative of the PBDD/Fs originally present in the material plus those formed during recycling. Additionally, in the case of electronic equipment, the elevated temperatures used during operation, may also contribute to PBDD/F formation.

Recycling of plastics may also lead to unexpected human PBDD/F exposure, particularly to children. A recent study (Budin et al., 2020) reported very high levels of PBDD/Fs in recycled

products including children's toys containing PBDEs and PBDFs. An earlier study showed a child's toy in Germany produced from recycled plastic with a PBDD/F concentration at 386,000 pg/g (3,800 pg TEQ/g) (Straková et al., 2018).

2.6 Environmental fate of PBDD/Fs

There is no substantial information on the fate of PBDD/Fs in the environment. As discussed, they have been shown to have high environmental persistence like PCDD/Fs, but individual congeners will behave differently in the environment depending on the configuration and the degree of bromination (Terauchi et al., 2009). PBDD/F degradation in soils and water have not been studied extensively, but one of the main degradation pathways is thought to be initiated by photolysis. Clearly this would be the predominant mechanism in atmospheric environments and is also likely in surface waters and at the surfaces of soils/sediments. Tue et al. (2014), noted that a higher proportion of lower brominated PBDFs rather than OBDF (which is the most abundant homologue in commercial PBDEs such as Deca-BDE) in soils from e-waste recycling sites, could be a result of extensive debromination from the effects of sunlight and also through open-burning processes. In aqueous environments, photolytic debromination is likely in upper water layers exposed to sunlight and debromination may also occur enzymatically (haloperoxidases) in marine biota, as part of the natural formation mechanism of PBDDs (Haglund, 2010). Additionally microbial debromination may occur in sediments or soils or in the intestinal microflora of some marine species.

3.0 Health Effects

Knowledge of the pharmacokinetic and pharmacodynamic behaviour of PBDD/Fs is scarce and in common with the physicochemical properties discussed earlier, much of this behaviour is

inferred from studies on PCDD/Fs. It is worth noting an important difference however – in comparison to the C-Cl bonding in PCDD/Fs, bromine substitution results in a slightly weaker bond (which is associated with both, the lower bond energy of the C-Br bond and the larger dimensions of the bromine atom), increasing susceptibility to enzymatic metabolism. Notwithstanding this difference, the similarities in chemical structure, formation processes, environmental and biological persistence, etc. to PCDD/Fs have unsurprisingly directed most toxicological studies on PBDD/Fs to consider the laterally substituted molecules. PCDD/F congeners substituted at the 2,3,7 and 8 positions provide a planar rigidity that elicits the most sensitive effects at relatively low chronic doses (Hurst et al., 2000; Bell et al., 2007). However, as described in section 2.4, there is abundant biogenic formation of lower brominated, non-2,3,7,8 congeners, with demonstrated occurrence in marine animals such as mussels, algae, sponges, etc. (Malmvärn et al., 2005, 2008; Unger et al., 2009; Haglund, 2010; Löfstrand et al., 2010). Additionally non-2,3,7,8 substituted PBDD/Fs have also been reported to occur abundantly in edible shellfish species such as mussels, oysters (two species) and scallops (Fernandes et al., 2008, 2009A). In view of this common occurrence in the marine food chain, it would be remiss to ignore any potential effects arising from this occurrence. Unfortunately there is little information on the toxicological effects of these congeners as most studies have only investigated laterally substituted compounds. The limited number of studies on non-2,3,7,8 substituted PBDD/Fs (Kedderis et al., 1994; van den Berg et al., 1994) showed rapid metabolism of 1,2,7,8-TeBDF in rodents relative to the planar compounds. On the other hand, EROD, AHH, and Ah-binding assays on some di- and tri-substituted compounds (2,7- and 2,8-DiBDD and 2,3,7-TrBDD (partial lateral substitution), displayed a relative potency (REP) range (0.002 to 0.85) that was significant in comparison to 2,3,7,8-TCDD (Mason et al., 1987; Olsman et al., 2007; Samara et al., 2009; Wall et al., 2015).

3.1 AhR mediated and other effects

The biological effects observed for laterally substituted PBDD/Fs are very similar to the chlorinated analogues and include lethality, carcinogenesis, thymic atrophy, teratogenesis, reproductive effects, chloracne, immunotoxicity, enzyme induction, etc. (WHO, 1998, Birnbaum et al., 2003, van den Berg et al., 2013). One of the principal effects of both these halogenated groups is the ability of the planar congeners to bind to the AhR, a process that sequentially influences the initiation, promotion, and progression of carcinogenesis and other immunological, developmental and reproductive effects in test animals and in humans (EFSA, 2018). The AhR is a soluble intracellular ligand-activated cytosolic transcription factor (a protein that modulates the transcription rate of genetic information from DNA to mRNA) that is named primarily after the xenobiotic group of aromatic hydrocarbons including polycyclic aromatic hydrocarbons and most relevantly in the present case, halogenated aromatic hydrocarbons such as PCDD/Fs, PCBs, PBDD/Fs, etc. (although the response in not limited solely to these types of compounds). Most of the toxic effects observed for PBDD/Fs are mediated by the AhR and the binding potencies for the various 2,3,7,8-Br substituted congeners are in the same range as the PCDD/Fs (Birnbaum et al., 1991, 2003; DeVito et al., 1997; Behnisch et al., 2003; van den Berg et al., 2013; Wall et al., 2015).

Apart from the promotion of carcinogenesis, teratogenic effects such as those observed from the action of 2,3,7,8-TCDD in children exposed to the defoliant, 2,4,5-T, are very likely. Similar toxic effects following dosing of 2,3,7,8-TBDD to rodents were noted on body weight, and on the liver, and overt effects like cleft palate and hydronephrosis were identical to those seen for 2,3,7,8-TCDD exposure (Birnbaum et al., 2003). Studies indicate that 2,3,7,8-TBDD, exerts these effects on rodents in the same dose range, suggesting a comparable potency for both analogues. Other potential effects investigated (Ao et al., 2009) for these analogues were immunological function where both compounds showed identical potencies for thymus and

spleen weight endpoints. Similarly, a study on brain function in mice offspring, investigating the acquisition and retention of fear memory following maternal exposure, suggests that low doses of these analogues elicited similar disruptive responses for emotion and memory in males (Haijima et al., 2010). However, the response was not observed for all congeners. Investigating REPs based on humoral immunity (immunity mediated by extracellular fluid macromolecules) response in mice, a comparative study on laterally substituted PBDD/Fs and PCDD/Fs reported that although TCDD showed the highest potency, a number of other brominated congeners were more potent than their chlorinated analogues (Frawley et al., 2014). REPs for both 2,3,7,8-TBDF and 2,3,4,7,8-PBDF were higher than the chlorinated analogues, with 2,3,7,8-TBDF being significantly higher.

There is a scarcity of information on the effects of PBDD/Fs in humans, probably linked to poor analytical access (see section 4) and perhaps also, a lower level of awareness to these chemicals in risk assessment studies. This is surprising considering the fact that most incidents such as workplace and domestic fires in recent decades would give rise to PBDD/Fs (because of the use of BFRs in furniture, electronic equipment, etc.) and certain occupations such as firefighting and other emergency workers have the greatest potential for adverse impact (in addition to the victims of these incidents). The considerably higher levels of PBDD/Fs (relative to PCDD/Fs) generated in these incidents have been reported (Zelinski et al., 1993; Litten et al., 2003) as well as the higher levels of PBDD/Fs in firefighter serum (Shaw et al., 2013) and the blood of occupationally exposed workers (Zorber et al., 1992). A report on an earlier case of a chemist exposed to TBDD, developing chloracne has also been reported (Birnbaum et al., 2003), but most associations to the toxicological effects of PBDD/Fs have been extrapolated from the effects in humans, through exposure to PCDD/Fs, PCBs and polychlorinated naphthalenes (van den Berg et al., 2006; Fernandes et al., 2017; EFSA, 2018). The

compositional and structural similarity of these molecules to PBDD/Fs and known effects such as carcinogenicity, provide a high degree of toxicological plausibility to the extrapolations.

3.2 Expression of toxic content as toxic equivalence factors (TEFs)

The comparability between biological effects for PCDD/Fs and PBDD/Fs as well as the parity, in some cases, of the relative potencies, has understandably prompted calls for a similar method of expressing the toxicity associated with PBDD/F content. For a range of studies such as risk assessment, risk management, regulation, etc., the toxicity of PCDD/F concentrations are conveniently expressed as toxic equivalents (TEQs), most commonly as a summed value for all seventeen laterally substituted compounds (van den Berg et al., 2006). TEQ values are easily derived as a product of the congener concentrations and the corresponding toxic equivalence factors (TEFs) which were established following a meta-analysis of the REP values from different studies (van den Berg et al., 2006). The scheme for PCDD/Fs already incorporates PCBs, and summed TEQ values have been in use for several years. Just under a decade ago, an expert panel was tasked with reviewing the potential inclusion of the brominated analogues of these contaminants within the scheme. As environmental and food occurrence at this time had already been demonstrated by a number of studies (Fernandes et al., 2005A, 2005B, 2008, 2009B; Ashizuka et al., 2004) and human exposure confirmed, the panel recommended using the analogous chlorinated TEF values on an interim basis, to express the toxicity from PBDD/Fs for human risk assessment (van den Berg et al., 2013).

The recommendation facilitates a practical means of expressing PBDD/F toxicity but it should be considered as a short term or interim measure due to the small number of studies on sub-chronic exposure and the uncertainties in the estimates that are inherent in the limited number of observations. Additionally as discussed above, there are differences in relative potencies for

congeners such as 2,3,7,8-TBDF and 1,2,3,7,8-PeBDF which are reported to show higher REPs than their chlorinated analogues. Also, the occurrence profiles in the majority of food and biota samples shows low or undetected concentrations for PBDDs. This has an unexpected consequence on the expression of the TEQ, as large differences are observed between upper and lower bound estimates, even when using very sensitive analytical methods. This difference is mainly due to the higher suggested REP/TEF values for PBDDs (van den Berg et al., 2013) which would account for 70% of the total TEQ if all congener concentrations were at parity. Another question relates to the potential toxicity contribution from tri-brominated planar congeners that are not included in the TEF scheme. 2,3,7- TrBDD and 2,3,8-TrBDF both occur commonly in marine and animal tissues as well as human adipose tissue, blood and milk (Pratt et al., 2013; Deshmukh et al., 2020), and also bind with significant potency to the AhR (Olsman et al., 2007; Wall et al., 2015).

The existing evidence on occurrence nonetheless shows that many 2,3,7,8-substituted PBDD/Fs are present in food and wildlife and contribute to the cumulative burden of dioxin-like toxicity which justifies a means of quantitatively expressing this contribution. Although tentative to some extent, inclusion within the PCDD/F and PCB TEQ scheme, would be more protective of public health as it would provide a combined evaluation of similar toxic effects, rather than considering the PBDD/Fs separately. Practically, a wide margin of uncertainty on resulting PBDD/F TEQs should be assumed when the scheme is used and considering potential re-evaluations of TEF values in the future, it would be useful for future reports to include the concentrations of individually occurring congeners (as supplementary information) so that the data could be re-evaluated for risk assessment purposes if required.

4.0 Methods for food and human tissue analysis

The low incidence of data on PBDD/Fs may be due to some extent, on poor access to the relevant analytical methodology. However the situation continues to show improvement with a steady increase in new information. Until recently, the lack of a full set of reference standards was also a drawback. Nonetheless most reported methodologies have used good quality control procedures, often using the acceptance and quality criteria that are used for PCDD/Fs, for greater confidence.

In addition to the 2,3,7,8-substituted PBDD/F congeners, a number of studies have also included the laterally substituted tri-BDD/Fs (2,3,7-trBDD and 2,3,8-trBDF) as these compounds show potencies in a range similar to the 2,3,7,8-substituted compounds (Olsman et al., 2007, van den Berg et al., 2013; Wall et al., 2015).

4.1 Extraction and purification

The similarities in chemical properties, structure and configuration to PCDD/F congeners, noted in section 1.0, previsu a corresponding similarity in analytical determination of PBDD/Fs. In terms of extraction, purification and fractionation procedures, a number of studies (Fernandes et al., 2004, 2008; Zacs et al., 2013; Fromme et al., 2016; Pajurek et al., 2019; Diletti et al., 2020) report using the same or very similar methodology to PCDD/Fs.

A number of ^{13}C labelled PBDD/F standards are available commercially (Cambridge Isotope Laboratory, Mass., USA; Wellington Laboratories, Ont., Canada), and these will allow reliable internal standardisation and satisfactory indications of analytical recovery but some 2,3,7,8-Br substituted PBDFs (some hexa- and hepta-brominated congeners) may not yet be available. However, as there is at least one ^{13}C labelled PBDD/F standard available for each homologue group from tri- to octa-BDD/F, the majority of planar congeners may be determined.

A full description of the extraction and purification procedures for food analysis (Fernandes et al., 2004) shows simultaneous collection of PBDD/Fs in the same elution fraction as the PCDD/Fs. The validated and accredited methodology used mixed solvents (DCM:hexane 40:60) to extract homogenised and blended aliquots of food samples (a full range of food types) through a glass column containing individual layers of H_2SO_4 and KOH modified silica gel. The procedure exploited the similar planarity of PBDD/Fs and PCDD/Fs to exclude other potentially interfering compounds such as PCBs and PBDEs. The column was connected in series with an activated carbon column, and the simultaneous extraction and primary purification proceeded through a gravity fed elution, to provide a PBDD/F fraction that was free of non-polar interferants. Further chromatographic purification of the fraction involved elution through activated basic alumina, initially using hexane to remove any residual lipid material and any residual co-extracted non-polar contaminants. This procedure (Fernandes et al., 2004) was further validated as a basis of the European standard methodology (CEN, 2012) for PCDD/Fs. Similar procedures using acid modified silica gel and activated carbon were reported for the analysis of PBDD/Fs in fish, shellfish, and milk (Ashizuka et al., 2004, 2005; Malmvärn et al., 2005; Pratt et al., 2013; Zacs et al., 2013), and an automated version was used in a later study on a range of food types (Diletti et al., 2020). Most variations on the above procedure either lie with the choice of secondary purification, using celite (Haglund et al., 2007) instead of alumina, or more often, the extraction process used either soxhlet extraction (Zacs et al., 2016), liquid-liquid extraction (Haglund et al 2007; Diletti et al., 2020) with acetone/hexane or ethanol, or automated solvent extraction (Pajurek et al., 2019; Diletti et al., 2020) depending on the matrix.

The purified extracts were concentrated to a final volume ranging from 10 µL (Pajurek et al., 2019) to 150 µL (Haglund et al., 2010), with addition of a keeper solvent (isooctane/

nonane/dodecane) and the internal sensitivity standard (ISS). In order to reflect analyte characteristics during the measurement process and allow meaningful recovery calculations, the preferred ISS should be brominated compound(s) eluting within the same retention window during measurement. Convenient ISS include ^{13}C labelled PBDE 139 and ^{13}C labelled 1,2,3,7,8,9-HxBDD (Fernandes et al., 2008; Diletti et al., 2020). A number of laboratories incorporate measures to minimise or prevent photodegradation of PBDD/Fs during sample preparation and analysis. Laboratory lighting and particularly, windows were coated with UV-absorbing paint or foil to prevent debromination.

4.2 Measurement

In order to reliably measure and quantify PBDD/Fs, GC-HRMS in selected ion monitoring mode offers the best combination of robustness, selectivity and sensitivity, although GC-APCI-MS/MS may also provide similar levels of sensitivity. At a resolution of 10,000 or more, the molecular ions corresponding to tri- to octa-PBDD/Fs can be monitored in discrete mass groups, in much the same way as PCDD/Fs (Fernandes et al., 2004, 2008; Kotz, 2006; Ashizuka et al., 2008; Zacs et al., 2013; Pajurek et al., 2019; Diletti et al., 2020). Mass calibration however, requires extension to much higher masses as the molecular ion for ^{13}C labelled OBDD has an m/z value of 831.3645 daltons, considerably above the corresponding OCDD at 475.7691 daltons. High boiling perfluorokerosene is commonly used to allow calibrated monitoring at this mass range.

More significant differences from PCDD/F measurement are however most evident in the parameters used for gas chromatography. Although 60 m, 5% phenylmethyl bonded phase type columns with a 25 µm phase loading are most commonly used for PCDD/Fs, the chromatography of PBDD/Fs under these conditions, would suffer from adsorption resulting in

poor peak shapes and reduced or poor sensitivity. Although these phases may be used, a lighter phase loading (0.1 µm) reduces adsorption and provides more consistent results (Fernandes et al., 2008), but preferably, a 30 m 5% diphenyl, 95% dimethyl polysiloxane phase column allows shorter retention times, with lower rates of on-column degradation and better reproducibility. However, other GC columns have also been used and cover the range of available GC columns from long polar types (e.g. a 60 m cyanosilicone phase with a 0.20 µm loading) (Haglund et al., 2007), to short (15 m) non-polar, 5% phenylmethyl, with a 0.10 µm loading (Diletti et al., 2020). Two other precautions are essential in order to achieve robust and sensitive results for PBDD/F measurements. These are a scrupulously clean injector and the use of injection liners that are inert and deactivated, such as those with silanised coatings. Most of the common chromatography problems (Fernandes et al. 2004; Hagberg 2010, Hagberg et al., 2011; Fromme et al., 2016) encountered with PBDD/Fs arise from adsorption on the residual carbon deposits found in injectors and also in the first few centimetres of the GC columns that can sometimes suffer from charring due to the higher injector temperatures used to volatilise PBDD/Fs (up to 325 °C). The other area where adsorption can occur is in the GC to MS transfer line, and here the maintenance of the correct temperature without cold spots is essential. A range of 250 ° to 290 °C has been found to provide adequate results for PBDD/Fs.

4.3 Validation and quality aspects

The complexity of the analytical methodology and the relatively low concentration levels that are detected in foods and animal/human tissues, demand robust quality control measures that should be regularly implemented to ensure reliable data. This is particularly essential for food data that is used to estimate human exposure, assess health risks and formulate regulatory policy. There are no specific guidelines for the performance of analytical methods for PBDD/Fs, but given the obvious similarities to PCDD/Fs, the regulatory guidance (European

Commission, 2017) on PCDD/F and PCB analysis provides a good indication of the requirements for reliable analysis. The regulation requires the use of HRMS, control of analytical recovery, use of ^{13}C labelled surrogates/internal standards and provides specifications on sensitivity, accuracy, precision and measurement uncertainty (European Commission, 2017). Additionally, there must be an awareness that due to the chemical differences between PBDD/Fs and PCDD/Fs, more attention should be given to some aspects of PBDD/F analysis (such as PBDD/F adsorption during measurement, the requirement for very clean instrumentation as already described, photo-lability, etc.), and the experience of the analyst is also key to ensuring reliable results. Laboratories that analyse food should be able to demonstrate analytical proficiency for quantitation of PBDD/Fs at the sub-part per trillion (0.01 to 0.1 pg/g) level by validation, ongoing internal quality control and performance testing when this is available. In practice, this sensitivity is achievable for most congeners apart from the higher brominated hepta- and octa-brominated congeners where LOQs are higher (Table 1).

Adsorption of PBDD/Fs during the measurement process can lead to non-detection of congeners, (Hagberg et al., 2011; Fromme et al., 2015) particularly higher brominated congeners, so it is absolutely essential that appropriate ^{13}C labelled surrogates/internal standards are used for analysis and quantitation. Poor response to these standards would alert the analyst to take corrective action to reduce any adsorption that was occurring and to improve the sensitivity of the instrumentation (e.g. by cleaning affected surfaces, removing adsorbent residues, etc.).

5.0 Occurrence in food and dietary intake

As in the case of PCDD/Fs, dietary intake is likely to be the most significant pathway of human exposure to PBDD/Fs. Inadvertent ingestion, e.g. through hand to mouth contact after handling

of plastic materials that are known to be contaminated with PBDD/Fs (Straková et al., 2018) may also be a potentially significant pathway, particularly for young children. Dietary intake is also the most likely exposure pathway in land animal (Fernandes et al., 2019) and aquatic biota, particularly fish and shellfish species and their predators such seals, whales and penguins (Fernandes et al., 2009A; Mwangi et al., 2016; Bjurlid et al., 2018; Zacs et al., 2013). PBDD/Fs also have higher log K_{OW} values (between 5.0 and 10 for 2,3,7,8- substituted congeners), so dietary uptake is likely to be more significant than uptake from water in marine species (but filter feeding species may be impacted in waters with PBDD/F contaminated particulate matter). Although there are some studies (e.g. Haglund, 2010; Malmvärn et al., 2005) that have measured non-2,3,7,8-substituted PBDD/F congeners, these are not included in the estimation of TEQ, and all studies described here have measured 2,3,7,8- substituted PBDD/F congeners.

5.1 Marine foods

Early studies investigating PBDD/Fs in fish such as carp (Loganathan et al., 1995) and salmon (Wiberg et al., 1992) were unable to detect these contaminants, either because levels were not elevated during this period or because the LOQs of the methodology used (2-8 pg/g and 1 pg/g respectively for these studies), were too high. However, approximately a decade later, a study on marine fish and shellfish (Fernandes et al., 2005A), investigating 50 composited samples (edible muscle tissue, excluding skin and organs) of different species reported TEQs of 0.02 to 0.26 pg/g ww. The highest congener concentration was reported for 2,3,7-TrBDD in an oyster sample, at 6.28 pg/g ww (although this congener was not included in the TEQ calculation), but for fish samples, the highest concentration was seen for HpBDF at 0.45 pg/g ww in wild dogfish. Some species such as mussels, crab, sea bass, sprats and whitebait, appeared to be more prone to contamination, displaying a range of PBDF congeners, but only tri- and tetra-BDDs. Two later studies on marine shellfish sampled from Scottish waters and from coastal

regions around the UK (Fernandes et al., 2008, 2009A) confirmed the earlier observations. Data for edible species (mussels, native and pacific oysters, scallops and clams) that were harvested for retail and export markets, provided the first consistent evidence that PBDF congeners occurred more frequently and predominated over PBDDs. However, the studies also showed high levels of tri- and tetra-PBDDs, up to the maximum observed concentration of 14.5 pg/g ww of 2,3,7-trBDD, but undetectable levels of other PBDDs. The PBDD/F TEQ ranged from 0.01 to 0.23 pg TEQ/g ww. For the same regions, species selective differences were observed, with mussels and oysters generally showing greater levels of contamination, although the highest reported concentration (0.23 pg TEQ/g ww) was found in a sample of scallop gonad (which are often retailed separately). The high concentrations observed for 2,3,7-trBDD appear to be characteristic of marine species, particularly shellfish (at least in the North Atlantic region) which also display the presence of other lower brominated PBDDs, and is likely to be associated with a combination of marine pollution and biogenic formation (Haglund et al. 2007, 2010; Malmvärn et al., 2005, 2008) as discussed in section 2.4. In a study on fish from Japanese waters, Nakagawa et al. (2006), reported 1,2,3,4,6,7,8-HpBDF in seerfish, sole, conger eel, sea bream, flatfish and pike eel in concentrations increasing from 0.104 pg/g in sea bream to 25.6 pg/g ww in pike eel. 2,3,7,8-TeBDD was detected at 0.016 pg/g ww in natural sea bream and 2,3,7,8-TBDF was detected at 0.029 pg/g ww in conger eel. The mean concentration and range of PBDD/Fs was highest in the Seto Inland Sea at 0.19 pg TEQ/g ww and ND to 0.256 pg TEQ/g ww (Nakagawa et al., 2006).

Zacs et al. (2016), reported PBDD/F concentrations ranging from 0.07 to 0.14 pg TEQ/g ww in one to three year old salmon, and 0.02 to 0.14 pg TEQ/g ww in eels taken from Latvian rivers (Zacs et al., 2013, 2016). TEQ concentrations were lower relative to PCDD/Fs and PCBs in the same samples, but persistent organic pollutant (POP) contamination in general, increased with the proximity of the sampling sites to the Baltic Sea. The levels also appeared comparable to

cod liver (n = 51) from the Baltic Sea, with concentrations ranging from < 0.11 pg/g fat for 2,3,7,8 TBDD to 19 pg/g fat for 2,3,4,7,8-PeCDF (Roszko et al., 2015) and also compared well to canned Baltic Sea cod liver products retailed in Poland with a mean concentration of 0.08 pg PBDD/Fs TEQ/g ww (Falandysz et al., 2020). Comparatively, a number (n = 75) of edible fish species such as mackerel, sardines, herring, mullet, sea bass, sprat and turbot from other North Atlantic waters such as the Western coasts of Europe from Norway to Portugal in the south showed lower concentrations with levels ranging from < 0.002 to 0.04 pg TEQ/g ww (Fernandes et al., 2018). Additional occurrence data for fish and other foods is collated in Table 3 which lists the TEQ ranges (or concentration ranges where TEQs are not specified), generally as upper bound values.

5.2 Other foods

In 2005, a total diet study (TDS) in the UK (Fernandes et al., 2005B), investigating a full set of different foodstuffs, reported the presence of PBDD/Fs in all foods with TEQs ranging from 0.003 to 0.18 pg TEQ/g ww (green vegetables to oils/fats, respectively). Marine and animal products, such as meat, processed meat, milk products, offal and fish generally contained higher levels on average. Surprisingly, a food group comprising of sugars and preserves (sugar, chocolates, jams, syrups and other confectionary) showed positive detection for the full range of measured PBDF congeners.

The PBDD/F concentrations in eggs, milk, liver and fat from poultry, cows, sheep and pigs from Ireland, were reported (Fernandes et al., 2009B) to range from 0.09 pg TEQ/g to 3.5 pg TEQ/g fat (0.003 to 0.25 pg TEQ/g ww). Individual mean values for milk (n = 30), eggs (n = 20), fat (n = 38) and liver (n = 12) were 0.006, 0.03, 0.15 and 0.05 pg/TEQ/g ww respectively.

A later UK TDS study (Mortimer et al., 2013) also confirmed PBDD/Fs detection in all food groups. The PBDD/F TEQs ranged from 0.003 (canned vegetable) to 0.1 pg TEQ/g ww in sugars and preserves. A comparison to the range reported for the earlier 2005 UK TDS suggested a decline in concentrations, but the later study reported TEQs using WHO_{2005} TEF values which inherently lowers the TEQ because of the lower TEFs for some congeners. However more importantly, a later study investigating a trend in PBDD/F concentrations over nine years, reported that the observed decline in upper bound concentrations was simply a measure of the improvement in measurement sensitivity in later studies and that lower bound concentrations showed marginal increases over time for some food groups (Fernandes et al., 2014). Bramwell et al. (2017), reported that the most abundant congener in duplicate diet (DD) samples (DD samples are collected to be representative of an individual's dietary intake by retaining a duplicate portion of all food and drinks consumed during the study period – Bramwell et al., 2017) was 1,2,3,4,6,7,8 HpBDF, present in nearly all samples (median = 0.13, range = 0.05 - 0. 68 pg/g ww). These concentrations were higher than those for OCDD, the most abundant PCDD/F in the DD samples. 1,2,3,4,7,8-HxBDF was the next most abundant PBDD/F, though concentrations were over 10 times lower.

The PBDD/F content of hen's eggs in Poland were investigated in a recent study (Pajurek et al., 2019) that compared concentrations from different rearing methods. Concentrations ranged from 0.05 to 0.57 pg TEQ/g fat with mean values of 0.18, 0.17, 0.23 and 0.16 pg TEQ/g fat for free range, organic, barn and caged birds respectively. These concentration are similar to the PBDD/F TEQ concentrations for eggs reported in the UK, at 0.38, 0.31 and 0.17 pg/TEQ/g fat for three different sampling periods – 2003, 2007 and 2012 respectively (Fernandes et al., 2014).

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A study investigating the uptake of PBDD/Fs into the tissues and eggs of farmed animals, through the use of recycled materials used in farming, detected PBDD/Fs in muscle tissue and organs of pigs and chickens as well as in hen eggs (Fernandes et al., 2019). Evidence of uptake from some of the materials was seen in the skin and eggs of laying chickens with median levels ranging from 0.8 to 1.0 pg TEQ/g fat relative to the control (0.3 ng TEQ/g). The highest median value for eggs was 0.36 pg TEQ/g fat (control, 0.26 pg TEQ/g fat) comparing favourably with earlier studies from Poland and the UK. PBDD/F concentrations in the muscle tissue and liver of pigs ranged from 0.17 to 0.21 pg TEQ/g and 0.61 to 0.74 pg TEQ/g fat respectively.

The most recent study on PBDD/Fs in food (Diletti et al., 2020) included the simultaneous determination of PCDD/Fs and PCBs, in marine and animal products. Compared to other recent studies, the levels of PCDD/F and PCB contamination were generally low for all foods. PBDD/F concentrations in fish and shellfish ranged from 0.02 to 0.09 pg TEQ/g ww, and from 0.01 to 0.05 pg TEQ/g ww in other foods such as muscle tissue from poultry, pigs and cattle, milk from sheep and cows, and hen's eggs.

There is very little information on other foods or dietary supplements. Several di- to tetra-PBDD/Fs (including 2,7,8-TrBDF, 2,3,7-TrBD and 2,3,7,8-TBDD and TBDF) were identified in food supplements or products that are used to produce foods (e.g. sushi,) and included four different types of algae (green, red, brown, blue-green (cyanobacteria) algae) and krill oil (Salehi, 2013). Of the laterally substituted congeners, the highest concentration of 39 pg/g dry weight (dw) was seen for 1,3,6,8-TeBDD in a sample of red algae. 2,3,7,8 TBDF was not detected and 2,3,7,8-TBDD occurred in a number of samples with a maximum of 3.2 pg/g dw in brown algae. Falandysz et al. (2020), reported concentrations of 0.14 to 0.17 pg TEQ/g ww in historical samples of medicinal cod liver oil from the Baltic Sea and 0.16 to 0.17 pg TEQ/g

ww in similar products sourced from the Norwegian Sea. The samples were taken between 1972 and 2001 but there was no apparent trend in concentrations. The data for all the above studies and others are collated in Table 3.

5.3 Dietary Intake

For food contaminants such as PCDD/Fs and PBDD/Fs, where the majority of the population is not likely to be occupationally exposed, the main pathway to human exposure is through dietary intake, estimated (for PCDD/Fs) to account for ~ 90% of total exposure (WHO, 2016). For these types of contaminants, the estimation of dietary intake is thus indispensable for assessing human exposure and evaluating the associated risk to human health. Dietary intake that is estimated from individual foods at a particular period, provides an indication of exposure, but better estimates of exposure for wider populations can be made using total diet studies which consider the average intake (of a nutrient or contaminant) by different sections of the general population, from twenty main food groups collected over a defined period (Mortimer et al., 2013). Duplicate diet studies may also be used although these are dependent to some extent on personal habits and preferences.

There are very few estimates for the dietary intake of PBDD/Fs. Based on a TDS study, Mortimer et al. (2013), estimated PBDD/F + PBB (polybrominated biphenyl) intakes ranging from 0.29 (adults) to 0.95 (toddlers) pg TEQ/kg bodyweight (bw)/day for average consumption, and 0.51 (adults) to 1.64 (toddlers) pg TEQ/kg bw/day for higher level (97.5 percentile) consumption. Although the TEQ included a contribution from three dioxin-like PBB congeners, this was considered negligible (around 3%, upper bound) as PBBs were mostly undetected in the TDS samples. The contribution of the PBDD/F TEQ to the summed TEQ (which included PCDD/Fs, PCBs, PXDD/Fs and PXBs in the same samples) was consistently

around 30% for all age groups and represented a significant proportion of the summed TEQ intake (Mortimer et al., 2013). A duplicate diet study (Bramwell et al., 2017) using samples from around the same period (2011), reported corresponding upper bound mean and 97.5 percentile exposure for adults at 0.2 and 0.56 pg TEQ/kg bw/day, which was similar to the TDS study. An earlier Japanese market basket study (Ashizuka et al., 2007) reported an average upper bound adult intake of 1.58 pg TEQ/kg bw/day, for samples collected in 2004/2005, almost a decade earlier than the UK TDS study. However, the highest adult intakes for PBDD/Fs were reported (Miyake et al., 2008) for two coastal cities in China with lower bound estimates of 7.56 and 6.26 pg TEQ/kg bw/day and upper bound estimates of 8.74 and 8.08 pg TEQ/kg bw/day for Guangzhou and Zhoushan respectively. Up to 70% of the intake was attributed to fish and bivalve consumption. In the most recent report based on marine and animal products, Diletti et al. (2020), reported upper bound PBDD/F intakes of 0.17 to 0.42 pg TEQ/kg bw/day for adults and one to three year-old children, which were very similar to the corresponding PCDD/F intakes of 0.19 and 0.43 pg TEQ/kg bw/day. When the estimated intakes from these studies are considered with respect to the proposed tolerable weekly intake (TWI) of dioxin-like toxicity of 2 pg/kg bw/week (EFSA, 2018), the contribution from PBDD/F toxicity represents a significant proportion of the cumulative intake.

6.0 Occurrence in human tissues

The widespread distribution of PBDD/Fs seen in foods combined with the long half-lives for these compounds, previses occurrence in human tissues. As with food, there is limited information, but some occurrence data on adipose tissue, blood, liver and particularly milk is available. Most of these studies have investigated laterally substituted (2,3,7,8-Br-substituted) tetra- to octa-brominated congeners, although 2,3,7-TrBDD and 2,7,8-TrBDF have also been

measured. Most of the more recent reports have used the PCDD/F TEF scheme to summarise tissue occurrence.

6.1 Human milk

One of the earliest studies (Ohta et al., 2004) examined 9 pooled milk samples collected from nursing mothers (16 first-time and 20 multiparous) in Japan, reporting a concentration range of 0.13 to 1.2 pg TEQ/g lipid (max. of 0.54 pg TEQ/g for first time and 1.2 pg TEQ/g for multiparous, mothers). The more abundant congeners were 2,3,7,8-TBDF and 2,3,4,7,8-PeBDF, but two non-planar TBDD congeners (1,3,7,8- and 1,3,7,9-TeBDD) were also noted at comparatively high levels. A PBDD/F TEQ of 0.67 pg/kg lipid was reported (Colles et al., 2008) for a pooled milk sample from Belgian mothers, and a later, pooled Belgian milk sample from Flanders (Croes et al., 2013) reported a TEQ of 0.42 or 0.34 pg/g lipid, depending on whether TEF_{1998} or TEF_{2005} was used. Similar concentrations (0.45 to 2.64 pg TEQ /g lipid) and a similar frequency of occurrence of 2,3,7,8-TBDF and 2,3,4,7,8-PeBDF as the Japanese study, were seen in 31 pooled breast milk samples from 25 countries (Asia-Pacific, Europe and North/South America), (Kotz et al., 2005; Kotz, 2006). Samples from Europe showed relatively higher TEQ (mostly > 1 pg TEQ/g lipid) compared to other regions.

In an Irish study (Pratt et al., 2013), breast milk provided by 109 first-time mothers (average age 32.7 years) was pooled by location of collection centres to yield 11 composite samples. PBDD/Fs

were detected in all samples averaging 0.72 pg TEQ/kg fat with a range of 0.58 to 1.23 pg/g fat. The occurrence was characterised by the presence of all 6 measured PBDFs being present in almost all samples (1,2,3,4,6,7,8-HpBDF occurred at the highest concentrations – max. 2.3 pg/g), while conversely only 2,3,7,8-TBDD was detected among the 6 PBDDs analysed. The

corresponding range for PCDD/Fs in the same samples was 4.48 to 8.8 pg TEQ/g fat. The concentrations were similar to breast milk from the UK with a range of 0.53 to 1.78 pg TEQ/g fat, with the detection of mainly PBDF congeners (2,3,7-TrBDD and 2,3,7,8-TBDD were detected in a single sample). This compared to a range of 3.95 to 6.9 pg TEQ/g fat for PCDD/F TEQ in the same samples. A Vietnamese study (Tue et al., 2014) on dioxin-like compounds in 25 human milk samples from women working at three e-waste recycling sites, was only able to detect 2,3,7,8-TBDF at levels of < 0.49 to 1.4 pg/g lipid. Similarly, another Vietnamese study (Chen et al., 2018) reported undetectable levels from 25 breast milk samples from southern Taiwan.

6.2 Blood and serum levels

PBDD/Fs, were detected in the serum of twelve Californian fire fighters at relatively high concentrations (Shaw et al., 2013) ranging from 1350–7200 pg/g fat (mean 3340 pg g fat, median 2490 pg/g fat) for ΣPBDD/Fs. The most frequently detected congener was OBDF which accounted for much of the above concentrations, but 2,3,7,8-TBDD, 2,3,7,8- TBDF, 1,2,3,7,8- and 2,3,4,7,8- PeBDFs were also detected in a few of the samples. The corresponding TEQ concentrations (mean value 104 pg/g fat) in the same samples were reported to be 21 times higher than the PCDD/F TEQ, at 5 pg/g fat and suggests that occupational exposure to some population groups from PBDD/Fs was substantial, and similar to historical occupational exposures (1975-1985) seen in the blood (n = 42) of German extrusion and blending plant workers (Zorber et al., 1992), with a median, fasted blood TEQ of 116 pg/g fat (although a different TEF system was used - see Neubert et al., 1990). Mean serum values of 0.44 and 0.55 pg TEQ/g fat for two locations were reported (Bruce-Vanderpuije et al., 2019) for 34 Ghanaian mothers, compared to a PCDD/F levels of 1.55 and 2.6 pg TEQ/g fat for the same cohorts. Similarly, another recent study (Fromme et al., 2016)

reported corresponding PCDD/F and PBDD/F concentrations in the blood of 42 randomly selected German subjects aged between 20 and 68 years. The mean PBDD/F TEQ reported was 3.4 up to a maximum of 9.3 pg/g fat, compared to a mean and maximum of 7.2 and 20.6 pg/g fat for PCDD/F TEQ.

6.3 Adipose tissue and liver

Adipose tissue performs a key function in the storage and toxicokinetics of lipophilic contaminants such as PCDD/Fs and PCBs (Kim et al., 2011; La Merill et al., 2013), and studies on the PBDD/F contents in adipose tissue show similar bioaccumulation. One of the first studies (Choi et al., 2003) investigating PBDD/F concentrations in a general population (rather than occupational exposure) measured five 2,3,7,8-substituted tetra- and penta-PBDD/F congeners in adipose tissue from ten subjects in Tokyo in 1970, and again in 2000. Only 2,3,7,8-TBDD, 2,3,7,8-TBDF, and 2,3,4,7,8-PeBDF were measured, with levels of up to 4.3 pg/g fat for 2,3,7,8-TeBDF. Although the levels of the detected congeners decreased from 1970 to 2000 (median sum value, from 6.1 to 3.4 pg/g respectively), the proportions of these congeners relative to the corresponding PCDD/Fs increased. Investigating a similar number of subjects (aged from 19 to 65 yrs.) in the Swedish general population in 2007, Ericson-Jogsten et al. (2010), reported a range of 0.26 to 0.96 pg TEQ/g fat for five measured 2,3,7,8-substituted congeners which contributed 1–10% (depending on the subject), of the total (all 17 congeners) PCDD/F TEQ (5–18 pg TEQ/g fat). 2,3,7,8-TeBDF was the most frequently occurring congener and generally the most abundant, followed by the penta-BDFs. A follow-up study on 10 individuals was able to detect additional congeners (1,2,3,4,7,8-/1,2,3,6,7,8-HxBDD, 1,2,3,4,6,7,8-HpBDD and 1,2,3,4,6,7,8-HpBDF) due to better LOQs (Hagberg et al., 2011). Although the TEQ was not reported, the sum of PBDD/F congeners ranged from 0.33 to 3.9 pg/g fat.

In 2015, Thatcher et al., reported PBDD/F concentrations in the adipose tissue and liver of UK patients undergoing gastric bypass surgery for weight loss as well as other non-bariatric surgery patients. All six PBDF congeners that were analysed (Fernandes et al., 2008), were detected in almost all of the samples, while among the 6 measured PBDDs, 2,3,7,8-TeBDD was the most frequently detected, followed by 2,3,7-TrBDD, but 1,2,3,7,8-PeBDD. 1,2,3,4,7,8/1,2,3,6,7,8- and 1,2,3,7,8,9-HxBDDs were rarely detected. The mean concentrations measured in separate samples of visceral and sub-cutaneous fat from the same patients (n = 21) were very similar at 0.84 and 0.85 pg TEQ/g lipid respectively, (mean PCDD/F concentrations were 21.1 and 21.2 pg TEQ/g lipid respectively, n = 59/60) and samples of liver tissue showed a mean concentration of 3.88 pg TEQ/g lipid (mean PCDD/F TEQ 41.2 pg TEQ/g lipid). The relative concentrations in adipose tissue were similar to those reported for the Swedish samples. Table 4 summarises the occurrence of PBDD/Fs in the various human tissues discussed in this section.

7.0 Discussion

The occurrences in food, confirmed by detection in human tissues establish beyond doubt that humans are exposed to PBDD/Fs and hence to their associated dioxin-like toxicity. However, any current assessments of the toxicity contribution from this existing data will always have an element of underestimation as not all contributing congeners are included. There will also be an element of uncertainty due to the use of analogous chlorinated TEFs. The number of congeners being measured continues to improve with more standards becoming available, and recent studies have reported up to 12 or more compounds compared to early studies where up to four congeners were included (Zorber et al., 1992; Choi et al., 2003). To date, there is no reported food or human tissue data with reported concentrations for all the laterally substituted congeners that are considered toxic. Most studies report TEQ for five to twelve congeners and

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although the relative potency values suggest that tetra- and penta- substituted congeners (most commonly measured) will contribute most to the TEQ, more recent studies report more significant contributions from the higher brominated congeners (Pratt et al., 2013; Zacs et al., 2016; Bramwell et al., 2017; Diletti et al., 2020). Additionally, the tri-brominated compounds measured in some studies (but not included in the TEQ) are also reported to show relatively potent AhR activity (Olsman et al., 2007; Samara et al., 2009; Wall et al., 2015) and occur at high concentrations in some foods (e.g. shellfish). Although most food and human tissue studies have used the PCDD/F TEF scheme, the uncertainties of using analogous REP values combined with the lack of chronic dosing studies or comparative toxicokinetics for PBDD/Fs from rodents and human studies, are significant gaps in our understanding of the magnitude of the contribution to overall toxicity.

Despite these gaps, the existing data provide some consistent observations. It is clear from the data for food and human tissues that PBDFs occur more frequently and to a greater extent in most cases (marine shellfish are a notable exception). This pattern of occurrence (See Figure 2A) corresponds well with the patterns observed in the major sources – industrial production of brominated chemicals, combustion, etc. as described in section 2 - and is observed for many different food types (Figure 2B). The very low and infrequent occurrence of PBDDs in foods leads to a wide difference (typically between 40 and 70%) between upper and lower bound TEQ data - both in terms of occurrence and dietary exposure, principally because of the higher relative potencies assigned to PBDDs. The most recent study on PBDD/Fs in food (Diletti et al., 2020) also included medium bound TEQ estimates. In terms of dietary exposure and the protection of human health, medium or even upper bound levels may be more realistic as currently, not all planar PBDD/F congeners are measured and the proposed TEF values for some of the more frequently occurring and relatively more abundant congeners (e.g. 2,3,7,8,-

TBDF, 1,2,3,7,8-PeBDF) may be underestimated (Okimoto et al., 2008; van den Berg et al., 2013; Frawley et al., 2014; Suzuki et al., 2017).

Insert Figure 2

When compared to PCDD/Fs, qualitative as well as quantitative differences are observed for PBDD/F occurrence in food. The most frequently occurring PBDD/F congeners were 2,3,7,8-TeBDF, 2,3,4,7,8-PeBDF, 1,2,3,4,6,7,8-HpBDF and 2,3,8-TrBDF of which the first three, contributed most to the TEQ. This contrasts with PCDD/Fs in similar food matrices, where most 2,3,7,8-Cl-substituted PCDDs and PCDFs are usually present. Quantitatively, PBDD/F TEQ is generally lower than PCDD/F TEQ, although there are considerable variations depending on the food type with fish and animal based products generally showing lower PBDD/F to PCDD/F ratios. To some extent this may be due to the underestimation of PBDD/F TEQ as not all congeners are reported. In a TDS that measured a full range of food types (Fernandes et al., 2012; Mortimer et al., 2013), PBDD/F TEQ in food of animal origin, was lower on average, at 30% (lower bound basis) and 50% (upper bound basis) of the PCDD/F TEQ in the same foods. Fish and shellfish were relatively, even lower, as seen in Figure 3. The corresponding proportions in a later study on individual foods (Diletti et al., 2020), were 6% (LB) and 100% (UB) for a similar range of foods in which PBDD/Fs were detected. However, for other foods (e.g. bread, cereals, vegetables, fruits, nuts, sugars and preserves, etc.), the PBDD/F contribution is generally greater than the PCDD/F TEQ, on average ~ 200% (LB or UB) as seen in Figure 3. Therefore the ratios seen in the duplicate diet study (Bramwell et al., 2017) at 70% LB and 140% UB may provide a better estimate as they reflect the integral of an individual's daily consumption of different foods. Notwithstanding, the variation in ratios from these studies, it is evident from this limited number of studies that there is a significant proportion of PBDD/F TEQ intake through the diet. Additionally, studies that base dietary intake estimates solely on food of marine and animal origin may exclude a very significant

proportion of PBDD/F intake from other foods. This is of current significance, given the shift toward sustainable diets, vegetarianism and veganism, with less fish and meat being consumed.

When reported PBDD/F TEQ intakes (Mortimer et al., 2013; Bramwell et al., 2017; Diletti et al., 2020) are considered relative to the new TWI for dioxin-like contaminants (2 pg TEQ/kg bw/week) reported in 2018 (EFSA, 2018), it is clear that some population groups, and in particular, young children, would exceed the weekly tolerable intake of PBDD/F TEQ, in some cases, even for mean consumption estimated with LB data.

Insert Figure 3

The average PBDD/F congener distribution in human tissues (Figure 4) appears to be similar to food (Figure 2A) with PBDFs dominating the profile. PBDD/F concentrations in human tissues are generally lower than PCDD/Fs. Thus, the PBDD/F TEQ was approximately 11.4% of the PCDD/F TEQ, (Pratt et al., 2013), in Irish human milk and approximately18% in UK human milk, which are comparable to the levels of up to 15% reported for adipose tissue (Erickson-Jogsten et al., 2010). Reported levels in blood, in the occupationally exposed (Zorber et al., 1992; Shaw et al., 2013; Bruce-Vanderpuije et al., 2019) were generally higher, mostly reflecting occupational exposure pathways.

The equivalent PBDD/F TEQ concentrations observed in human subcutaneous and visceral fat (Thatcher et al., 2015) indicated equilibrium between these two tissues and also with blood as the transporting fluid. The positive association between tissue concentrations and age observed for PCDD/Fs, but not for PBDD/Fs, (Thatcher et al., 2015; Fromme et al., 2016), may possibly be a result of different patterns and timelines of environmental and food contamination for PCDD/Fs and PBDD/Fs (PBDD/F contamination is likely to have been more prominent in recent times, corresponding to the later, increasing usage of bromine and BFRs), or differences

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in the elimination half-lives for these two sets of analogues. The relatively higher concentrations of PBDD/Fs in liver (on a lipid basis, the concentration ratio of liver to adipose tissue was ~ 2:1 for PCDD/Fs, but greater than 4:1 for PBDD/Fs) however, suggest that PBDD/Fs may target the liver to a greater extent than PCDD/Fs.

8.0 Conclusions

PBDD/Fs occur in most commonly consumed foods and contribute to the dietary intake of dioxin-like toxicity. The pattern observed in most foods is dissimilar to PCDD/Fs with occurrence favouring the PBDFs over the PBDDs which reflects the major source profiles. On the basis of the currently available data on occurrence in food and human tissues, as well as the reported toxicological effects, it is evident that the omission of PBDD/Fs from the toxic equivalence scheme used for dioxin-like contaminants (currently only PCDD/Fs and PCBs are included) underestimates the cumulative toxicity arising from this mode of action. This observation has obvious implications for monitoring studies, regulation and risk assessment.

Insert Figure 4

The use of analogous PCDD/F TEFs, now used by most of the recent studies on PBDD/Fs, requires consolidation and updating through new relative potency studies which should include all of the relevant PBDD/F congeners. This would reduce the uncertainties inherent in the assumption that the effects for the two sets of analogues are equivalent. This should be complemented by new studies on occurrence and dietary intake that would help establish the current levels of contamination and refine the assessment of human exposure to these contaminants. The results from these studies suggest that although food derived from animal tissues contains PBDD/Fs, other foods also contribute significantly to body burdens.

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Figure 1: PBDD/F molecules showing 2,3,7,8-tetrabromodibenzodioxin (upper) and 2,3,4,7,8-pentabromodibenzofuran (lower) configurations

Figure 2: PBDD/F occurrence in food showing A. typical congener profile and B. congener distribution in different food types

Figure 3: Relative occurrence of PBDD/F and PCDD/F TEQ in different foods.

Figure 4: Mean PBDD/F congener profiles in human tissues.

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Table 1: Typical analytical method performance parameters reported for PBDD/F analysis in food

PBDD/F analytes	Intermediate Precision	Recovery Range	Limit of Quantitation	Linear Range	[§]Measurement uncertainty	Reference
	%	%	pg/g	pg	%	
Tri- to hepta-congeners	10 to 20	50 to 90	<0.01 to 0.05*	0.1 to 100	25 at 0.5 pg/g; Up to 200 at 0.02 pg/g	Fernandes et al., 2009
Tetra- to octa-congeners	7 to 20	72 to 96	0.001 to 5*	0.4 to 500	29 to 46% at 1.0 to 4.0 pg/g	Diletti et al., 2020

*For HpBDD/F and OBDD/F congeners. [§]Expanded uncertainty (f=2)

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Table 2: Most relevant source types with concentrations of emitted or by-produced PBDD/Fs

Source Type	Product	Measured congeners/ homologues	Concentration or (TEQ)	Notes	Reference
BFR production	Penta-BDE (DE-71) Octa-BDE (DE-79) Deca-BDE	PBDFs sum	0.26 mg/kg 10 to 19 mg kg 31 to 50 mg/kg	Sum of PBDFs	Hanari et al., 2006
	PBDE mixtures	PBDDs	<100-200 µg/kg	not detected	Hanari et al., 2006
	Deca-BDE mixtures	PBDD/F sum Octa-BDD	3.4 to 13.9 µg/g 1.9 to 139 ng/g	v. low levels of other PBDDs also observed	Ren et al., 2011
Combustion	Metallurgical process	PBDD/F sum	0.02 - 3.0 ng/Nm^3 0.56 - 5.8 ng Nm^3	Taiwan China	Wang et al., 2010 Du et al., 2010
	Electronic waste	2,3,7,8-PBDD/F congeners	(19 µg TEQ/kg) solid (160 µg TEQ/kg) liquid (0.057 µg TEQ/kg) gas	Experimental study; printed circuit boards	Duan et al., 2011
	Residential fires	sum of twelve, 2,3,7,8-PBDD/F congeners	4220–18,700 pg/m^3, gas phase 76–4092 pg/m^2 soot	Experimental study; emissions during firefighting	Bjurlid et al., 2017
Photolytic formation	Decomposition of BFRs	Homologue sum, mono- to hepta- PBDFs	1,600-14,000 ng/ml test solution	Experimental study; decomposition of Deca-BDE	Hagberg et al., 2006
	Decomposition by natural sunlight	Homologue sum, PBDFs	Max. concentration - 8.9 mg/kg on day 7	Deca-BDE in high impact polystyrene	Kajiwara et al., 2008
Recycling processes	Electronic shredder waste Soil around facility workshop floor dust	11 congeners, 2,3,7,8-PBDD/Fs	0.39−18.5 ng/g dw 0.72−800 ng/g dw 89.6−143 ng/g dw	Large -scale electronic waste recycling facility	Ma et al., 2009
	Polymers from electronic equipment housing and mixed polymers	Sum of 4 or 8 (regulated) congeners; 2,3,7,8-PBDD/Fs	1 to 35 µg/kg	Range of concentrations in 9 recycled materials	Schlummer et al., 2004

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Table 3: PBDD/F occurrence in foods

Food Type	No. of samples	Sampling period	Geographical origin	Measured congeners	TEQ Range pg/g whole (lipid) wt.	Notes	Reference
Fish and Shellfish							
Marine Fish/shellfish/ fish products	48, Composite	2003/2004	UK & imported	2,3,7,8-Br substituted PBDD/Fs (10 congeners, T_4 - H_7) + 2,3,7-TriBDD & 2,3,8-TriBDF	Fish 0.02 - 0.08 Shellfish 0.02 - 0.26 Products 0.02 - 0.05	30-60 sub-samples per composite. TEF_{1998}	Fernandes et al., 2005
Marine Fish/shellfish	23	2003 - 2004	East & South China Seas	2,3,7,8-Br substituted PBDD/Fs (9 congeners, T_4 - H_6)	(18.8 - 1430) (Σ congeners, NOT TEQ)	6 species- fish, crabs, shrimps, bivalves and cephalopods	Miyake et al., 2008
River Fish	30	2003	USA (East coast)	2,3,7,8-Br substituted PBDD/Fs (12 congeners, T_4 – O_8)	0.005 - 0.30	smallmouth and striped bass. TEF_{2005}	Skinner, 2012
Marine Fish	45, Individual	2004/2005	Japan	2,3,7,8-Br substituted PBDD/Fs (T_4 - H_7)	N.D. - 0.26	Samples from 3 marine regions TEF_{1998}	Nakagawa et al., 2006
Marine and freshwater Fish/shellfish	26, Composite	1995-2004	Baltic Sea	Range of Di-, Tri- and Tetra-PBDDs	N.D. - 4100 (Σ congeners, NOT TEQ)	Species of perch, eel and herring. Also mussels, crab and shrimps	Haglund et al., 2007
Marine shellfish	35, Composite	2006	Scotland	2,3,7,8-Br substituted PBDD/Fs (10 congeners, T_4 - H_7) + 2,3,7-TriBDD & 2,3,8-TriBDF	0.02 - 0.23	Mussels, Pacific oysters & scallops TEF_{1998}	Fernandes et al., 2008
Marine shellfish	25, Composite	2006/2007	UK (excluding Scotland)		0.01 - 0.21	Mussels, Native & Pacific oysters, Cockles TEF_{1998}	Fernandes et al., 2009
Marine Fish/shellfish	38, Individual (composite shellfish	2007	UK		<0.01 - 0.10	Retail fish, shellfish and products. TEF_{1998}	Fernandes et al., 2014
Marine (Deep Sea) fish, shellfish, Freshwater (FW) fish	48 Individual; 5, composite (shellfish)	2008	Scotland		Fish 0.01 - 0.04 Shellfish 0.01 - 0.02 FW fish 0.01 - 0.06	23 Deep Sea species, 5 freshwater species 1 shellfish species (mussels) TEF_{1998}	Fernandes et al., 2009C
Freshwater fish	17 Individual	2008	England	2,3,7,8-Br substituted PBDD/Fs (10 congeners, T_4 - H_7) + 2,3,7-TriBDD & 2,3,8-TriBDF	0.03 - 0.05	7 species TEF_{1998}	Rose & Fernandes, 2010
Salmon	25 Individual		Latvia, rivers/Baltic Sea	2,3,7,8-Br substituted PBDD/Fs (14 congeners, T_4 - OBDD/F)	0.07 - 0.14	TEF_{2005}	Zacs et al 2013
Cod Liver	51, Composite	2013	Baltic Sea	2,3,7,8-Br substituted PBDD/Fs (T_4 - H_6)	(0.8 - 38.9) (Σ congeners, NOT TEQ)		Roszco et al., 2015
Eels	58, Individual	2013/2104	Latvia (Inland Lakes)	2,3,7,8-Br substituted PBDD/Fs (10 congeners, T_4 - H_7)	0.02 - 0.14	TEF_{2005}	Zacs et al 2016
Marine fish	75, Individual	2013 - 2015	North Atlantic	2,3,7,8-Br substituted PBDD/Fs (10 congeners, T_4 - H_7) + 2,3,7-TriBDD & 2,3,8-TriBDF	0.01 - 0.04	Seven commonly consumed species TEF_{2005}	Fernandes et al., 2018
Cod Liver	2, Composite	2017	Baltic Sea		0.08	TEF_{2005}	Falandysz et al., 2020
Marine Fish/shellfish	19, Indiv. fish 8, comp. shellfish.	2014 - 2016	Italy	2,3,7,8-Br substituted PBDD/Fs (12 congeners, T_4 - Octa)	0.02 - 0.09	TEF_{2005}	Diletti et al 2020

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Table 3: (continued) PBDD/F occurrence in foods

Food Type	No. of samples	Sampling period	Geographical origin	Measured congeners	TEQ Range pg/g whole (lipid) wt.	Notes	Reference
Meat, offal & meat products							
Meat, offal and products	3, Composite	2003	UK	2,3,7,8-Br substituted PBDD/Fs (10 congeners, T_4 - H_7) + 2,3,7-TriBDD & 2,3,8-TriBDF	0.03 - 0.06	24 sub-samples per composite. TEF_{1998}	Fernandes et al., 2005
Animal fat (bovine, ovine & porcine)	25, Composite	2006 -2007	Ireland		0.12 - 0.25	10 - 40 sub-samples per composite. TEF_{1998}	Fernandes et al., 2009B
Offal	12, Composite	2007 -2007	Ireland		0.01 - 0.15	10 - 40 sub-samples per composite. TEF_{1998}	Fernandes et al., 2009B
Meat, offal and products	33, Individual	2007	UK		0.01 - 0.17	TEF_{1998}	Fernandes et al., 2014
Meat, offal and products	3, Composite	2012	UK		0.02 - 0.05	24 sub-samples per composite. TEF_{2005}	Mortimer et al., 2013
Beef & Pork	12, Individual	2014- 2016	Italy	2,3,7,8-Br substituted PBDD/Fs (12 congeners, T_4 - Octa)	0.02 - 0.05	TEF_{2005}	Diletti et al 2020
Eggs & Poultry							
Eggs & Poultry	2, Composite	2003	UK	2,3,7,8-Br substituted PBDD/Fs (10 congeners, T_4 - H_7) + 2,3,7-TriBDD & 2,3,8-TriBDF	0.03	24 sub-samples per composite. TEF_{1998}	Fernandes et al., 2005
Hens eggs and avian (duck, hen) fat	33, Composite	2006 -2007	Ireland		0.03 - 0.19	24 sub-samples per egg composite. TEF_{1998}	Fernandes et al., 2009B
Eggs & Poultry	7, Composite eggs; 4, Individual poultry	2007	UK		0.01 - 0.06	12 -18 sub-samples per egg composite. TEF_{1998}	Fernandes et al., 2014
Eggs & Poultry	2, Composite	2012	UK		<0.01 - 0.02	24 sub-samples per composite. TEF_{2005}	Mortimer et al., 2013
Hens eggs	82, individual samples		Poland	2,3,7,8-Br substituted PBDD/Fs (13 congeners, T_4 - Octa)	(0.05 - 0.57)	Eggs from free range, organic, barn, and caged hens. TEF_{2005}	Pajurek et al., 2019
Hens eggs	6 composite	2014- 2016	Italy	2,3,7,8-Br substituted PBDD/Fs (12 congeners, T_4 - Octa)	0.02 - 0.05	TEF_{2005}	Diletti et al 2020
Milk & Dairy products							
Milk & products	2, Composite	2003	UK	2,3,7,8-Br substituted PBDD/Fs (10 congeners, T_4 - H_7) + 2,3,7-TriBDD & 2,3,8-TriBDF	0.03 - 0.04	24 sub-samples per composite. TEF_{1998}	Fernandes et al., 2005
Cow's Milk	30, Composite	2006 -2007	Ireland		<0.01 - 0.01	Pooled sample from main farm tank. TEF_{1998}	Fernandes et al., 2009B
Milk (cows, goat, sheep) & cheese	10, Individual	2007	UK		0.01 - 0.07	TEF_{1998}	Fernandes et al., 2014
Milk & products	2, Composite	2012	UK		<0.01 - 0.03	24 sub-samples per composite. TEF_{2005}	Mortimer et al., 2013

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Milk (cows and sheep)	10, Individual	2014- 2016	Italy	2,3,7,8-Br substituted PBDD/Fs (12 congeners, T_4 - Octa)	0.01 - 0.02	TEF_{2005}	Diletti et al 2020

Table 3: (continued) PBDD/F occurrence in foods

Food Type	No. of samples	Sampling period	Geographical origin	Measured congeners	TEQ Range pg/g whole (lipid) wt.	Notes	Reference
Fruit, Vegetables & Nuts							
Fresh and tinned veg, fruits and nuts	7, Composite	2003	UK	2,3,7,8-Br substituted PBDD/Fs (10 congeners, $T_4 – H_7$) + 2,3,7-TriBDD & 2,3,8-TriBDF	<0.01 - 0.05	24 sub-samples per composite. TEF_{1998}	Fernandes et al., 2005
Fresh veg. and veg. products, fruits	16, Individual	2007	UK		<0.01 - 0.05	TEF_{1998}	Fernandes et al., 2014
Fresh and tinned veg, fruits and nuts	7, Composite	2012	UK		<0.01 - 0.03	24 sub-samples per composite. TEF_{2005}	Mortimer et al., 2013
Other foods							
Cooking oil/fat	1, composite	2003	UK	2,3,7,8-Br substituted PBDD/Fs (10 congeners, $T_4 – H_7$) + 2,3,7-TriBDD & 2,3,8-TriBDF	0.18	24 sub-samples per composite. TEF_{1998}	Fernandes et al., 2005
Cooking oils	3, Individual	2007	UK		0.18 - 0.21	TEF_{1998}	Fernandes et al., 2014
Cooking oil/fat	1, composite	2012	UK		0.08	24 sub-samples per composite. TEF_{2005}	Mortimer et al., 2013
Bread, cereals, preserves	3, composite	2003	UK		0.01 - 0.04	24 sub-samples per composite. TEF_{1998}	Fernandes et al., 2005
Bread, cereals, preserves	4, Individual	2007	UK		<0.01 - 0.05	TEF_{1998}	Fernandes et al., 2014
Bread, cereals, preserves	3, composite	2012	UK		0.01 - 0.10	24 sub-samples per composite. TEF_{2005}	Mortimer et al., 2013
Dietary supplements							
Cod liver oil	6, composite	1972 - 2001	Baltic & Norwegian Seas	2,3,7,8-Br substituted PBDD/Fs (10 congeners, $T_4 – H_7$) + 2,3,7-TriBDD & 2,3,8-TriBDF	0.14 - 0.17	TEF_{2005}	Falandysz et al., 2020

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Table 4: PBDD/F occurrence in human tissues.

Tissue Type	No. of samples	Sampling, period	Geographical origin	Measured congeners	TEQ Range pg/g lipid wt.	Notes	Reference
Human milk							
Human milk, primiparous & multiparous mothers	9, composite	2002	Japan	2,3,7,8-Br substituted T_4 - H_6 PBDD/Fs (10 congeners, Five each of PBDDs and PBDFs)	Primiparous: 0.13 - 0.54; Multiparous: 0.13 - 1.2	4 sub-samples per composite. TEF_{1998}	Ohta et al., 2004
Human milk, primiparous mothers, (18-30 yrs)	1, composite	2006	Belgium	2,3,7,8-Br substituted PBDD/Fs (9 congeners, T_4 - H_6)	0.67	178 sub-samples TEF_{1998}	Colles et al., 2008
Human milk	1, composite	2009/2010	Belgium	2,3,7,8-Br substituted PBDD/Fs (9 congeners, T_4 - H_6)	0.42	84 sub-samples TEF_{1998}	Croes et al., 2013
Human milk	31, composite	2000-2004	25 countries (Asia -Pacific, Europe, North, South America)	2,3,7,8-Br substituted PBDD/Fs (11 congeners, T_4 - H_6, and OBDD)	0.45 - 2.64	TEF_{1998}	Kotz et al., 2005; Kotz, 2006
Human milk, primiparous mothers, (20-41 yrs)	11, composite	2010	Ireland	2,3,7,8-Br substituted PBDD/Fs (10 congeners, T_4 – H_7) + 2,3,7-TriBDD & 2,3,8-TriBDF	0.58 - 1.23	109 sub-samples pooled to yield 11 composites. TEF_{1998}	Pratt et al., 2013
Human milk	5, Individual	2011	UK	2,3,7,8-Br substituted PBDD/Fs (10 congeners, T_4 – H_7) + 2,3,7-TriBDD & 2,3,8-TriBDF	0.53 - 1.78	TEF_{2005}	Fernandes, A., unpublished data
Human milk	14, individual	2008	Vietnam	-	<0.49 - 1.5 2,3,7,8-TBDF (NOT TEQ)	individuals working in e-waste recycling sites	Tue et al., 2014
Blood							
Whole blood	42, Individual	1990/1991	Germany	2,3,7,8-Br substituted PBDD/Fs (T_4BDD and T_4BDF only)	N.D. - 564	Occupationally exposed workers. TEQ = sum 2,3,7,8-TeBDD/F	Zorber et al., 1992
Serum	12, Individual	2009	California, U.S.	2,3,7,8-Br substituted PBDD/Fs. Six congeners, each of PBDDs and PBDFs	0.2 - 734	Firefighters (aged 32 to 59 years) TEF_{2005}	Shaw et al., 2013
Plasma	42, Individual	2013	Bavaria, Germany	2,3,7,8-Br substituted PBDD/Fs (13 congeners)	Median = 2.8; Max. = 9.3	20 - 68 yrs old. TEF_{2005}	Fromme et al., 2016
Serum	34, Individual	2017	Ghana	2,3,7,8-Br substituted PBDD/Fs (7 congeners)	Mean: 0.44 to 0.55	TEF_{2005}	Bruce-Vanderpuije et al., 2019
Adipose tissue							
Adipose tissue	20, Individual	1970/2000	Japan	2,3,7,8-Br substituted PBDD/Fs (4 congeners, T_4 - P_5)	1.9 - 8.3 (NOT TEQ)	Subjects from general population	Choi et al., 2003
Adipose tissue	9, Individual	2007	Sweden	2,3,7,8-Br substituted PBDD/Fs (5 congeners, T_4 - P_5). Also 8, M_1 - T_3 congeners	0.26 - 0.96	Subjects (19-65 yr) general population. TEF_{1998}	Jogsten et al., 2010
Adipose tissue	10, Individual	2009	Sweden	2,3,7,8-Br substituted PBDD/Fs (13 congeners)	0.33 to 3.9 Σ congeners NOT TEQ	Subjects (23-55 yrs) from general population.	Hagberg et al., 2011
Visceral/sub-cutaneous fat	21, Individual	2012 - 2014	UK	2,3,7,8-Br substituted PBDD/Fs (10 congeners, T4 - H7) + 2,3,7-TriBDD & 2,3,8-TriBDF	Mean values, 0.84 - 0.85	Bariatric surgery patients & controls TEF_{2005}	Thatcher et al., 2015
Liver							

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Liver biopsy samples	26, Individual	2013 - 2014	UK	2,3,7,8-Br substituted PBDD/Fs (10 congeners, T_4 – H_7) + 2,3,7-TriBDD & 2,3,8-TriBDF	Mean value, 3.88	Bariatric surgery patients & controls TEF_{2005}	Thatcher et al., 2015

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Highlights

- PBDD/F TEQ makes a significant contribution to dioxin-like toxicity in food
- Reported PBDD/F TEQs are underestimates as not all relevant congeners are included
- The new TWI of dioxin-like toxicity from PBDD/Fs may be exceeded for some populations

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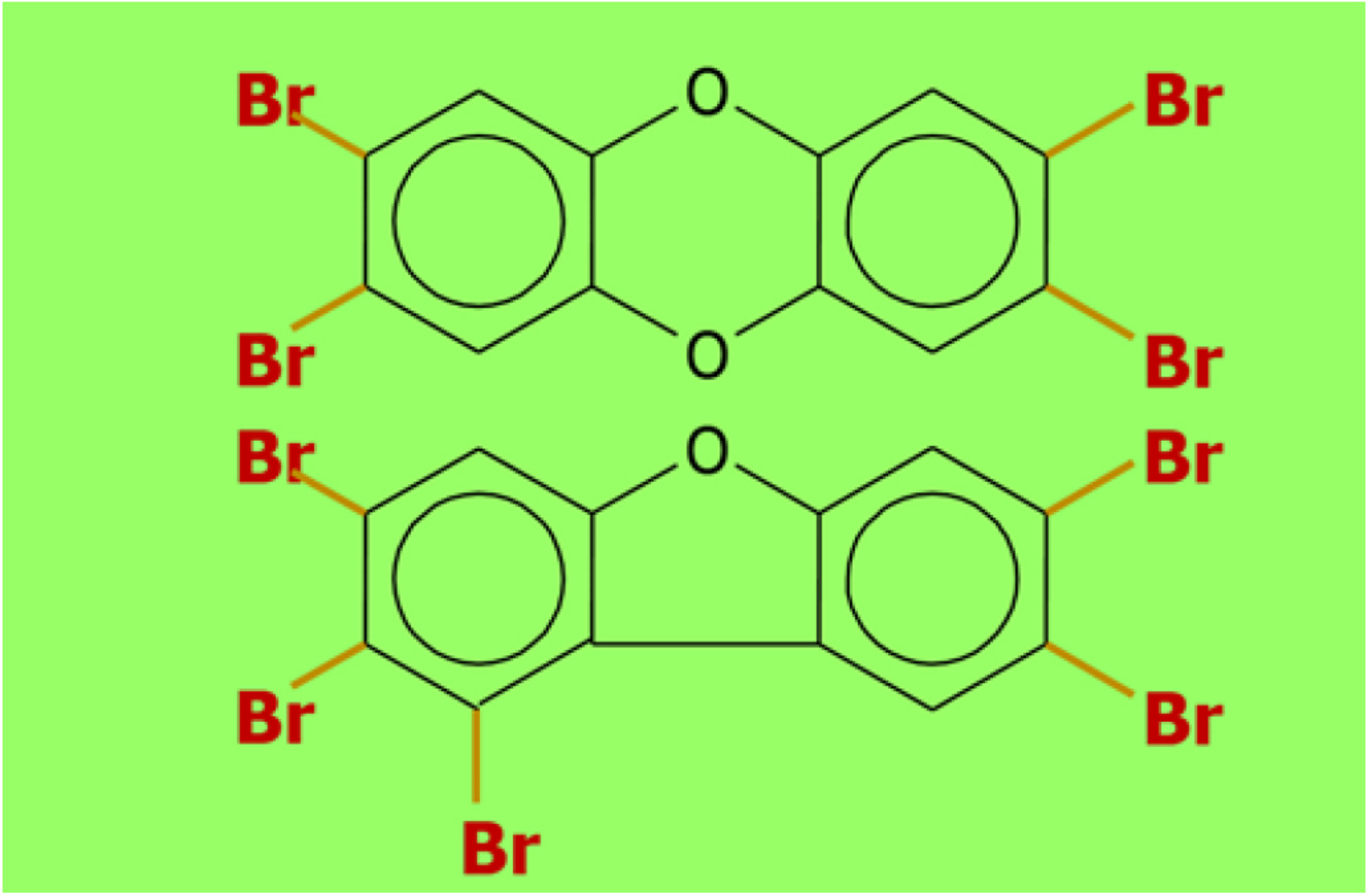

Figure 1

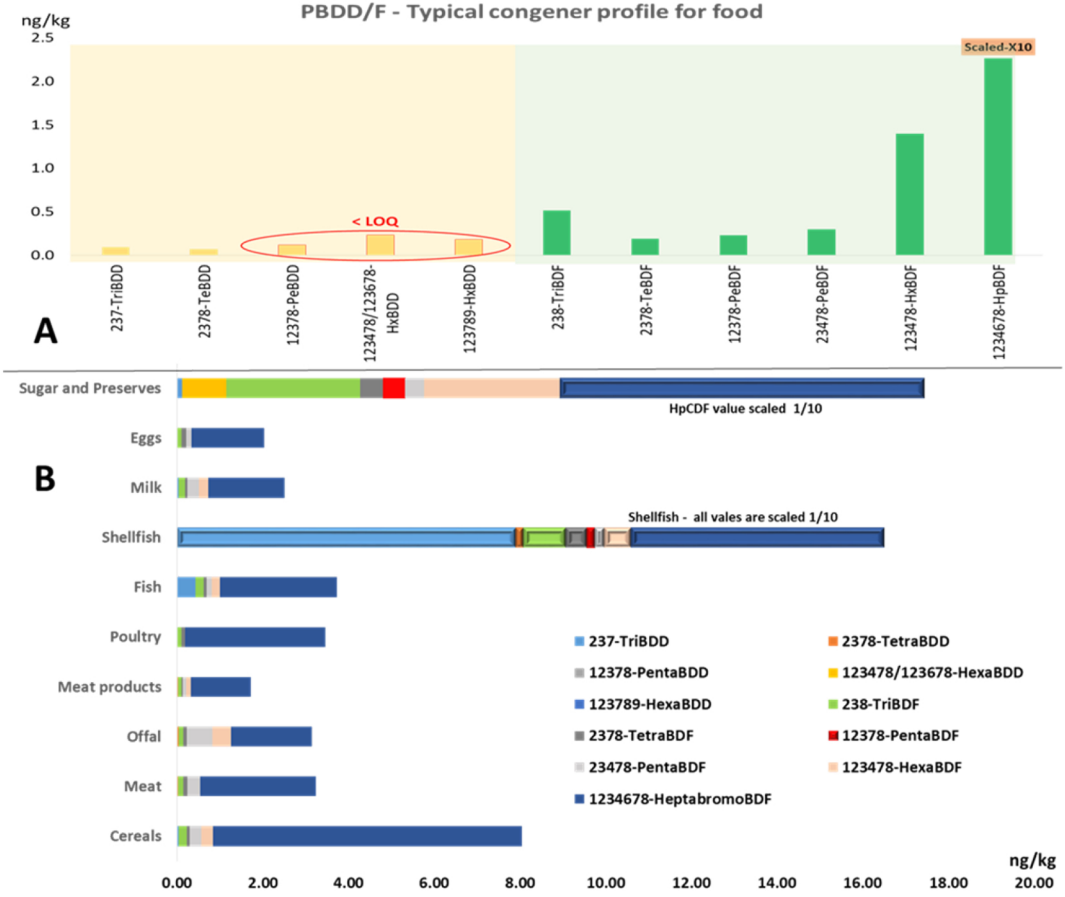
PBDD/F - Typical congener profile for food
ng/kg
2.5
2.0
1.5
1.0
0.5
0.0
Scaled-X10
< LOQ
237-TriBDD
2378-TeBDD
12378-PeBDD
123478/123678-HxBDD
123789-HxBDD
238-TriBDF
2378-TeBDF
12378-PeBDF
23478-PeBDF
123478-HxBDF
1234678-HpBDF
A
B
Sugar and Preserves
HpCDF value scaled 1/10
Eggs
Milk
Shellfish
Shellfish - all vales are scaled 1/10
Fish
Poultry
Meat products
Offal
Meat
Cereals
237-TriBDD
2378-TetraBDD
12378-PentaBDD
123478/123678-HexaBDD
123789-HexaBDD
238-TriBDF
2378-TetraBDF
12378-PentaBDF
23478-PentaBDF
123478-HexaBDF
1234678-HeptabromoBDF
ng/kg
0.00
2.00
4.00
6.00
8.00
10.00
12.00
14.00
16.00
18.00
20.00

Figure 2

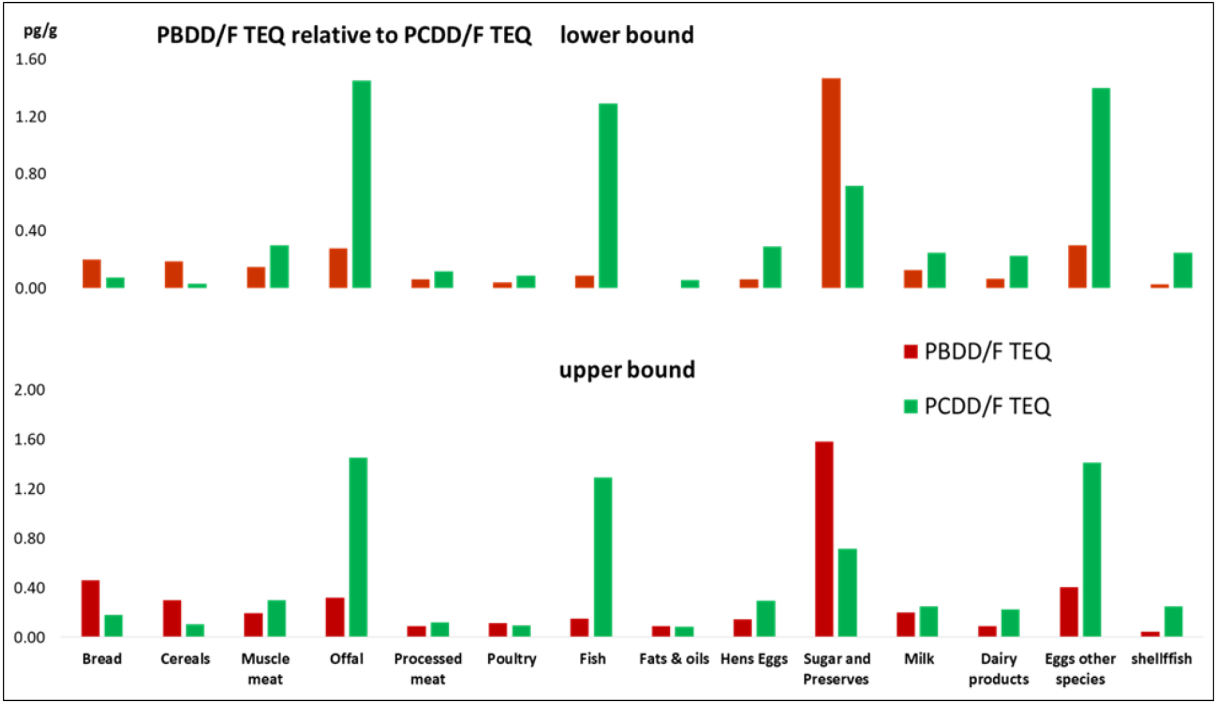
pg/g
PBDD/F TEQ relative to PCDD/F TEQ lower bound
1.60
1.20
0.80
0.40
0.00
upper bound
PBDD/F TEQ
PCDD/F TEQ
2.00
1.60
1.20
0.80
0.40
0.00
Bread
Cereals
Muscle meat
Offal
Processed meat
Poultry
Fish
Fats & oils
Hens Eggs
Sugar and Preserves
Milk
Dairy products
Eggs other species
shellffish

Figure 3

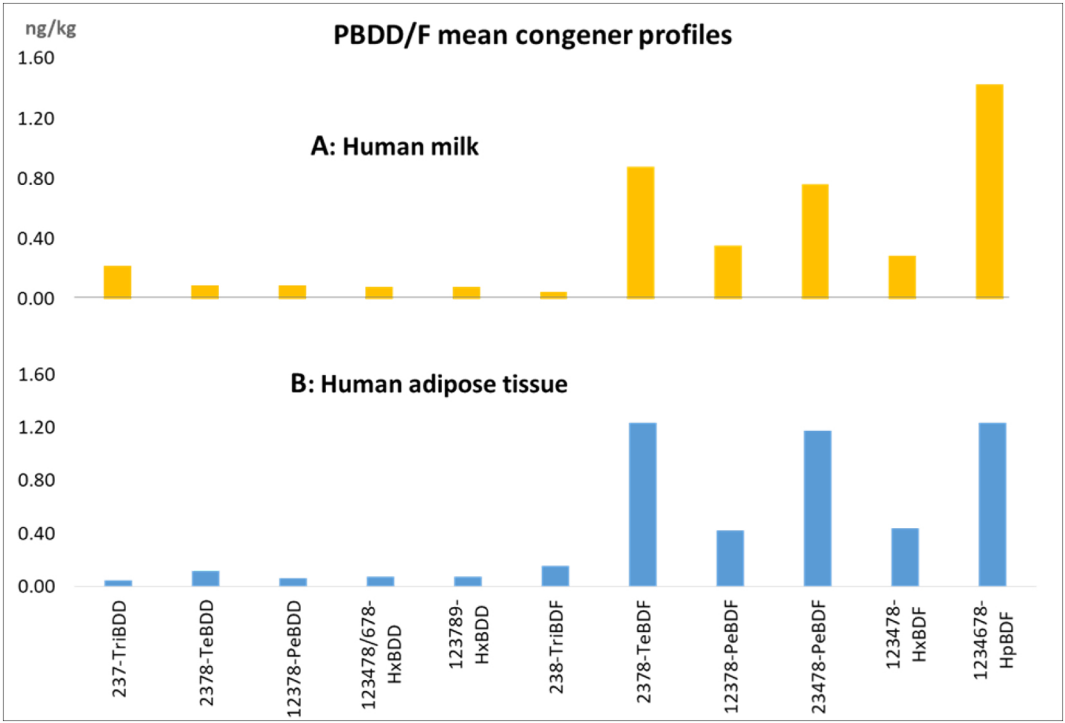
PBDD/F mean congener profiles
ng/kg
1.60
1.20
0.80
0.40
0.00
A: Human milk
1.60
1.20
0.80
0.40
0.00
B: Human adipose tissue
237-TriBDD
2378-TeBDD
12378-PeBDD
123478/678-HxBDD
123789-HxBDD
238-TriBDF
2378-TeBDF
12378-PeBDF
23478-PeBDF
123478-HxBDF
1234678-HpBDF

Figure 4