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Health effects of polybrominated dibenzo-*p*-dioxins (PBDDs) and dibenzofurans (PBDFs)

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Abstract

This article reviews the state of the science regarding the health effects of polybrominated dibenzo-*p*-dioxins (PBDDs) and dibenzofurans (PBDFs). While thousands of articles have been published on the health effects of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin and related polychlorinated dibenzodioxins (PCDDs) and dibenzofurans (PCDFs), little is know about the brominated and mixed chloro/bromo homologs. Available literature suggests that brominated compounds have similar toxicity profiles to their chlorinated homologs. However, further research investigating health effects will only be useful if exposure scenarios truly exist. Current exposure data is extremely limited, posing a major data gap in assessing potential risk of these chemicals. The rapid increase in the use of brominated flame retardants has raised the level of environmental concern regarding PBDDs/PBDFs as it is likely that human, as well as wildlife, exposure to brominated dioxins and furans will increase with their use.
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Keywords: Health effect; PBDD; PBDF

Thousands of articles have been published on the health effects of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD; dioxin) and related polychlorinated dibenzodioxins (PCDDs) and dibenzofurans (PCDFs). Detailed mechanistic studies as well as both toxicology and epidemiological investigations have been carried out for the past 50 years, since the early description of adverse effects of these chemicals. However, interest in the closely related brominated compounds has lagged, in part due to the lack of exposure information for these chemicals. While polybrominated dibenzodioxins (PBDDs) and polybrominated dibenzofurans (PBDFs) have been detected in incinerator emissions and in fly ash, as well as in certain occupational processes and chemicals in commerce, little attention has been given to any systematic environmental monitoring of abiotic systems, animal, or human samples. The rapid increase in the use of brominated flame retardants has raised the level of environmental concern regarding PBDDs/PBDFs, which are present as low-level contaminants in some of the commercial mixtures as well as being produced upon their combustion (Sakai et al., 2001). For example, processes used in production of polybrominated biphenyls (PBBs) tend to result in contamination with polybrominated naphthalenes, while combustion of PBBs leads to generation of PBDFs. Tetrabromobisphenol-A has low levels of PBDF contamination, but incineration increases PBDDs; similar trends have been observed with some of the polybrominated diphenyl ethers (PBDEs). While PBDD/PBDF concentrations have been measured in the blood of workers in plastics extrusion facilities, there have been no attempts to measure the levels of PBDDs and PBDFs in the non-occupationally exposed population (Zober et al., 1992). Additionally, no attention has been directed to the mixed chloro/bromo dioxins and furans, although their formation has been also demonstrated during incineration.

Why is there concern for chemicals for which we have only limited data suggesting potential for human and wildlife exposure? Heightened concern is attributable to the similarity in structure of the brominated dioxins and furans and the PCDDs and PCDFs. There are also very limited data demonstrating homology of effects between the chlorinated and brominated congeners. There have been several reviews

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on the health effects of PBDDs and PBDFs (Mennear and Lee, 1994; Weber and Greim, 1997; WHO, 1998). However, there have been few studies of health effects since these papers were published. Therefore, the focus of this paper will be on an overview of these earlier reports, information not captured in these earlier reviews, and data that have appeared since the review papers were published.

There is the potential for the existence of nearly 5000 brominated and mixed bromo/chloro dioxins and furans: 75 PBDDs, 135 PBDFs, 1550 mixed bromo/chloro dioxins, and 3050 mixed bromo/chloro furans (Behnisch et al., 2001a). The compounds vary in the number of halogen atoms and the position(s) of halogenation. The brominated and bromo/chloro dioxins and furans have different behaviors than their chlorinated homologs due to the bromine atom being bigger than chlorine, and the bromine–carbon bond being different in strength from the chlorine–carbon bond. In comparison to their chlorinated homologs, the PBDDs/PBDFs have higher molecular weights, higher melting points, lower vapor pressures, lower water solubilities, and higher log Kow values. Although the PBDDs/PBDFs are more lipophilic and less water-soluble than the PCDDs/PCDFs, the brominated compounds appear to be less environmentally persistent, and more sensitive to UV degradation, possibly because bromine is a better leaving group than chlorine. The biochemical properties of the dioxins and furans are also altered by the bromine atom, since the larger size of the bromine atom alters susceptibility to enzymatic attack, and the carbon–bromine bond has lower strength than the carbon–chlorine bond.

The biological effects of chemicals are governed by their pharmacokinetic and pharmacodynamic properties. For the PBDDs and PBDFs, the information on both classes is limited, and much of what we know comes from inferences drawn from the chlorinated analogs. Here, too, the position and degree of halogenation control both the physicochemical and biological properties of the chemicals (see Fig. 1). The only pharmacokinetic data that exist for the PBDDs are for the TCDD analog, 2,3,7,8-tetrabromodibenzo-*p*-dioxin (TBDD). TBDD is generally well absorbed following either oral or pulmonary exposure, although, as for TCDD, absorption appears to be dose-dependent: at high exposure concentrations, relatively less of the TBDD is absorbed. In contrast, the dermal absorption of TBDD is about three times lower than that of TCDD (Diliberto et al., 1993). Once absorbed, TBDD is distributed based on its lipid partition coefficient, with the liver and adipose tissue serving as major depots. However, similar to TCDD, TBDD appears to undergo hepatic sequestration, with the concentration in liver increasing with dose (Kedderis et al., 1991a). This is likely due to the induction of, and subsequent binding to, CYP1A2 (Diliberto et al., 1999). Kedderis et al. (1993) demonstrated that a high dose (100 nmol/kg) of TBDD to rats resulted in a much higher liver-to-fat ratio, which persisted for months, than for a 100-fold lower dose. In fact, 2 months after a single intravenous dose, the liver-to-fat ratio was ~ 3 at the high dose (100 nmol/kg), but at the environmentally relevant dose (1 nmol/kg), the liver-to-fat ratio was ~ 0.2, indicative of simple partitioning. Similarly, 90 days of treatment of mice with low doses of TBDD resulted in liver-to-fat concentrations ratios of 0.3–1.2, indicative of sequestration (DeVito et al., 1998).

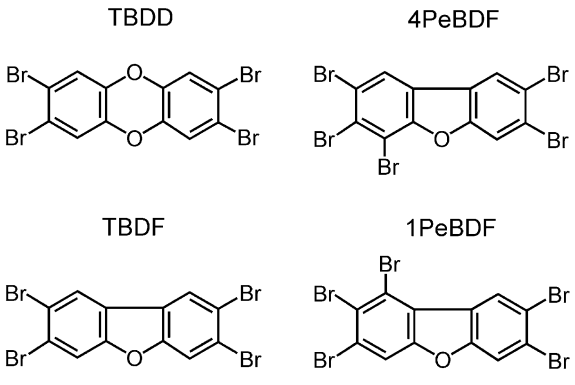

Fig. 1. Structures of PBDDs and PBDFs.

Elimination of TBDD, as for TCDD, is largely determined by metabolism, which is extremely slow. Studies of biliary elimination, a method used as an indirect measure of hepatic metabolism, have demonstrated that, in rats, TBDD is metabolized at a rate similar to TCDD (Kedderis et al., 1991b). DeJongh et al. (1993) have demonstrated that this metabolism occurs largely by hydroxylation and debromination. There was no evidence for cleavage of the ether linkage. Metabolites, because of their large molecular weight, are largely eliminated in the feces, with only small amounts being detected in the urine. There is also some passive elimination of unmetabolized TBDD. The elimination half-life for TBDD in rats is between 2 and 3 weeks, similar to recent data for TCDD (Santostefano et al., 1998). If the relationship between rat and human half-lives for TCDD holds for TBDD, this would suggest a half-life in the range of 5–10 years in people (US EPA, 2003). A physiologically based pharmacokinetic model for TBDD has been developed in rats and describes quite well both the dose- and time-dependency of its behavior (Kedderis et al., 1993).

Information on the pharmacokinetic behavior of PBDFs is even more limited than that for the PBDDs, which is limited to TBDD. However, in the available literature there are some surprises relative to the chlorinated furans. For instance, 2,3,7,8-tetrachlorodibenzofuran (TCDF) is rather rapidly metabolized in rats and mice, with a half-life under 2 days. In contrast, 2,3,7,8,-tetrabromodibenzofuran (TBDF) appears to be much more resistant to metabolism that its chlorinated analog, leading to a longer half-life (Golor et al., 1993). This is likely due to steric hindrance caused by the bromine atom, which blocks metabolism. A similar role for a chlorine atom on the C4 position in 2,3,4,7,8-pentachlorodibenzofuran (4PeCDF) has been shown by Brewster and Birnbaum (1987). On the other hand, the C1 chlorine in 1,2,3,7,8-PeCDF (1PeCDF) does not block metabolism

(Brewster and Birnbaum, 1988). Despite the differences in metabolism, both the 1- and 4-PeBDF are extremely persistent, which is likely due to the increased size of the bromine atom. 2,3,7,8-TBDF is likely to be persistent in the guinea pig, which also lacks the capability to rapidly metabolize 2,3,7,8-TCDF (Decad et al., 1981). The rapid metabolism and elimination of 1,2,7,8-TBDF (Kedderis et al., 1994) is not surprising given the presence of two unsubstituted carbon atoms leading to ease of enzymatic attack.

What is known concerning the biological effects of PBDDs/PBDFs in experimental animal models? Essentially, all of the classic effects demonstrated for TCDD and the other chlorinated dioxins and furans—lethality, wasting, thymic atrophy, teratogenesis, reproductive effects, chloracne, immunotoxicity, enzyme induction, decreases in T4 and vitamin A, and increased hepatic porphyrins—have been observed in the limited studies with PBDDs and PBDFs (WHO, 1998). Those responses have been seen in several mammalian species including rats, mice, rabbits, guinea pigs, and monkeys, as well as fish. Classic TCDD-like responses have also been measured in vitro, including enzyme induction, anti-estrogen activity in human breast cancer cells, and transformation of mouse macrophages into tumor cells (WHO, 1998).

The homology of response between the brominated and chlorinated dioxins and furans is due to a common mechanism of action, the first step of which involves binding to the Ah (or dioxin) receptor (AhR) (Birnbaum, 1994). Table 1 shows data from a report from Mason et al. (1987), in which the authors showed that binding to the Ah receptor by brominated, as well as mixed bromo/chloro dioxins, varied with the number and position of halogen atoms. While 2,3,7,8-TBDD had a slightly lower binding affinity than TCDD, the 2,8-dibromo-3,7-dichloro-dibenzo-*p*-dioxin had twice the binding affinity of TCDD. Changing the species of halogen and the degree of halogenation also led to variation in dioxins' binding affinities to the AhR. While 1,2,3,7,8-PeCDD has a binding affinity very close to that of TCDD, the brominated congener is only about 1/10 as potent. This is likely due to the large size of the bromine atom resulting in a ligand which has more difficulty than chlorinated ligands fitting into the binding pocket of the AhR. Another interesting comparison is between tri-substituted congeners; while the laterally substituted trichlorodioxins are extremely poor ligands for the AhR, with affinities 1/100 or less of TCDD, 2,3,7-TBDD demonstrates binding intermediate between TBDD and TCDD.

In vitro studies have focused mainly on comparing the induction of CYP1A1 enzyme activities. Using rat hepatoma cells in culture, Mason et al. (1987) compared the induction of two CYP1A1-mediated activities, aryl hydrocarbon hydroxylase (AHH) and ethoxyresorufin-*O*-deethylase (EROD), between various bromo- and mixed bromo/chloro-dioxins with TCDD (Table 2). The two different catalytic activities gave similar results, both of which are consistent with the ligand binding data from their laboratory. TBDD is slightly less potent than TCDD, while at least one of the mixed bromo/chloro congeners-1,2-dibromo-7,8-dichloro-dibenzo-*p*-dioxin is more active than TCDD. Again, as for binding to the AhR, the pentabromo-dioxins are only 1/10 to 1/100 as active as TCDD. Lateral substitution is required for induction of enzyme activities. Recently, Behnisch et al. (2001b) used a genetically engineered cell line in which the promoter for the CYP1A1 gene is linked to the firefly luciferase enzyme, resulting in a highly sensitive assay for the activation of the AhR by ligands (known as the "CALUX" assay). Their results with the CALUX assay were essentially identical to what they observed using a more traditional EROD activity measurement (Table 3). As the earlier studies of Mason et al. (1987), they observed that TBDD was slightly less potent than TCDD. They observed that the mixed bromo/chloro con-

Table 1
AhR binding: PBDDs vs. TCDD

Congener	Relative potency	Congener	Relative potency
$2378Br_4$	0.66	$1378Br_4$	0.50
$23Br_278Cl_2$	0.68	$12378Br_5$	0.15
$28Br_237Cl_2$	2.00	$12478Br_5$	0.05
$2Br378Cl_3$	0.10	$237Br_3$	0.80
$2468Br_4$	0.01	DBDD	0.07

The effects of structure on in vitro rat hepatic Ah receptor binding relative to TCDD. Relative potency values calculated from Mason et al. (1987, Table 1) by comparing the EC_{50} value for each chemical to TCDD ($EC_{50} = 1.0 \times 10^{-9}$ M).

Table 2
In vitro enzymatic activity relative potency in rat hepatoma cells

Congener	AHH	EROD
TBDD	0.14	0.35
$12Br_278Cl_2$	1.80	1.40
$28Br_237Cl_2$	>0.10	0.14
$2Br378Cl_3$	<0.10	0.10
$12378Br_5$	0.10	<0.10
$12478Br_5$	0.02	0.01
$non2378Br_4$	<0.01	<0.01

The effects of structure relative to TCDD on in vitro enzymatic activity in rat heaptoma cells. Relative potency values were calculated from Mason et al. (1987, Table 1), by comparing AHH induction and EROD induction values to TCDD (7.60×10^{-11} and 8.00×10^{-11}, respectively).

Table 3
Relative potency of PBDDs/PBDFs using DR-CALUX and Micro-EROD

Congener	DR-CALUX	Micro-EROD
TBDD	0.54	0.65
$23Br_278Cl_2$	0.72	0.69
$2Br378Cl_3$	0.39	0.94
$12378Br_5$	0.49	0.30
TBDF	0.82	0.62
$23478Br_5DF$	0.09	0.21

Relative AhR binding potencies of selected brominated dioxins and furans compared to TCDD as reported by Behnisch et al. (2001b) using DR-CALUX and EROD analysis.

geners were a little more potent than the ones used by the earlier investigations, as were the PeBDD congeners. Behnisch et al. (2001b) included 2,3,7,8-TBDF and 2,3,4,7,8-PeBDF in their studies, which were 1/2 and 1/10, respectively, as potent in activating the AhR, as measured by enzyme induction, as TCDD.

Results of in vivo induction of CYP1A1 enzymatic activities were compared in the review by Weber and Greim (1997). TBDD was 50% more potent than TCDD in the induction of AHH in the rat, while equal in EROD induction. The greater potency observed for AHH than for EROD was also seen for 2,3-dibromo-7,8-dichloro-dibenzo-*p*-dioxin, which resulted in 2.5 times greater induction of AHH than did TCDD, but was slightly less active when EROD was the endpoint. Interestingly, the 2-bromo-3,7,8-trichloro-dibenzo-*p*-dioxin was nearly five times as active as TCDD. This is not consistent with the results of ligand binding or of the in vitro enzymatic studies in which this congener was less potent than TCDD. However, 2,3,7,-tribromo-dibenzo-*p*-dioxin was 1/2 as active and PeBDD was 1/10 as active in inducing EROD as TCDD, consistent with the ligand binding and in vitro data. Interestingly, measurements of AHH induction in chick embryos demonstrated that 2,3,7,8-TBDD, 2,3,-dibromo-7,8,-dichloro-dibenzo-*p*-dioxin, and TCDD were equipotent. Subchronic exposure of mice supported the decreased potency of TBDD relative to TCDD when compared on the basis of administered dose, the most commonly used method of comparison (DeVito et al., 1998). However, if compared using tissue dose as the metric, TBDD appears more potent in regard to CYP1A induction than TCDD in the liver and equipotent in skin (Table 4).

The comparative potency for the induction of thymic atrophy by brominated dioxins as compared to TCDD was examined by Mason et al. (1987). Consistent with some of the enzyme induction data, TBDD and 2-bromo-3,7,8-trichloro-dibenzo-*p*-dioxin were nearly three times as potent as TCDD, while PeBDD was 1/4 as active. Of concern is the observation that 2,3,-dibromo-7,8-dichloro-dibenzo-*p*-dioxin was 13 times as potent in causing thymic atrophy as TCDD. The PeBDD congener without full lateral substitution—1,2,4,7,8-PeBDD, as well as the non-2,3,7,8-substituted TBDDs, were essentially inactive in inducing thymic atrophy. While little information is available on the induction of thymic atrophy by PBDFs, Moore and coworkers (1979) did demonstrate that 2,3,7,8-TBDF was as potent as TCDD in causing thymic atrophy in the guinea pig. This is surprising since TBDF is approximately seven times less potent in killing guinea pigs than TCDD (Moore et al., 1979). However, the oral LD_{50} in guinea pigs for TBDF and TCDF appears similar. In the rat, where TCDF has an LD_{50} more than 10 times that of TCDD, the LD_{50} for TBDD is more similar to TCDD, with males being slightly less sensitive than females to acute lethality (Ivens et al., 1993). Using fish as a model system, Hornung and coworkers (1996) also suggested that TBDD was as toxic or even more toxic than TCDD in causing early life stage mortality in trout, with TBDF being about 1/4 as potent as TCDD (Table 5). Mixed bromo/chloro-tetrahalodioxins were almost as potent as TCDD if they were fully laterally substituted, in contrast to 1,3,7,8-TBDF which was essentially non-toxic. As shown for multiple other responses, 2,3,4,7,8-PeBDF is significantly less potent than TBDF, and 1,2,3,4,7,8-HxBDF is inactive, reflecting the larger size of the bromine atoms. While TBDD is essentially as immunotoxic to monkeys as TCDD, as shown by changes in lymphocyte subsets, it is much less chloracnegenic in rabbits (WHO, 1998). This may reflect its greater log Kow and lower dermal permeability (Jackson et al., 1993).

A comparison of the teratogenic effects of TBDD, TBDF, and two PeBDFs—1,2,3,7,8 vs. 2,3,4,7,8—with that of TCDD, was conducted in mice examining the two sensitive endpoints of hydronephrosis and cleft palate (Birnbaum et al., 1991). Both PeBDFs were only 1/100 as active as TCDD in the induction of these two responses. TBDF was 1/3 and TBDD was 1/2 as effective as TCDD in disrupting kidney development, and 1/4 and 1/10 as active, respectively, in terms of induction of cleft palate. Thorough analysis of the data demonstrated that the dose/response curves for the induction of cleft palate were parallel for the four brominated compounds and for TCDD. The parallel dose/response curves support a common mechanism of action involving the AhR which had already been shown for TCDD.

The in vivo and in vitro experimental studies demonstrate several similarities and differences in toxicity patterns

Table 4
Effect of dose metric on relative potency for TBDD vs. TCDD in mice

Response (tissue)	Relative potency based on dose metric	
	Administered dose	Tissue dose
ACOH (Liver)	0.05	1.2
EROD (Liver)	0.21	5.6
EROD (Skin)	0.17	0.9
EROD (Lung)	0.60	ND

Relative potency of TBDD induction of liver, lung, and skin EROD activity and liver ACOH activity compared to TCDD in mice as reported by DeVito (1998). Potency values are dependent on the specific dose metric used for analysis.

Table 5
Relative potency of PBDDs/PBDFs trout early life stage mortality

Congener	Trout early life stage mortality
TBDD	1.1–2.5
$37Br_228Cl_2$	0.68
$8Br237Cl_3$	0.65
1378TBDD	0.01
TBDF	0.25
$23478Br_5DF$	0.07
$123478Br_6DF$	<0.01

Relative potencies of selected brominated and mixed bromo/chloro dioxins and furans as compared to TCDD in rainbow trout (Hornung et al., 1996).

between the chlorinated and brominated compounds. TBDD and the mixed bromo/chloro-tetrahalodibenzo-*p*-dioxins have similar toxicity. TBDF is more toxic than TCDF, while 1,2,3,7,8-PeBDF is equitoxic to 2,3,4,7,8-PeBDF. This is in contrast to the situation with the PeCDFs, where chlorination in the C4 position results in much greater toxicity than at C1 due to differential effects on metabolism. The difference in size between bromine and chlorine atoms also explains the greater toxicity of tribromodioxin as compared to trichlorodioxin. In all cases, however, lateral substitution is required. As noted in relative potency comparisons of the chlorinated dioxins and furans (Van Den Berg et al., 1998), relative potency estimates vary widely. This is a reflection of differences in sensitivity of various responses, comparisons based on body burdens or tissue dose vs. administered dose, and in vivo vs. in vitro endpoints. For these considerations, the difference in pharmacokinetic behavior, especially half-lives between the congeners, plays a major role.

There is almost no data on effects of PBDDs or PBDFs in people. This is likely due to the lack of evidence for general population exposure. There have been few case reports of individuals inadvertently exposed to high concentrations of TBDD. However, in one such case, a chemist was exposed to high levels of TBDD on separate occasions after which he developed chloracne, the classical response to high dose TCDD poisoning (Schecter and Ryan, 1992). The persistence of TBDD in this individual was demonstrated, with an estimated half-life on the order of that seen with TCDD. An occupational cohort working with brominated flame retardants has also been followed and no major impact on their health status was detected. There were, however, minor changes in cellular immunological parameters, but no evidence of clinical immune suppression was observed (Zober et al., 1992).

Overall, the limited data base on the health effects of PBDDs and PBDFs supports the hypothesis that these brominated congeners have similar biological properties to their chlorinated relatives. With the increasing use and the environmental presence of brominated flame retardants, it is likely that human, as well as wildlife, exposure to the PBDDs/PBDFs will increase. Given the common mechanism of action and effects, it is reasonable to predict that their presence will incrementally add to the total dioxin body burden (5 ng TEQ/kg body weight), which is already at or near to that where effects may be occurring in the general population (US EPA, 2003). The real question is not that of the toxicological potential of this class of brominated compounds, but one of exposure. Are these chemicals existing/persisting in the environment? Are they entering the food chain? To date, there is essentially no data to address this key issue. In the past, methodological barriers existed to obtaining this information however, methods now exist to identify and quantify the fully brominated dioxins and furans of concern. This is not yet true for the mixed bromo/chloro congeners which may be of greater concern as limited data suggests that the mixed bromo/chloro congeners may be more toxic. The need for methods development in this area is clearly demonstrated by the presence of AhR active material in commercial flame retardant mixtures (Zhou et al., 2001), which have been reported by the manufacturer to be free of PBDDs/PBDFs.

There are several factors to consider when assessing the environmental and human health risk of brominated dioxins and furans. However, there is little need for additional research on the health effects of these chemicals unless exposure truly exists. Several steps should be taken in evaluating exposure, beginning by determining whether combustion episodes lead to significant environmental occurrence, and if so, whether these compounds persist in the environment. It is also important to determine if the PBDDs and PBDFs are truly more sensitive to photolytic degradation than the PCDDs/PCDFs, as they may not turn out to be of environmental concern. Regardless of the environmental scenario, brominated dioxins and furans may have the potential to be an occupational hazard, and therefore should not be overlooked when assessing potential risk.

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