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Are some "safer alternatives" hazardous as PBTs? The case study of new flame retardants☆

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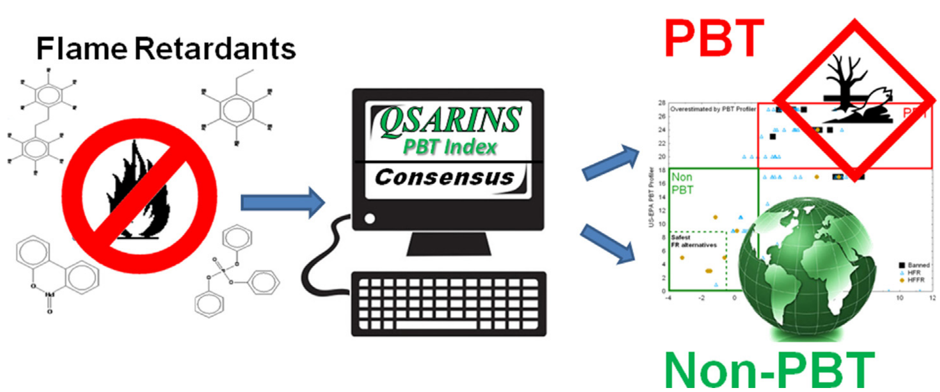
HIGHLIGHTS

- Structural screening for the identification of hazardous flame retardants (FRs)
- PBT consensus predictions by different models help in focusing experimental tests
- The PBT Index can be applied to design safer alternatives to hazardous FRs

GRAPHICAL ABSTRACT



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ABSTRACT

Some brominated flame retardants (BFRs), as PBDEs, are persistent, bioaccumulative, toxic (PBT) and are restricted/prohibited under various legislations. They are replaced by "safer" flame retardants (FRs), such as new BFRs or organophosphorous compounds. However, informations on the PBT behaviour of these substitutes are often lacking. The PBT assessment is required by the REACH regulation and the PBT chemicals should be subjected to authorization. Several new FRs, proposed and already used as safer alternatives to PBDEs, are here screened by the cumulative PBT Index model, implemented in QSARINS (QSAR-Insubria), new software for the development/validation of QSAR models. The results, obtained directly from the chemical structure for the three studied characteristics altogether, were compared with those from the US-EPA PBT Profiler: the two different approaches are in good agreement, supporting the utility of a consensus approach in these screenings. A priority list of the most harmful FRs, predicted in agreement by the two modelling tools, has been proposed, highlighting that some supposed "safer alternatives" are detected as intrinsically hazardous for their PBT properties. This study also shows that the PBT Index could be a valid tool to evaluate appropriate and safer substitutes, *a priori* from the chemical design, in a benign by design approach, avoiding unnecessary synthesis and tests.

Abbreviations: AD, applicability domain; BCF, bioconcentration factor; BDBP-TAZTO, 1.3-bis(2,3-dibromopropyl)-5-allyl-1,3,5-triazine-2,4,6(1H,3H,5H)-trione; BFR, brominated flame retardants; bor AD, borderline applicability domain; BPA-BDPP, bisphenol A tetraphenyl diphosphate; BTBPE, 1,2-bis(2,4,6-tribromophenoxy)ethane; CAS, chemical abstracts service; CFR, chlorinated flame retardant; DBDPE, decabromodiphenylethane; DBHCTD, dibromo-

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1. Introduction

Flame retardants (FRs) are chemicals widely used in various industrial products, for example, in foam, carpets and in the plastic parts of electronic devices, in order to enhance fire safety. They have a direct and obvious benefit because they are produced to prevent or slow down fires. Two classes are primarily used as organic flame retardants: halogenated substances, and chemicals containing phosphorus, the latter can be halogenated as well. The halogenated substances are mainly brominated, because they are most effective, in relatively low amounts, compared to other FRs [1], and they have a low impact on the polymers' characteristics. Therefore the brominated flame retardants (BFRs) represent major industrial chemicals, their use has increased dramatically over the past few decades. In 2004, BFRs accounted for about 21% of the total world production of FRs [2]. Due to widespread production and use of BFRs there are strong evidences of increasing contamination of the environment, wildlife and people [3–9].

However, many BFRs have unintended negative effects on the environment and human health. Some are very persistent [10] and some bioaccumulate in aquatic and terrestrial food chains [11]. In a comprehensive review [12], they are associated with adverse health effects in animals and humans, such as immunotoxicity, reproductive toxicity, cancer, adverse influence on foetal and child development and neurologic function and also endocrine and thyroid disruption.

Three commercial mixtures of polybrominated diphenyl ethers (PBDEs) (including decaBDE, octaBDE, pentaBDE), hexabromocyclododecane (HBCD) and tetrabromobisphenol A (TBBPA) were among the most widely used BFRs. Mainly because of their hazardous properties regarding persistence, bioaccumulation potential and toxicity (PBT properties), the use of these substances is now prohibited, restricted or under evaluation in various national and international legislations, initiatives and action plans [13–18]. The European Union (EU) banned pentaBDE and octaBDE in 2004, and the use of decaBDE in electric and electronic products in 2009. Similarly, the United States Environmental Protection Agency (US-EPA) banned these mixtures, and announced a phase out of decaBDE by the end of 2013 [19]. Penta-, hexa- and octaBDE were included in the persistent organic pollutants (POPs) list under the Stockholm Convention [16].

In addition, published studies show that HBCD, which has been produced since the 1960s and has been the most used cycloaliphatic additive BFR in polystyrene foam insulation for building, can bioaccumulate in various types of biota, can disrupt thyroid hormone in laboratory animals, is toxic to aquatic organisms and persists in the environment [20,21]. Parties to a United Nations meeting in Geneva in 2013 [22] decided that HBCD can continue to be produced and used in expanded or extruded polystyrene insulation for buildings until 2019, but the exemption shall take necessary measures to ensure that these materials containing HBCD can be easily identified by labelling or other means throughout its life cycle.

TBBPA is reported to be the FR with the highest production volume, covering around 60% of the total BFR market [23]. TBBPA is on the fourth European list of priority chemicals [24,25] and it is recognized as potential PBT by the Washington State's PBT Rule [26] and by the OSPAR Commission, even though is not considered to meet the REACH PBT criteria [18]. Furthermore, there is evidence that TBBPA can be considered a chemical of environmental concern [27].

The phase-out of several high-production-volume BFRs, recognized as global contaminants, has led to an increasing production and application of alternative flame retardants [28]: other novel BFRs (frequently named NBFRs), halogen-free flame retardants (HFFRs) [29], which include organophosphorus FRs (PFRs). PFRs are also named organophosphate esters (OPEs) [30].

Moreover, some flame retardants are directly incorporated in the chains of polymers, improving their fire behaviour. An additional aim is to reduce the release of flame retardants, however polymers can undergo different ageing processes with loss and migration of FRs [31].

Recently, information regarding the wide environmental occurrence of several NBFRs has become available [5,32–34]. A review by de Wit et al. [5]. indicated that a number of these NBFRs, of unknown toxicity, are of particular concern as they are being found even in the Arctic, indicating long-range atmospheric transport (LRAT).

The use of organophosphate esters has increased since manufacturers have phased out BFRs, mainly because researchers thought they would break down in the environment (being easily hydrolysable) and not pose much harm [35,36]. On the contrary, recent detections of such flame retardants in remote areas suggest that also OPEs are more persistent than once thought. The publication of various papers which highlight the global occurrence, outdoor and indoor, of various alternatives to the banned BFRs is increasing in an exponential way with detailed information on the concentration of these chemicals, even 2–3 order of magnitude higher than the concentration of BFRs they are replacing [37–44], demonstrating that also these new FRs are persistent, bioaccumulative and subjected to long range transport. Recent studies on the toxicity on *Daphnia magna* of some HFFRs [45,46] and on the occurrence and the potential estrogenic effect of some PFRs [47] have raised serious concern on the toxicity of these FRs, already introduced in the market, as "safer alternatives" of the banned BFRs.

Unfortunately, the chemical and toxicological properties, the environmental behaviour of the majority of these substitutes are

hexachlorotricyclotridecene; DDC-DBF, Dechlorane 602; DfE, design for environment; DOPO, 9,10-dihydro-9-oxa-10-phosphaphenanthrene-10-oxide; ECHA, European chemicals agency; EH-TBB, 2-ethylhexyl-2.3.4.5-tetrabromobenzoate; EPI, estimation programme interface; FR, flame retardant; HBBz, hexabromobenzene; HBCD, hexabromocyclododecane; HEDP, etidronic acid; HFFR, halogen-free flame retardant; HFR, halogen flame retardant; in AD, inside applicability domain; LRAT, long-range atmospheric transport; NBFR, novel brominated flame retardant; NOEC, no observed effect concentration; OECD, organization for economic cooperation and development; OPE, organophosphate ester; out AD, outside applicability domain; PBB, polybrominated biphenyls; PBB-Acr, pentabromobenzyl acrylate; PBBB, pentrabromobenzyl bromide; PBBC, pentabromobenzyl chloride; PBBz, pentabromobenzene; PBDE, polybrominated dyphenyl ethers; PBDPP, resorcinol bis-diphenylphosphate; PBEBz, pentabromoethyl benzene; PBP, pentabromophenol; PBP-AE, pentabromophenol allyl ether; PBT, pentabromotoluene; PBT, persistent, bioaccumulative and toxic; PC, principal component; PCA, principal component analysis; PFR, organophosphorus flame retardant; POP, persistent organic pollutants; PT, persistent, toxic; Q2LOO, Q2 leave-one-out; QSAR, quantitative structure–activity relationship; QSARINS, qsar-insubria; REACH, registration, evaluation, authorisation and restriction of chemicals; RMSE, root mean squares of errors; RMSEcv, root mean squares of errors in cross validation; SMILES, simplified molecular input line entry system; TBBPA, tetrabromobisphenol A; TBBPA-BA, tetrabromobisphenol A bisacrylate; TBBPA-BGE, tetrabromobisphenol A bis(glycidyl)ether; TBBPA-BHEE, tetrabromobisphenol A bis(2-hydroxyethyl)ether; TBBPA-BHEEBA, tetrabromobisphenol A bis(2-hydroxyethyl)ether bisacrylate; TBBPA-BME, tetrabromobisphenol A bismethylether; TBBPA-BOAc, tetrabromobisphenol A bisacetate; TBBPA-BP, tetrabromobisphenol A bispropanoate; TBBPS, tetrabromobisphenol S; TBBPS-BME, tetrabromobisphenol S bismethyl ether; TBCO, 1,2,5,6-tetrabromocyclooctane; TBCT, 2.3.4.5-tetrabromo-6-chlorotoluene; TBOEP, tri(2-butoxyethyl) phosphate; TBP, 2,4,6-tribromophenol; TBP-AE, 2,4,6-tribomophenyl allylether; TBP-DBPE, 2,4,6-tribromophenyl-2,3-dibromopropyl ether; TBX, tetrabromoxylene; TCEP, tri(2-chloroethyl) phosphate; TDBP-TAZTO, 1,3,5-tris(2,3-dibromopropyl)-5-allyl-1,3,5-triazine-2,4,6-trione; TEBP-Anh, tetrabromopthalicanhydride; TiBP, tri-isobutylphosphate; TMP, trimethylphosphate; TnBP, tri-*n*-butylphosphate; TPP, triphenylphosphate; US-EPA, united states environmental protection agency; vPvB, very persistent very bioaccumulative.

☆ Part 3 of the Series: "Early PBT assessment and prioritization of emerging environmental contaminants".

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