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Review

Evaluation of *in vitro* vs. *in vivo* methods for assessment of dermal absorption of organic flame retardants: A review

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ABSTRACT

There is a growing interest to study human dermal exposure to a large number of chemicals, whether in the indoor or outdoor environment. Such studies are essential to predict the systemic exposure to xenobiotic chemicals for risk assessment purposes and to comply with various regulatory guidelines. However, very little is currently known about human dermal exposure to persistent organic pollutants. While recent pharmacokinetic studies have highlighted the importance of dermal contact as a pathway of human exposure to brominated flame retardants, risk assessment studies had to apply assumed values for percutaneous penetration of various flame retardants (FRs) due to complete absence of specific experimental data on their human dermal bioavailability. Therefore, this article discusses the current state-of-knowledge on the significance of dermal contact as a pathway of human exposure to FRs. The available literature on *in vivo* and *in vitro* methods for assessment of dermal absorption of FRs in human and laboratory animals is critically reviewed. Finally, a novel approach for studying human dermal absorption of FRs using *in vitro* three-dimensional (3D) human skin equivalent models is presented and the challenges facing future dermal absorption studies on FRs are highlighted.

Contents

Abbreviations: BFRs, brominated flame retardants; BPA, bisphenol A; BTBPE, 1,2-bis(2,4,6-tribromophenoxy)ethane; DBDPE, decabromodiphenylethane; EU, European Union; EVCAM, European Centre for Validation of Alternative Methods; FRs, flame retardants; FT, full-thickness skin; HBCD, hexabromocyclododecane; HSE, human skin equivalent; KC, keratinocytes; K_{OW}, octanol/water partition coefficient; LCs, Langerhans cells; NBFRs, novel brominated flame retardants; OATP, organic anion transporting polypeptides; OECD, organisation for economic co-operation and development; PA, percutaneous absorption; PBDEs, polybrominated diphenyl ethers; PBT, persistent, bioaccumulative and toxic; PCBs, polychlorinated biphenyls; PFRs, organophosphate flame retardants; PK, pharmacokinetic; POPs, persistent organic pollutants; RDP, resorcinol bis-diphenylphosphate; SC, stratum corneum; RHE, reconstructed human epidermis; TBB, 2-ethylhexyl-2,3,4,5-tetrabromobenzoate; TBBPA, tetrabromobisphenol A; TBPH, bis(2-ethylhexyl)tetrabromophthalate; TCEP, tris(2-chloroethyl) phosphate; TCIPP, tris(2-chloro-1-methylethyl) phosphate; TDCPP, tris(1,3-dichloro-2-propyl) phosphate; TRIS, tris(dibromopropyl) phosphate; USEPA, United States Environment Protection Agency.

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1. Introduction

Organic flame retardants (FRs) are a diverse group of chemicals used to prevent or reduce the flammability and combustibility of polymers and textiles. The major members of this group are polybrominated diphenyl ethers (PBDEs), hexabromocyclododecane (HBCD), tetrabromobisphenol A (TBBPA), novel brominated flame retardants (NBFRs), as well as organophosphate flame retardants (PFRs) (Ghosh et al., 2011; van der Veen and de Boer, 2012).

Although polychlorinated biphenyls (PCBs) were mainly applied as heat transfer fluids in electric equipment, capacitors and transformers, one of their major advantages as heat transfer fluids was flame-retardancy. Thus, PCBs were highly desirable for applications where fire was a threat to life and property, such as in electrical equipment in commercial buildings, in hospitals, in hydraulic systems in foundries, and in heat transfer systems. Furthermore, PCBs were also applied to flame-proof polyimide (nylon-type) and polyolefin yarns. Due to their persistent, bioaccumulative and toxic (PBT) properties, the production and usage of PCBs were banned throughout most of the industrialized world in the 1970s (Erickson and Kaley, 2011; Fiedler, 2001).

PBDEs have found wide application as FRs for plastics, textiles, electronic casings and circuitry. The fully brominated product (DecaBDE) dominated worldwide production with a global demand of 56,100 t in 2001, compared to 7500 and 3790 t for the less brominated PentaBDE and OctaBDE formulations, respectively (BSEF, 2013). In 2001, the world market demand for HBCD was 16,700 t, 57% of which was in Europe (Covaci et al., 2006). The principal application of HBCD is in expanded and extruded polystyrene foams used for building insulation, but it has also been used to flame retard textiles and housing for electrical items (KEMI (National Chemicals Inspectorate), 2008). TBBPA is the most widely used BFR with a production volume of 170,000 t in 2004, applied mainly for epoxy resins used in printed circuit boards of electric and electronic equipments (Covaci et al., 2009). As PBDEs, HBCD, and ~20% of the production of TBBPA are blended physically within (and referred to as "additive" FRs) rather than bound chemically (and known as "reactive" FRs) to polymeric materials, they migrate from products, following which their persistence and bioaccumulative character leads to contamination of the environment including humans (Harrad et al., 2010a). This is of concern owing to their potential environmental and toxicological risks including: endocrine disruption, neurodevelopmental and behavioural disorders, hepatotoxicity and possibly cancer (Darnerud, 2008; Hakk, 2010; Wikoff and Birnbaum, 2011). Moreover, the few data available from human epidemiological studies imply effects on: male reproductive hormones (Johnson et al., 2013; Meeker et al., 2009), semen quality (Akutsu et al., 2008), thyroid hormone homeostasis (Turyk et al., 2008), cryptorchidism (Main et al., 2007), hormone levels and fecundability in adult women (Harley et al., 2010), as well as lower birth weight and length (Chao et al., 2007; Lignell et al., 2013). Such evidence has contributed to complete EU bans for the Penta- and Octa-BDE formulations, and restrictions on the use of Deca-BDE (Roberts et al., 2012). In addition, PBDEs associated with Penta- and Octa-BDEs are listed under the UNEP Stockholm Convention on POPs, while Deca-BDE is currently under consideration for listing under Annexes A, B and/or C of the convention (Stockholm convention on POPs, 2009). Furthermore, HBCD will be phased out following its recent listing under Annex A of the Stockholm Convention (Stockholm convention on POPs, 2013). Despite such restrictions on their production and use, human exposure to PBDEs and HBCD is likely to continue for some time, given the ubiquity of flame retarded products remaining in use and entering the waste stream, coupled with the environmental persistence of these BFRs (Harrad and Diamond, 2006).

These restrictions on the use of PBDEs and HBCD have paved the way for the use of NBFRs as replacements with an estimated global production volume of 100,000 t in 2009 (Harrad and Abdallah, 2011). Major NBFRs are: DBDPE (decabromodiphenylethane), BTBPE (1,2-bis(2,4,6-tribromophenoxy)ethane), TBB (2-ethylhexyl-2,3,4,5-tetrabromobenzoate), and TBPH (bis(2-ethylhexyl)tetrabromophthalate) (further details are provided in Table SI-1). While information regarding the environmental occurrence of several NBFRs has become available recently (Covaci et al., 2011), very little is known about their toxicological properties and the pathways and magnitude of human exposure to these chemicals. Nevertheless, several NBFRs bear striking structural similarity to PBDEs (*e.g.* DBDPE is a very close analogue of BDE-209) and are reported to have similarly low vapour pressures and water solubilities, as well as high K_{OW} values, and PBT characteristics (Covaci et al., 2011; Harrad and Abdallah, 2011).

In addition to BFRs, PFRs have been associated with a wide range of applications (Table SI-1). Likely linked to the aforementioned restrictions on PBDEs, EU market demand for PFRs increased from 83,700 t in 2004 to 91,000 t in 2006 (EFRA, 2007). Tris(2-chloroethyl) phosphate (TCEP), tris(2-chloro-1-methylethyl) phosphate (TCIPP) and tris(1,3-dichloro-2-propyl) phosphate (TDCPP) were all subject to an EU risk assessment process under an Existing Substances Regulation (EEC 793/93) (Regnery and Puttmann, 2010). Despite less stability and overall environmental persistence than PBDEs, they were classified as persistent organic compounds in the aquatic environment and reported to fulfil PBT criteria. In addition, several studies have reported them to display adverse effects including reproductive toxicity and carcinogenic effects on lab animals (Regnery et al., 2011). Hence TCEP is classified by the EU as a "potential human carcinogen" (Regnery and Puttmann, 2010), while TDCPP is classified under regulation EC 1272/2008 as a category 2 carcinogen (ECHA, 2010).

2. Human exposure to FRs

Several studies have reported on levels of different FRs in various environmental and human matrices (Covaci et al., 2009, 2011; Harrad et al., 2010b; Law et al., 2014; van der Veen and de Boer, 2012). The current understanding is that non-occupational human exposure to BFRs occurs mainly *via* a combination of diet, ingestion of indoor dust, dermal contact with dust/consumer products, and inhalation of indoor air (Fig. 1) (Abdallah M.A. et al., 2008; Frederiksen et al., 2009; Watkins et al., 2011). The exact contribution of these pathways varies substantially between chemicals and between individuals according to lifestyle, and is further complicated by international variations in FR use (Abdallah and Harrad, 2009; Abdallah M.A.E. et al., 2008; Abdallah M.A. et al., 2008; Harrad et al., 2008b). While it is established that the main exposure route to several POPs (*e.g.* PCBs and DDT) is through diet, studies from North America report indoor dust (*via* ingestion or dermal contact) as the major exposure pathway for all age groups to PBDEs contributing 70–80% to the average overall daily exposure (Lorber, 2008; Trudel et al., 2011). Elsewhere, while dust ingestion appears particularly important for toddlers and young children, other exposure pathways make substantial contributions to the overall adult intake of BFRs (Abdallah M.A. et al., 2008; Harrad et al., 2008a, 2010b; Roosens et al., 2009). In contrast to PBDEs, only a few studies are available that address human exposure to NBFRs and PFRs (Ali et al., 2012; Covaci et al., 2011; Stapleton et al., 2011). Currently very little is known about dermal exposure as a route of human exposure to FRs in indoor dust or FR-treated products. This paucity of information was evident in the EU risk assessment reports on TBBPA (EU Risk Assessment Report, 2006) and BDE-209 (EU Risk Assessment Report, 2002) where the lack of experimental data has led to the assumption of dermal absorption efficiencies based on consideration of compound-specific physicochemical properties and extrapolation from data available for PCBs. Furthermore, several authors have discussed the absence of experimental data on dermal absorption of various FRs and highlighted the potential inaccuracies of the current estimates of human exposure to these FRs owing to a general lack of knowledge on the percutaneous route (Boyce et al., 2009; Garner et al., 2006; Trudel et al., 2011; U.S. EPA, 1992). Therefore, the lack of experimental information on human dermal uptake of FRs from dust and source materials, represents an