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Neurodevelopmental and neurobehavioural effects of polybrominated and perfluorinated chemicals: A systematic review of the epidemiological literature using a quality assessment scheme

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HIGHLIGHTS

- No consistent neurodevelopmental/-behavioural effects were seen after PBDE/PFC exposure.
- Consistency was only observed for PFOA which did not show any effects.
- Problems of sample size, confounders and absence of dose–response were frequent.
- Further hypothesis-driven studies using more harmonized study designs are needed.
- Epidemiological data should be reported in accordance with existing guidelines.

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ABSTRACT

Concerns over effects of halogenated persistent environmental contaminants on the developing brain have been expressed for many years, and human biomonitoring has confirmed that low-level, prenatal and/or postnatal exposure of children to these chemicals is ubiquitous. Over the last decade there have been increasing reports in the epidemiological literature of the potential association of exposure to polybromo diphenylethers (PBDEs) and perfluorinated chemicals (PFCs) with neurodevelopmental and/or neurobehavioural effects in infants and children, such as adverse birth outcomes, cognitive deficits, developmental delay and attention deficit hyperactivity disorders (ADHD). However, direct evidence from epidemiology studies has been limited and contradictory. Given the general lack of comparability across studies in terms of design, conduct, methodology and reporting, we developed a checklist-type quality assessment scheme based on the STROBE guidelines and the proposed HONEES criteria, and conducted a systematic review of the epidemiological peer-reviewed literature published since 2006 on neurodevelopmental and/or neurobehavioural effects following prenatal and postnatal exposure to PBDEs and PFCs. We rated 7 of the 18 studies that met our inclusion criteria as being of high quality, 7 of moderate quality and 4 of low quality. Frequently observed shortcomings were the lack of consideration of confounding factors; uncertainties regarding exposure characterization; inadequate sample size; the lack of a clear dose–response; and the representativeness/generalizability of the results. Collectively, the epidemiological evidence does currently not support a strong causal association between PBDEs and PFCs and adverse neurodevelopmental and neurobehavioural outcomes in infants and children. However, despite their limitations, the studies raise questions that require further investigation through hypothesis-driven studies using more harmonized study designs and methodologies, more detailed exposure assessments and repeated testing with larger study populations.

1. Introduction

Many industrial halogenated chemicals and their by-products such as polychlorinated biphenyls (PCBs), dibenzodioxins and dibenzofurans (PCDDs/PCDFs), organochlorine pesticides (OCs), polybrominated diphenylethers (PBDEs) and perfluorinated (perfluoroalkyl) chemicals (PFCs) are of concern because of their

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potential toxicity to humans and wildlife. They are structurally closely related and share many common characteristics, most notably their persistence and ubiquitous distribution in the environment, their potential for bioaccumulation in the fatty tissues of living organisms and for biomagnification in the food chain. While this is already well known for PCBs, dioxins and OCs, evidence has emerged only more recently for PBDEs and PFCs (Butt et al., 2010; de Wit, 2002; Law et al., 2006; Letcher et al., 2010; Martin et al., 2004; Salamova and Hites, 2011; Yogui and Sericano, 2009).

Exposure to persistent chemicals has been increasingly associated with environmentally related diseases in children and recognized as a major public health issue, resulting in increased research efforts and regulatory action (Berkowitz et al., 2001; Grandjean and Landrigan, 2006). In particular, concerns have been expressed over potential adverse effects on the developing brain during the most sensitive stages of human development throughout pregnancy into early childhood. Since the 1980s a vast body of epidemiological literature has shown that prenatal and/or postnatal exposure to well-known neurotoxicants such as heavy metals (e.g. methylmercury, lead), PCBs, OC's and organophosphate pesticides (OPs) may impact on the development and maturation of motor, cognitive and behavioural functions (Bjørling-Poulsen et al., 2008; Eskenazi et al., 2008; Jacobson and Jacobson, 1997; Perera et al., 1999, 2005). However, comparatively little human hazard and exposure information exists for chemical classes such as PBDEs and PFCs despite the fact that they have been commercialized since the 1970s and 1950s, respectively (Lindstrom et al., 2011; WHO, 1994). Their toxicological characterization is complicated by the fact that they are usually commercialized as technical mixtures of varying composition (Alaee et al., 2003; Stahl et al., 2011). Suspicions concerning potential neurodevelopmental toxicity of PBDEs and PFCs have arisen over the last decade as more epidemiological evidence has been obtained suggesting a link between prenatal and/or postnatal exposure and various health outcomes, including motor functions disorders, lower IQ, learning and intellectual disabilities, attention deficit hyperactivity disorder (ADHD), autism spectrum disorders and developmental delay (Betts, 2010; Eriksson et al., 2001; Jurewicz et al., 2013; Messer, 2010; Olsen et al., 2009).

PBDEs and PFCs are used as chemical additives in many daily consumer products such as plastic polymers, food contact materials, furniture, textiles and paper for their flame retardant and surfactant properties, respectively (Bellinger, 2013; Talsness, 2008; WHO, 1994). Because PBDEs and PFCs are semivolatile substances chemically unbound to their substrate (e.g. food packaging, furniture, matresses, cushions, etc.), they can easily migrate into the environment, which makes them ubiquitous indoor contaminants. Children may be particularly at risk of continuous exposure at all critical life stages, throughout pregnancy until early childhood. Indeed, it has been shown that breastfed infants and toddlers have higher concentrations than children or adults (Fromme et al., 2010; Johnson-Restrepo and Kannan, 2009; Toms et al., 2009), and that PBDEs and PFCs can be widely detected in maternal and umbilical cord blood (Wu et al., 2010; Arbuckle et al., 2013), breast milk (Barbarossa et al., 2013; Dunn et al., 2010) and in the amniotic fluid (Stein et al., 2012). While infants are thought to be primarily exposed through breastfeeding, the indoor environment represents a significant source of exposure for small children via household dust inhalation, ingestion, or dermal absorption due to hand-to-mouth, object-to-mouth and crawling activities (Chen et al., 2009; Coakley et al., 2013; D'Hollander et al., 2010; Frederiksen et al., 2009; Fromme et al., 2009; Stapleton et al., 2008; Toms et al., 2009; Vorkamp et al., 2011).

Increasing reporting in the literature of potential adverse effects on human health and the environment (Betts, 2002; Birnbaum and Staskal, 2004; McDonald, 2002; Renner, 2001) has led US industry to the voluntary phasing out of perfluorooctane sulfonate (PFOS) in 2002 (ATSDR, 2009; Vierke et al., 2012) and of penta-BDE and octa-BDE in 2004 (USEPA, 2013), and regulatory authorities in the US and EU to take action to restrict the production, use and sale of those chemicals (Betts, 2008; EC, 2003; ECHA, 2013a, 2013b; EU, 2011; OECD, 2013), in particular perfluorooctanoate (PFOA), whose complete phasing out is scheduled for 2015 (ATSDR, 2009). However many PBDE-based flame retardants are also being phased out and more suitable, safer alternatives are sought, a full ban is not yet foreseen for both consumer safety and economic reasons (Brown, 2012). As a result of the phasing out, human exposure to some PBDEs and PFCs has significantly declined in the US and EU over the last decade (Calafat et al., 2007; Kato et al., 2011; Ma et al., 2013; Olsen et al., 2012), but the pattern of time exposure trends in humans is complex (Harada et al., 2010; Kato et al., 2011; Ode et al., 2013; Schecter et al., 2012). Half-lives have been estimated to range from 2 to 12 years for lower PBDEs but only 15 days for PBDE-209 (Geyer et al., 2004) and from 4 to 8 years for PFCs (Olsen et al., 2007). Given their widespread environmental dispersion, their persistence and potential bioaccumulation, PBDEs and PFCs will likely remain a cause of concern in the foreseeable future.

Only a limited number of epidemiological studies dealing with PBDEs and PFCs have focused on neurodevelopmental or neurobehavioural endpoints as a health outcome. Some significant exposure/outcome associations have been found, but direct evidence has been limited and contradictory, and is far from conclusive. Since it was not possible to perform a meta-analysis due to the paucity and heterogeneity of available epidemiological data, we have developed a qualitative scheme to allow a systematic assessment of the literature in order to identify some pointers that may be taken into account by future studies. Our analysis shows that, despite their limitations, these studies raise questions which require further investigation through hypothesis-driven studies using more harmonized study designs and methodologies.

2. Material and methods

2.1. Search strategy

A comprehensive search of the primary scientific literature was carried out in the following databases: MEDLINE (http://www.pubmed.org), TOXNET (http://toxnet.nlm.nih.gov/) and EMBASE (http://www.embase.com), with the following keyword combinations: halogenated OR polybromodiphenylethers OR flame retardants OR PBDE OR perfluorinated OR perfluoroalkyl OR PFOA OR PFOS; AND neurodevelopmental OR neurobehavioural OR cognitive OR head circumference OR psychomotor OR autism OR attention deficit hyperactivity disorder; AND children OR infant. Among the selected papers that met our inclusion criteria, we used cited references in the peer-reviewed literature to cross-identify relevant articles that may have been missed by the initial electronic search. We also looked directly for articles in selected epidemiological or other relevant journals. Key characteristics of the studies selected for analysis are briefly summarized in Tables 1 and 2. More detailed information is provided as supplementary material (S1).

2.2. Inclusion and exclusion criteria

Minimum requirements for inclusion of studies were: (i) full access to original articles in English published in the peer-reviewed literature since January 1, 2006; (ii) longitudinal birth cohorts, case control or cross-sectional studies; (iii) neurotoxicological endpoints including head circumference, neurodevelopmental and/or neurobehavioural disorders; (iv) prenatal and/or postnatal exposure; (v) exposure assessment based primarily on monitoring of

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