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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

Table 1
Short summary table of PBDE-related studies that have evaluated neurodevelopmental and neurobehavioural endpoints, incl. head circumference, in children.

Reference (Author, Year)	Study name, location, period	Age, sample size	Exposure type, biological sampling	Association per functional domain assessed	Overall quality rating
Neurodevelopmental endpoint = head circumference (HC)					
Chao et al., 2007	Birth cohort, Taiwan, 2000–2001	At birth, $n = 20$	BM[a]	PBDEs-28, -47, -85, -99, -100, -153, -154, -209: ↓	Low
Harley et al., 2011	CHAMACOS Study, USA, 1999–2000	At birth, $n = 286$	MB (3rd trim.)	8PBDEs or Σ4PBDEs (PBDE-47, -99, -100, -153): ⌀	High
Other neurodevelopmental endpoints and neurobehavioural endpoints					
Chao et al., 2011	Birth cohort, Southern Taiwan, 2007–2010	8–12 months, $n = 70$	BM[b]	Motor: (Σ)14PBDEs ⌀ Cognition: Σ14PBDE ⌀; PBDE-209 ↓** Language: PBDE-196 ↑*** Behaviour (adaptive, socio-emotional): (Σ)14PBDEs ⌀ (Parental reports)	Low
Eskenazi et al., 2013	CHAMACOS Study, USA, 1999–2000, follow up 2005–2008	5 years, $n = 310$; 7 years, $n = 323$	MB (2nd trim. or at delivery) CB (7 years)	Motor (fine): Σ4PBDEs (PBDE-47, -99, -100, -153) ↓** Cognition (verbal skills, processing speed perceptual reasoning and full-scale IQ): Σ4PBDEs ↓* or **↓ Attention (maternal reports): Σ4PBDEs ↓** Hyperactivity (teacher reports): Σ4PBDEs ↑**	High
Gascon et al., 2011	Menorca birth cohort, Spain, 1997–1998, follow up 2001–2002	4 year, $n = 332$	UCB ($n = 88$), CB ($n = 244$)	Motor: PBDE-47 ↓ Cognition: PBDE-47 ↓ Behaviour (social competence): PBDE-47 ↓** Attention: PBDE-47 ↓** Impulsivity, hyperactivity: ⌀	Moderate
Gascon et al., 2012	Gipuzkoa-Sabadell birth cohort, Spain, 2004–2008	12–18 months, $n = 290$	BM (colostrum)	Motor (fine and gross): ⌀ Cognition (performance abilities, memory, and early language skills): Σ7PBDEs ↓[c] (PBDE-209)	High
Herbstman et al., 2010	WTC birth cohort, USA, 2001–2002	1–4, 6 years, $n = 96$–118	UCB	Motor (1y): PBDE-47: ↓** Cognition (performance (2-3y), full scale IQ + verbal IQ (4y, 6y): PBDE-47, 99, 100: ↓**	Moderate
Hertz-Picciotto et al., 2011	CHARGE case-control study, USA, 2003–2005	2 years, 5 years, $n = 100$	CB	Autism or developmental delay: Σ11PBDEs ⌀	Moderate
Roze et al., 2009	COMPARE Birth cohort, Netherlands, 2001–2002	5–6 years, $n = 62$	MB (3rd trim.)	Motor (fine): PBDE-154 ↓* Cognition (verbal memory): PBDE-153 ↓*** Behaviour (internalizing and externalizing, performance): PDBE-47, -99, -100 ↑*,** (self reports), Attention: PDBE-47, -99, -100 ↓*,** (self reports)	Moderate
Shy et al., 2011	Birth cohort, Southern Taiwan, 2007–2008	8–12 months, $n = 36$	UCB	Motor: ⌀ Cognition: PBDE-15 ↑***; PBDE-99, -197, Σ11PBDE ↑** Language: ⌀ Behaviour (adaptive, parental reports):P BDE-28, 99, 183 ↓**; PBDE-154 and Σ11PBDEs ↓*** Behaviour (socio-emotional, parental reports): ⌀	Low
Indirect evidence, questionnaire-based					
Hoffman et al., 2012	PIN birth cohort study, USA (2004–2006)	30 months, $n = 222$	BM[d]	Behaviour (externalizing, activity, impulsivity): PBDE-47, -99, -100 ↑ Other socio-emotional domains: PBDE-47, -99, -100 ⌀	n.a

Abbreviations: ↑ = positive (beneficial) association; ↓ = negative (adverse) association; ⌀ = no association; *$P < 0.10$; **$P < 0.05$; ***$P < 0.01$; BM = breast milk; CB = child blood; CHAMACOS = Center for the Health Assessment of Mothers and Children of Salinas; CHARGE = CHildhood Autism Risk from Genetics and the Environment; COMPARE = Comparison of Exposure-Effect Pathways to Improve the Assessment of Human Health Risks of Complex Environmental Mixtures of Organohalogens; IB = infant blood; MB = maternal blood; PIN = Pregnancy Infection and Nutrition Study; UCB = umbilical cord blood; [a]breast milk collected within two weeks after delivery; [b]breast milk collected 1 month after delivery; [c]association of borderline statistical significance, BDE-209 is the main congener responsible for the association; [d]breast milk self collected 3 months post-partum by mothers with kit.

human biomarkers; (vi) children 0–12 years of age. Studies where the exposure was not assessed analytically, or where the health outcome was not based on a clinical diagnosis by a health professional (e.g. self reporting by the childrens' parents) were not reviewed as part of our quality assessment but considered as a separate category and used as complementary information in the final evaluation of the body of evidence. Other exclusion criteria were: (i) association between prenatal exposure to environmental

Table 2
Short ummary table of PFC-related studies that have evaluated neurodevelopmental and neurobehavioural endpoints, incl. head circumference, in children.

Reference (Author, Year)	Study name, location, period	Age, sample size	Exposure type, biological sampling	Association per functional domain assessed	Overall quality rating
Neurodevelopmental endpoint = head circumference (HC)					
Apelberg et al., 2007	Baltimore THREE Study, USA, 2004–2005	At birth, $n = 293$	UCB	PFOS, PFOA: ↓**[a]	High
Chen et al., 2012	Taiwan Birth Panel Study, 2004–2005	At birth, $n = 429$	UCB	PFOS: ↓**; PFOA, PFNA, PFUA: ⌀	Moderate
Fei et al., 2008b	Danish National Birth Cohort, 1996–2002	At birth, $n = 1399$	MB (1st trim.)	PFOS: ⌀; PFOA: ↓	High
Lee et al., 2013	South Korea birth cohort, 2011	At birth, $n = 70$	MB at delivery + UCB	PFOS, PFOA, PFHxS: ⌀	Low
Washino et al., 2009	Hokkaido Study, Japan 2002–2005	At birth, $n = 429$	MB (2nd–3rd trim.)[b]	PFOA, PFOS: ⌀	Moderate
Other neurodevelopmental endpoints and neurobehavioural endpoints					
Chen et al., 2013	Taiwan Birth Panel Study, 2004–2005	2 years, $n = 239$	UCB	Motor (gross): PFOS ↓**; PFOA ⌀ Cognition (performance whole test): PFOS ↓**§; PFOA ⌀ Behaviour (social, self-help): PFOS ↓ or ↓**; PFOA ⌀	High
Gump et al., 2011	Oswego study, USA, n.a	9–11 years, $n = 83$	CB	Behaviour (impulsivity): PFOS, PFNA, PFHxS ↑**; PFOA ⌀	Moderate
Stein et al., 2013	C8 Health Project, USA (2005–2006) follow-up, 2009–2010	6–12 years, $n = 320$	MB (3rd trim.)[c] CB (3–4 years)	Cognition (IQ, reading, math skills, language, memory and learning, visual-spatial processing): PFOA ⌀ Attention, impulsivity: PFOA ⌀	High
Indirect evidence, questionnaire-based					
Fei et al., 2008a	Danish National Birth Cohort, 1996-2002	6 month, 18 month, $n = 1400$	MB (1st trim.)	Motor[d]: PFOS, PFOA ⌀ Cognition[d]: PFOS, PFOA ⌀	n.a
Fei & Olsen, 2011	Danish National Birth Cohort, 1996-2002, follow up, 2005-2010	7 years, $n = 1313$, n = 526 (DCDQ) $n = 787$ (SDQ)	MB (1st trim.)	Motor (developmental coordination disorder): PFOS, PFOA ⌀ Behavioural health (emotional, conduct, attention, hyperactivity, peer and social disorders): PFOS, PFOA ⌀	n.a
Hoffman et al., 2010	cross-sectional study, NHANES-based (1999-2000, 2003-2004)	12–15 years, $n = 571$	CB	ADHD[d]: PFOS, PFOA, PFHxS ↓**[e]; PFNA ↑[e]	n.a
Stein & Savitz, 2011	C8 Health Project, cross-sectional, USA, 2005–2006	5–18 years, $n = 1503$ (ADHD), $n = 542$, (ADHD + medication)	CB	ADHD without medication[f]: PFOA ↓; PFHxS ↑**; PFOS, PFNA ⌀ ADHD with medication[f]: PFOA ↑ or ↓ (highest quartile[f]); PFOS, PFHxS ↑; PFNA ⌀ Learning problems: PFOS ↓**	n.a

Abbreviations: ↑ = positive (beneficial) association; ↓ = negative (adverse) association; ⌀ ¯ no association; **$P < 0.05$;° mean value (ng/mL) (range);°° mean value ± standard deviation (ng/mL);°°° median (range) (ng/mL); #median (ng/mL) (interquartile range, IQR); § geometric mean ± standard deviation (ng/mL); ADHD = attention deficit/hyperactivity disorder; BM = breast milk; CB = child blood; DCDQ = Developmental Coordination Disorder Questionnaire; IB = infant blood; MB = maternal blood; NHANES = National Health and Nutrition Examination Survey; SDQ = Strengths and Difficulties Questionnaire; UCB = umbilical cord blood; [a]one ln-unit increases of PFOS and PFOA were associated with decreases in mean head circumference but this was only observed for vaginal deliveries, after adjustment for the delivery mode in the model; [b]maternal blood was also collected post delivery if mothers had anemia; [c]an exposure model was used to estimate in utero PFOA exposure from contaminated drinking water based on the mother's estimated serum PFOA concentration at the time she was pregnant with the study child (2005–2006); [d]maternal-reports, questionnaire-based; [e]expressed as odd ratios (95%CI); [f]parental or self-report from doctors of diagnosed ADHD; [g]authors reported likelihood of spurious finding.

contaminants and thyroid hormone mediated effects on neurodevelopmental and neurobehavioural outcomes; (ii) co-investigation with other environmental contaminants that were not halogenated compounds such as lead and methylmercury; (iii) articles where only the abstract was available or unpublished data; (iv) studies on children more than 12 years of age.

2.3. Methodology of quality assessment

We assessed the methodological quality of the selected studies using a modified checklist-type approach based on the STROBE guidelines and the proposed HONEES criteria. The STROBE ("*STrengthening the Reporting of OBservational studies in Epidemiology*", http://www.strobe-statement.org/) guidelines have not been designed to evaluate the quality of epidemiological studies but rather focus on the conduct, reporting and dissemination of observational research (von Elm et al., 2007). Youngstrom et al. (2011) developed a set of criteria ("*Harmonization of Neurodevelopmental Environmental Epidemiology Studies*", HONEES) to evaluate the methodological quality of neurodevelopmental studies to facilitate weight-of-evidence assessments, based on PCBs as a proof of concept case study (Goodman et al., 2010). We also referred to the US National Toxicology Program's Office of Health Assessment and Translation (NTP OHAT) "*Draft OHAT Approach for Systematic Review and Evidence Integration for Literature-based Health Assessments–February 2013*" (http://ntp.niehs.nih.gov/go/38673), which provides a stepwise approach for a systematic literature-based evaluation to assess the body of evidence for environmental chemicals.

We developed a checklist composed of seven methodological items (*study design and setting*, *study population and sampling*, *variables*, *assessment procedures*, *bias*, *study size*, *statistical methods*) divided into a total of 15 questions (Q1-Q15, see Table 3). For a given study each question was scored: *yes* (fully addressed), *partially* (partially addressed), *no* (not addressed), or *unclear* (cannot be assessed). In a second step, based on these question scores, we then qualitatively rated each of the 7 items as *good* (2 *points*), *medium* (1 *point*) or *poor* (0 *points*).

Table 3
Checklist for the quality assessment of individual neurodevelopmental studies. The list of items and questions (Q1–Q15) have been derived from the STROBE guidelines and the HONEES criteria developed by Youngstrom et al. (2011) to evaluate the methodological quality of neurodevelopmental studies in children. Scoring of each question is: *yes* (fully addressed), *partially* (partially addressed), *no* (not addressed) or *unclear* (cannot be assessed). The qualitative evaluation of each item is: *good*, *medium* or *poor*. Based on the rating of each item, an overall study quality score is given: *high*, *moderate* or *low*.

Study design and setting
1. Are the study setting, location, relevant dates including period of recruitment exposure, follow-up, and data collection clearly described?
Study population and sampling
2. Are the eligibility criteria, sources and methods of participants selection, incl. follow-up clearly described?
3. Were there clearly defined groups of participants (incl. control group), similar in all important ways other than exposure to the chemical? (e.g. IQ scores, SES, age) Alternately, are sufficient details reported to allow stratification or any appropriate adjustment?
4. Were the participants representative of the population to whom results would be generalized in practice?
Variables
5. Does the study design account for confounders and effect modifying variables? Does the study design adjust/control for other exposures likely to bias the results?
Assessment procedures
6. Are sources of data and details of methods of exposure measurement and health outcome assessment clearly described for each variable of interest?
7. Was the physical measurement and/or neurodevelopmental assessment procedure appropriate and clearly described? Was the administration valid, or were there major departures from standardization? (e.g. outside age norms test, poor training investigators, translated version without supporting psychometric data, lack validity check such as video recording, etc.)
8. Did the protocol avoid differential burden or fatigue effects across groups that might invalidate results?
9. Was exposure status determined without knowledge of the results of the neurodevelopmental assessment, resp. were the neurodevelopmental assessment results interpreted without knowledge of the exposure status (e.g. blinding of assessment administration and scoring staff; computerized administration)?
10. Is it clear that the exposure preceded the onset of the outcome?
11. Is there a dose–response gradient?
Bias
12. Are potential sources of bias reported? (e.g. all health outcomes reported, loss to follow up, missing data or non-interpreted results addressed, etc.)?
Study size
13. Is the study size adequate?
14. Are there deviations from the study protocol which are likely to impact the results? (e.g. withdrawals, loss to follow-up, etc.)
Statistical methods
15. Are all statistical methods, including those used to control for confounders and modifying variables clearly described?

As a last step, an overall quality rating was given for each individual study based on the summed scores of the methodological items: *high quality* (10–14 points), *moderate quality* (6–9 points) and *low quality* (0–5 points). The overall quality rating of each individual study is summarized in Tables 1 and 2 and details of the full quality assessment can be found in the supplementary material (S2–S4). Neurodevelopmental endpoints were divided into three functional domains: head circumference, motor function and cognitive development; neurobehavioural endpoints were divided into: attention, impulsivity/hyperactivity, attention and hyperactivity disorders (ADHD). Autism/autism spectrum disorders and developmental delay were treated as separate categories. In order to interpret the overall body of evidence for each chemical class, we looked for trends/patterns and consistency of findings, starting with the higher quality studies. If conflicting evidence and/or lack of sufficient information were found, then moderate quality studies were considered in a second step. The strength of evidence for neurodevelopmental and neurobehavioural effects was evaluated in relation to the specific functional domains/endpoints/health outcomes defined. Low quality studies were considered in a last step when looking for consistency of findings among studies. Findings were compared with indirect evidence from questionnaire-based studies as complementary epidemiological information (see Tables 1 and 2).

3. Results

We found 18 articles – 10 articles for PBDEs and 8 articles for PFCs – that met our criteria. Among those articles selected for further analysis, 15 were longitudinal birth cohorts, one was a case-control study and 2 were cross-sectional studies. Individual study characteristics and main findings are summarized for PBDEs in Table 1 and PFCs in Table 2. Studies differed to a very large degree in terms of timing and type of exposure assessment, sampling and type of biological matrix used, study population size, age of children, neurotoxicological endpoints assessed, age at which the tests were administered, type of tests used to assess neurodevelopmental and/or neurobehavioural functional domains, statistical models and tools used. This is fully in agreement with several previous reports (Bellinger, 2013; Goodman, 2010; Olsen et al., 2009).

Our quality assessment provided an overall individual estimate of the quality of the design, conduct, methodology and reporting of each reviewed study, but also gave a good picture of the variability observed for each question and item, highlighting the different strengths as well as frequently observed shortcomings. We identified a number of similarities between PBDEs and PFCs studies in term of general performance and shortcomings. Studies performed generally well in the description of neurodevelopmental assessment procedures (Q7; refer to Table 3) and of analytical and statistical methods (Q15), and it was in most cases clear (i.e. with a prospective birth cohort study design) that exposure would precede the onset of the outcome (Q10). Performance in terms of study design and setting (Q1), study population and sampling (Q2-Q3), and effect modifying variables (Q5) was usually satisfactory. In many cases, lack of a clear and sufficiently detailed reporting was the primary cause of a *poor* or *unclear* rating of the questions. This applies in particular to aspects related to study population and sampling (Q2–Q3), bias (Q12), and assessment procedures (Q6, Q8, Q9). For example, it was not possible to determine if investigators were blinded to the results of exposure status when administering the neurodevelopmental tests in 73% of the studies (Q9). 50% of the studies failed to report sufficient details regarding the characteristics and demographics of the study population to allow for further stratification (Q3). For most of the studies it was not possible to determine whether the neurodevelopmental testing itself could cause some degree of fatigue to the child and impact the outcome of the test (Q8). The representativeness of the study findings and their generalizability to the general population (Q4) were uncertain in more than 50% of the studies evaluated, for example due to investigations in communities with a particular pattern of exposure or dominance of one ethnicity. Only 3 studies (18%) reported a clear dose–reponse relationship (Q11). None of the 18 studies seemed to have performed a power calculation to determine the size of the population (Q13) needed to detect the expected health outcomes.

Our overall evaluation of the 18 studies showed that 7 were of high quality (39%), 7 of moderate quality (39%) and 4 of low quality (22%). The overall quality scores for each individual studies are summarized in Table 1 (PBDEs) and 2 (PFCs). The full results and complete checklist for each individual PBDE or PFC study along with their detailed quality rating are available as supplementary material S2–S4.

3.1. PBDEs

Only two studies evaluated a potential link between prenatal exposure to PBDEs and *head circumference*, and their findings diverge slightly. Harley et al. (2011) reported no statistically significant association between head circumference with any of the 8 PBDEs analysed or the sum of 4 PBDEs (-47, -99, -100, -153), whereas Chao et al. (2007) found a non significant negative association for eight PBDE congeners, including PBDE-47, -99, -100, -153 and -209 (see Tables 1 and 2). Lack of adjustment for counfounders may explain the inverse association found with both head circumference and birth weight by Chao et al. (2007) (see supplementary material S5). No dose–response relationship was observed. These extremely limited data suggest very little if no evidence at all for an association between exposure to PBDEs and reduced head circumference.

Seven studies evaluated both *motor function and cognitive development*. There were many inconsistencies among the studies that evaluated *motor function*. Four studies evaluated gross and fine motor skills in children aged 8–18 months using the Bayley's Scales of Infant Development (Chao et al., 2011; Gascon et al., 2012; Herbstman et al., 2010; Shy et al., 2011). While Herbstman et al. (2010) showed a statistically significant inverse association between prenatal exposure to PBDE-47 and the Bayley's psychomotor scale, no association was shown by any of the three other studies for either individual PBDEs congeners or their sums. Three other studies reported negative association between fine motor skills and PBDE-47 or the sum of PBDE-47, -99, -100 and -153 (penta-BDE) (Eskenazi et al., 2013; Gascon et al., 2011) or PBDE-154 (Roze et al., 2009), but the strength of association differs notably among them. It is difficult to compare the findings from all these studies directly with one another as the exposure, the age of the children, the tests, the different subdomains assessed and the scales to measure them differed. In summary, the evidence for adverse effects on fine motor skills from high quality and moderate quality studies is far from clear, and suffers from several limitations, including the lack of consistency in the outcome for the same PBDE congener from one study to another, the lack of a clear dose–response, and, with the exception of three studies (Eskenazi et al., 2013; Gascon et al., 2011, 2012), small sample sizes with a limited control of potential confounders, most notably for other environmental contaminants.

There was more consistency among the high quality and moderate quality studies that evaluated *cognitive development*. They all reported significant or highly significant inverse associations between prenatal and/or postnatal exposure to individual PBDEs congeners or their sum (mainly PBDE-47, -99, -100, -153, -154, -209) and the various test cognitive scales (i.a. Bayley, Wechsler, McCarthy), however, the outcome of these tests cannot be directly compared with one another. In children aged 8–18 months all domains were affected, whereas in older children (3–6 years), results suggested that cognitive subdomains affected were primarily full scale IQ, verbal IQ, verbal skills and memory. In contrast, low quality studies showed significant positive associations or null effects between cognition and exposure to PBDE-15, -99, -197 or the sum of PBDEs (Chao et al., 2011; Shy et al., 2011). Some associations were observed only for a specific PBDE congener and health outcome, e.g. PBDE-196 and language or PBDE-153 and verbal memory. Several limitations apply; studies were unable to show a clear dose–reponse relationship, some were limited by their small sample size and lack of control for potential confounders (Chao et al., 2011; Herbstman et al., 2010; Roze et al., 2009; Shy et al., 2011).

Attention and hyperactivity disorders were evaluated by several studies and were primarily based on parental and/or teacher self-reports. Here again we observed a good overall consistency among and across studies of high quality and moderate quality, with statistically significant or highly significant associations reported. Eskenazi et al. (2013) found that the sum of PBDE-47, -99, -100 and -153 was significantly positively associated with maternal report of inattention and teacher report of hyperactivity. Roze et al. (2009) reported a negative association between PBDE-47, -99 and -100 and sustained attention. Gascon et al. (2011) found that higher postnatal exposure to PBDE-47 was significantly associated with teacher-reported attention deficits, but not with hyperactivity. These findings are in line with another questionnaire-based study by Hoffman et al. (2012) who reported a significant positive association between exposure to PBDE-47, -99, -100 and activity/impulsivity. Only Eskenazi et al. (2013) reported a dose–reponse but it was limited to teacher-reported self evaluation of attention.

For *other behavioural endpoints* such as internalizing and externalizing behaviours, adaptive behaviour, socio emotional skills and social competence, there was less consistency across studies, independent of their quality rating. Gascon et al. (2011) reported a significant negative association between PBDE-47 and poorer social competence, whereas Roze et al. (2009) found significant positive associations between PBDE-47, -99 and -100 and internalizing and externalizing behaviours. Based on mother self-evaluations, Shy et al. (2011) reported significant negative associations between PBDE-28, -99, -183, -154 and the sum of PBDEs and adaptive behaviour, whereas Chao et al. (2011) did not find any association for the sum of PBDEs. Hoffman et al. (2012) reported a positive association between exposure to PBDE-47, -99, -100 and externalizing behaviours but no association with any other socio-emotional domains assessed. Clarifications are needed to confirm the results observed with penta-BDE in relation to attention and hyperactivity disorders and other behavioural endpoints, given the heterogeneity of testing methodologies and age of children, strength of association, inconsistencies among PBDE congeners in relation to the health outcomes and general lack of dose–reponse. Again, interaction with other environmental contaminants may be a confounding factor (see supplementary material S5).

3.2. PFCs

Five PFC studies included *head circumference* as a neurodevelopmental endpoint. There are many inconsistencies in the outcome, regardless of the study quality rating. Apelberg et al. (2007) found that both PFOA and PFOS were significantly associated with reduced head circumference, but this was only observed for vaginal deliveries, after adjustment for the delivery mode in the model. Fei et al. (2008b) did not report any statistically significant association between PFOS and head circumference, but a negative non-significant association for PFOA. Chen et al. (2012) reported that only PFOS was significantly inversely associated with head circumference, but not PFOA, perfluorononanoic acid (PFNA) or perfluoroundecanoic acid (PFUA). These findings contrast with the results from Washino et al. (2009) who found no statistically significant association between head circumference and PFOA but a negative non significant association for PFOS, or from Lee et al. (2013) who reported no statistically significant association for PFOS, PFOA and perfluorohexane sulfonate (PFHxS). Only one study reported a dose–response for PFOS after categorization of PFOS levels into quartiles (Chen et al., 2012). Four studies added smoking during pregnancy as a potential confounder to their

statistical model, and only a single study controlled for alcohol (Fei et al., 2008b), but none adjusted for co-exposures to other environmental contaminants (see supplementary material S5). Collectively, results suggest that reporting of a reduced head circumference is clearly associated with a lower birth weight (see supplementary material S1). The evaluated epidemiological literature shows rather inconsistent association between birth weight and exposure to specific PFCs in contrast to PBDEs, for which lack of adjustment for gestational age in Chao et al. (2007) may have biased the reported negative association. Measure of head circumference at birth has been classically used as a simple tool to evaluate foetal brain development as well as a predictor of potential adverse neurological outcomes and cognitive deficits postnatally or in later life (Lindley et al., 1999). It has been postulated that neurodevelopmental toxicants could adversely impact the developing brain and that this could be reflected by a reduced head circumference at birth (Ivanovic et al., 2004; Rushton and Ankeny, 1996), but causality is often difficult to establish due to numerous confounding risk factors (Lagiou et al., 2005; Leary et al., 2006; Lindley et al., 2000; Lunde et al., 2007). Measurement of head circumference is inherently associated with a larger degree of error than other types of anthropometric measurements, e.g. due to head molding during vaginal deliveries (Apelberg et al., 2007). Besides, as noted by Savitz (2007), small biological variations in the normal range of distribution for birth parameters such as weight, length or head circumference are common in a population without necessarily bearing clinical significance.

Only one study evaluated assessed *motor function* (Chen et al., 2013). The authors reported a significant negative association between exposure to PFOS and motor coordination, primarily the gross motor domain, but no association with PFOA. In two questionnaire-based studies that were not evaluated in the present work, PFOA and PFOS exposure were not significantly related to maternal report of *motor development* (Fei et al., 2008a; Fei and Olsen, 2011). However, the testing methodologies differed substantially, making the comparison difficult.

Two studies investigated *cognitive development* (Chen et al., 2013; Stein et al., 2013). Both studies reported no association for PFOA. They are of high quality and benefit from a prospective cohort design and larger sample sizes, but assessed the children at different ages (2 y and 6–12 y, respectively) and with different tests (see supplementary material). Models were adjusted for neurotoxicants such as smoking, alcohol or lead but no other environmental contaminants. Chen et al. (2013) found a significant negative association between exposure to PFOS and cognitive development (whole test performance), whereas an additional cross-sectional study by Stein and Savitz (2011) showed a similar trend for PFOS with learning problems, based on parental report of previous physician-diagnosed ADHD. A dose–response gradient was found by Chen et al. (2013) when PFOS levels were categorized into quartiles. In contrast with these findings, Fei et al. (2008a) reported no significant association between PFOS and maternal reporting of cognitive development.

A few studies have assessed general *behavioural endpoints* such as attention (Stein et al., 2013), impulsivity (Gump et al., 2011; Stein et al., 2013) or social competence (Chen et al., 2013). Regardless of their quality rating, none of the PFOA studies evaluated have shown any behavioural effects on the various functional domains assessed, in contrast to observations with PFOS. Chen et al. (2013) found a statistically significant negative association between social competence and self help skills and PFOS exposure, but no association for PFOA. Stein et al. (2013) reported no significant association between PFOA and sustained attention or impulsivity, a finding in line with a report by Gump et al. (2011) who found no significant association between PFOA and a behavioural measure of impulsivity assessed with an inhibition response test; however, Gump et al. (2011) reported a significant positive association between higher serum levels of PFOS, perfluorodecanoate (PFDA), PFNA, PFHxS, perfluorooctanesulfonamide (PFOSA) and impulsivity. Less consistency was observed, most notably for PFOA, from three complementary studies based on teacher and/or parental reports of general behavioural health (Fei and Olsen, 2011) or of previously diagnosed ADHD (Hoffman et al., 2010) or of parental report or self-report of previous doctor-diagnosed ADHD with and without medication (Stein and Savitz, 2011).

4. Discussion

Over the last decade, reporting in the literature of potential adverse effects of persistent brominated and perfluorinated chemicals on the human developing brain has increased. So far, direct epidemiological evidence has been limited and contradictory. Yet there is a need at risk assessment and risk management level for a more systematic appraisal of the literature to better evaluate the available body of evidence. Therefore we have developed a quality assessment scheme based on a checklist approach to evaluate the methodological performance of epidemiological studies dealing with neurodevelopmental and/or neurobehavioural effects following environmental exposures to PBDEs and PFCs. Given the paucity and the large heterogeneity observed in the selected literature, it was not possible to assess the evidence quantitatively, therefore we developed a qualitative scoring system using best professional judgment.

We interpreted the overall body of evidence for each of the two chemical classes, according to study quality and to specific neurodevelopmental and neurobehavioural endpoints, and considering dose–response, consistency and strength of the association. Complementary epidemiological information based on self-reported questionnaires was only identified for studies related to behavioural outcomes such as ADHD or to a more general evaluation of social performance and socio-emotional domains.

Our systematic review of the literature largely confirmed the difficulty of appraising the body of evidence for a given neurodevelopmental or neurobehavioural outcome. Collectively, when looking at general effects that may be attributed to either or both the brominated or the perfluorinated class (“class effects”), studies suggest a certain number of potential neurodevelopmental and neurobehavioural adverse effects in various functional domains such as fine motor skills, cognitive performance and general behavioural health, including attention deficits, impulsivity or hyperactivity. However, upon closer examination of the evidence for each individual chemical on a case-by-case basis, many inconsistencies emerge with some associations being observed only for a specific health outcome in relation to a specific chemical. This considerably increases the difficulty of fully appraising of the overall body of evidence due to: (i) the general lack of comparability across studies, most notably in term of exposure characterization, age of the children, and functional domains assessed; (ii) the limited number of available studies, in particular for PFCs; (iii) the general lack of consistency of effects for a given chemical between studies; (iv) the lack of individual data on the specific toxicological profile of each PBDE congener which are often assessed as the sum of their total concentrations. We also identified several frequently observed shortcomings that may diminish the strength of evidence for certain specific effects and more generally contribute to questioning the validity of certain studies: (i) the lack of consideration of certain confounding factors; (ii) uncertainties regarding exposure characterization (timing of exposure or life stage of assessment); (iii) the inadequacy of sample size (underpowered studies); (iv) the lack of a clear dose response) the representativeness/generalizability of the results.

In general, we found that assessment of *causality* was difficult. In many instances, the reported associations could be confounded by other factors that could influence neurodevelopment and that were not controlled for in the statistical models. This may lead to inappropriate inference. The selection of relevant confounding variables from a larger set of potential confounds should be determined a priori based on empirical evidence from previous research, thus avoiding over-fitting the statistical model (Babyak, 2004). In practice though, there is a need to find the right balance between a limited, manageable set of covariates and an adequate control of the potential confounders, especially when the study population size is modest. Confounders and effect modifiers may be important both at the individual level and in the environment, such as poor education and low socio-economic status of the family, various maternal and pregnancy characteristics, smoking or alcohol consumption during pregnancy, as well as co-exposures to other environmental contaminants (see supplementary material S5). Most notably, with the exception of a few studies that controlled for PCBs and OCs (DDE, HCB) (Gascon et al., 2012), PCBs and OPs (Eskenazi et al., 2013) or heavy metals (lead, mercury) (Gump et al., 2011), exposure to other neurotoxicants could have interfered with the outcome of these studies. Interestingly, none of the PBDE studies adjusted for PFCs, and vice-versa. When linking exposure to effects, limitations may result from the study design and an inadequate *exposure characterization*; e.g. in Gascon et al. (2011) postnatal exposure to PBDEs was measured at the same time as the neurodevelopmental tests were administered, which makes the interpretation of any association difficult, whereas in Hertz-Picciotto et al. (2011), current children PBDEs blood levels were measured after children were assessed for autism or developmental delay and were used as a proxy for exposures that preceded the neuropathologic changes leading to those health outcomes. Cohorts and cross sectional studies usually include a comparison group, whereas case series typically do not. Ten studies (56%) divided their partipants into quartiles or percentiles *a posteriori* once the exposure measurement was done, the lowest quartile being typically used as the referent group. However, without an appropriate control group in the general population, it becomes more difficult to evaluate the association between an exposure and an outcome.

Collectively, a major identified limitation is that none of the studies evaluated appeared to have performed a *power calculation* to assess if the study size was appropriate to detect an effect or no effect. Only a single nationwide, population-based birth cohort (Fei et al., 2008b) had a large enough study sample ($n = 1399$) to possibly warrant the assumption of an adequately powered study. Many studies had a population below 100 participants. An appropriate sample size is crucial for the statistical power of a study, because underpowered studies can give an overestimation of the effect. This is particularly true for those evaluated small sample size studies that suffer from loss to follow up or missing data (Herbstman et al., 2010; Lee et al., 2013; Shy et al., 2011). The need for adequately powered studies was already recognized by Roze et al. (2009). If failing to do a power calculation is understandable for early, small exploratory studies for which it is a priori difficult to hypothesize an expected effect because the association between the variable and the outcome has simply not been investigated before, subsequent studies designed to confirm suspected associations should perform a sample size calculation as a prerequisite (Amler et al., 2006) and include it in the reporting. Large birth cohort studies with a long-term follow up are therefore needed to better evaluate the role of environmental contaminants exposure in the development of adverse neurological and neurobehavioural disorders to detect a sufficient number of those cases above the low background incidence rate typically observed in the general population (Savitz, 2007).

A large majority of studies did not report a clear dose–response relationship between levels of PBDEs or PFCs and the measured health outcomes. Potential effects of mixtures due to the combined effect of possibly numerous environmental contaminants should also be taken into account. If prenatal exposure to neurotoxicants during critical developmental periods leads to irreversible effetcs, the possibility of reversibility of certain effects following postnatal exposures in later life stages should also be taken into account.

Some studies raise the question of the representativeness of the study population and generalizability of their findings, due to: (i) differences in term of ethnicity, e.g. study participants were predominantly non-Hispanic white (C8 Health Project), Afro-American (THREE study) or Mexican-American (CHAMACOS study); (ii) poor education, low socio-economic status population background (e.g. CHAMACOS and THREE studies); (iii) unusual exposure scenarios following accidents or outbreaks (C8 Health Project and 9/11 WTC cohorts).

Collectively, the epidemiological evidence currently does not support a strong causal association between PBDEs and/or PFCs and adverse neurodevelopmental and neurobehavioural outcomes in infants and children. However, despite some limitations (dose–response, strength of association, sample size, consistency), these studies raise questions that require further investigation. As pointed out by Savitz (2007), even if of small magnitude, discrete observed effects following exposure to prenatal and/or postanal exposure to these environmental contaminants that are not necessarily showing clinical significance at the individual level may have a larger impact at a population level. While many of the persistent halogenated chemicals covered in this review have been restricted or prohibited under EU and US regulations, the widespread exposure to these environmental contaminants will likely remain a cause of concern in the future. Although it is expected that the exposure will continue to drop over the coming years, the overall picture is complex (Kato et al., 2011; Ode et al., 2013; Olsen et al., 2012; Schecter et al., 2012). Consequently, there is a need for regulatory risk assessment to make better use of environmental epidemiological data to more efficiently inform risk management. In turn, this will enable decision-making to enact more efficient and sustainable public health policies to protect human populations, and among them most notably pregnant women and children.

There is a need for future research to strengthen the currently inconclusive evidence. Hypothesis-driven studies should be conducted that rely on a better understanding of the mode of action of PBDEs and PFCs to link exposure to the neurodevelopmental and neurobehavioural effects; this will help in turn to clarify the a priori working hypothesis and to adequately power studies. More detailed exposure assessments are critical, in particular with regard to specific periods of vulnerability to specific neurotoxicants. Adjustment of larger sets of environmental contaminants as potential confounders and other effect modifiers, both at the individual level and in the environment, is essential. Repeated testing with larger birth cohorts needs to be conducted to observe a sufficient number of those cases above the low background incidence rates typically observed in the general population, as well as long-term follow up, including differently exposed populations. In particular, epidemiological studies reporting incidents/breakouts in highly exposed communities should be matched with similar events in similar populations across the globe. Exposure determinants and specific toxicological profiles, in particular for PBDEs congeners, should be clarified, including potential role of their metabolites.

There are limitations to the approach we have taken to examine the epidemiological literature. Firstly, we did not evaluate all the available epidemiological literature but focused on those studies published since 2006. We also chose to exclude from our quality assessment those studies that would rely solely on indirect measurements of the health outcomes, such as parental self-reports or

other questionnaire-based assessments. However, because these tools are routinely used in research and national surveys (e.g. for ADHD, see Stein and Savitz, 2011), these studies were handled as a separate category and used as complementary information when interpreting the overall body of evidence. Secondly, for several studies, the HONEES criteria could not be fully applied, due to: (i) the large heterogeneity in study designs, methodologies, analysis and reporting of the epidemiological studies selected; (ii) the non-relevance of certain components to the purpose of our review; (iii) the complexity of applying certain criteria beyond the scope of our qualitative analysis. Thirdly, in order to keep the scoring system qualitative and simple, we rated each individual study items with equal weight and systematically applied semiquantitative cut-off criteria, rather than applying differential weighting to specific core methodological items. Fourthly, our qualitative approach was based on best professional judgement and may suffer from a potential lack of consistency in the interpretation of the evidence when assessing the quality of individual studies. This was primarily related to the difficulty of applying quality criteria to such a diverse and hugely heterogenous collection of studies. It should also be noted that a poorly rated study does not necessarily imply that the study is "bad" per se, but often that it lacks proper quality in the reporting.

Many regulatory authorities worldwide have expressed the need for a better use of epidemiological data in the human health risk assessment process. Yet for the non-specialist in a regulatory setting, assessing the epidemiological evidence is a daunting task. It becomes all the more difficult when the available data lack consistency and comparability, especially when causality is difficult to establish. Risk assessors need more standardized, robust and clearly reported studies, enabling a faster and more comprehensive review of the evidence and a better understanding on how this evidence has been collected. We strongly support the view that studies reporting epidemiological data should align with guidelines such as the STROBE or other existing evidence-based quality criteria frameworks such as the proposed HONEES criteria (Youngstrom et al., 2011). This may contribute to fostering a more harmonized use of epidemiological data for improved regulatory risk assessment and risk management of environmental contaminants.

5. Conclusion

The present work confirmed the difficulties in assessing neurodevelopmental and neurobehavioural effects of PBDEs and PFCs in children. Our qualitative assessment of the selected articles from the literature (2006–2013) also confirmed the extremely large variability that has been reported so far in term of study design, conduct, methodology, analysis and reporting. However, our impression is that the quality of reporting is increasing over time, and some of the most recent studies have already aligned to guidelines such as STROBE. We have pointed out some of the most frequently observed shortcomings that contribute to questioning the validity of and undermining confidence in the available epidemiological data. In some instances associations were only observed for specific chemicals for a given health outcome, and nearly all studies could have been confounded by exposures to other environmental contaminants. There is little evidence for "class effects", and chemicals have to be evaluated on a case-by-case basis, though many inconsistencies have to be reported for some PBDE congeners and to a lesser degree PFOS. The only consistent results were obtained for PFOA, for which none of the studies evaluated have shown any developmental or behavioural effects on all the different functional domains assessed. Further research is needed in larger birth cohorts to confirm the current state of knowledge for both chemical classes.

6. Conflict of interest

We declare no conflict of interest. The funding bodies of the authors' institution had no involvement in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the article for publication.

Transparency document

The Transparency document associated with this article can be found in the online version.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.toxlet.2014.02.015.

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