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Flame Retardants and Neurodevelopment: an Updated Review of Epidemiological Literature

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Flame Retardants and Neurodevelopment: an Updated Review of Epidemiological Literature

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Abstract

Purpose of Review Flame retardant (FR) compounds can adversely impact neurodevelopment. This updated literature review summarizes epidemiological studies of FRs and neurotoxicity published since 2015, covering historical (polybrominated biphenyls [PBBs], polychlorinated biphenyls [PCBs]), contemporary (polybrominated diphenyl ethers [PBDEs], hexabromocyclododecane [HBCD], and tetrabromobisphenol A [TBBPA]), and current-use organophosphate FRs (OPFRs) and brominated FRs (2-ethylhexyl 2,3,4,5-tetrabromobezoate [EH-TBB] TBB), bis(2-ethylhexyl) tetrabromophthalate [BEH-TEBP]), focusing on prenatal and postnatal periods of exposure.

Recent Findings Continuing studies on PCBs still reveal adverse associations with child cognition and behavior. Recent studies indicate PBDEs are neurotoxic, particularly for gestational exposures with decreased cognition and increased externalizing behaviors. Findings were suggestive for PBDEs and other behavioral domains and neuroimaging. OPFR studies provide suggestive evidence of reduced cognition and more behavioral problems in children.

Summary Despite a lack of studies of PBBs, TBBPA, EH-TBB, and BEH-TEBP, and only two studies of HBCD, recent literature of PCBs, PBDEs, and OPFRs are suggestive of developmental neurotoxicity, calling for more studies of OPFRs.

Keywords Flame retardants · Developmental neurotoxicity · Children · Cognition · Behavior · Epidemiology

Introduction

Flammability regulations required that chemical flame retardants (FRs) be embedded in consumer products, including textiles, plastics, furnishings, electronics, building materials, and transportation products, to reduce flame propagation and prevent combustion. Historical FRs, polybrominated biphenyls (PBBs) and polychlorinated biphenyls (PCBs), were initially used due to their resistance to fire. However, most industrialized nations banned their production amid evidence supporting their toxicity, major accidental human poisoning incidents, and their persistence in the environment and in humans [1–4]. Contemporary FRs, including polybrominated diphenyl ethers (PBDEs), hexabromocyclododecane (HBCD), and tetrabromobisphenol A (TBBPA), replaced PBBs and PCBs. Since the 1970s, PBDEs have been the most

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commonly used FR until their voluntary phase-out from the United States (US) market in 2004 for mixtures penta-BDE and octa-BDE and in 2013 for deca-BDE. Production ceased once studies confirmed their presence in a wide range of environmental samples and human tissues, their tendency to bioaccumulate, and evidence of their neurotoxicity, thyrotoxicity, estrogenicity, and carcinogenicity [5–8]. TBBPA and HBCD are still in production, though both are highly scrutinized, because of their persistent, bioaccumulative, and toxic properties [9, 10]. Consequently, organophosphate FRs (OPFRs), including tris(1,3-dichloropropyl) phosphate (TDCIPP), triphenyl phosphate (TPHP), and mono-substituted isopropyl triphenyl phosphate (mono-ITP), which were used since the 1970s, have emerged as high production substitutes for PBDEs. Toxicological studies indicate that OPFRs may adversely affect human health, with findings suggesting developmental toxicity, endocrine disruption, and carcinogenicity [11, 12]. Other brominated FRs, including 2-ethylhexyl 2,3,4,5-tetrabromobezoate (EH-TBB) and bis(2-ethylhexyl) tetrabromophthalate (BEH-TEBP), were also used to replace PBDEs as components of Firemaster 550 (along with TPHP and mono-ITP).

Fetuses and children are highly susceptible to neurotoxic insults from exogenous chemicals due to marked structural and functional brain development during gestation and childhood [13]. Toxicological studies have found evidence that FRs disrupt thyroid hormone homeostasis, interfere with γ-aminobutyric acid (GABA) signaling, affect neuronal viability via apoptosis and oxidative stress, modify intracellular calcium signaling, alter gene and protein expression in cellular targets, and affect neuronal differentiation [11, 14, 15, 16–26]. Human exposure to FRs is nearly universal as evidenced by their detection in maternal serum, cord/child serum, urine, and breastmilk [27–41].

Several of the halogenated FRs are stringently regulated, but they remain a public health concern due to their persistence in the environment and in humans. Chlorinated and brominated FRs have long half-lives. For instance, CB-153 and CB-180 have half-lives of 7–9 years [42], PBB has an estimated half-life of 10.8 years [43], congeners within the penta-BDE mixture have half-lives between 2 and 4 years, and BDE-153 has a half-life of 14–16 years [44, 45]. Further, humans continue to be exposed to PBDEs despite the phase-out, because of exposures to reservoirs that remain in usage; reservoir sources, such as recycled items containing PBDEs, contribute to environmental levels as compounds are released as dust particles and higher-brominated PBDEs metabolize into lower-brominated congeners [46]. Despite the phase-out, the body burden of BDE-47 and BDE-99 plateaued between 2011 and 2014 and BDE-28 has increased after an initial period of decline among pregnant women in California [47].

Epidemiological Studies on FRs and Neurodevelopment Published Prior to 2015

Chronic exposure to FRs in the general population and evidence of neurotoxicity from animal studies raise concerns of neurodevelopmental impacts in humans. Numerous epidemiological studies have reported adverse associations between PCB and PBDE exposures and neurodevelopment in childhood [47–54], although the findings are not entirely consistent for various neurodevelopmental domains.

Inverse associations have been reported between in utero PCB concentrations and verbal and memory scores at 4 years and full-scale intelligence quotient (FSIQ) scores at 11 years among children living in the Great Lakes region in Michigan [55, 56]. These findings were similarly observed in the Oswego cohort, with a reduction of 3 FSIQ points ($p = 0.02$) for each 1 ng/g (wet weight) increase in placental concentrations of PCBs [49]. Poorer cognitive development in children has similarly been reported in cohorts in Japan and Slovakia [57,58]. Decrements in IQ scores were also noted among children ages 4 and 5 years who were prenatally exposed to PCBs as a result of cooking-oil contamination in Taiwan as compared to children born before the mass poisoning [51]. In contrast, birth cohorts from the Netherlands and upstate New York did not observe a persistent inverse association between prenatal PCBs and cognition in subsequent analyses of children at an older age [59, 60]. Further, null associations were reported in the North Carolina birth cohort and in the Collaborative Perinatal Project [61,62]. Prenatal PCBs may also impact neurobehavior in children as positive associations were noted with impulsivity, impairments in information processing and executive function, attention deficit hyperactivity disorder (ADHD) behaviors, and feelings of unhappiness and anxiety in children [54, 63–68]. In other studies, however, no relationship was observed between prenatal PCBs and various neurobehavioral domains, including response inhibition, autistic behaviors, ADHD-like behaviors, and emotional disorders [52, 60, 69–74].

Prenatal PBDEs were first reported to be significantly associated with decreased FSIQ in children at 48 months in the New York City cohort [75]. Concordant findings were later reported in the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) Study; specifically, a 10-fold increase in ∑PBDEs (BDE-47, -99, -100, and -153) was associated with a decrease of 4.7 points (95% CI − 9.4, 0.1) in FSIQ at age 7 years [76]. Eskenazi et al. [77] additionally reported inverse associations between child serum concentrations of ∑PBDEs at 7 years and FSIQ ($\beta = -5.6$, 95% CI − 10.8, − 0.3). Statistically significant inverse associations

were also observed in the Health Outcomes and Measures of the Environment (HOME) Study, with a reduction of 4.5 points (95% CI − 8.8, − 0.1) in FSIQ at 5 years [78]. In contrast, the Menorca birth cohort did not find a relationship between prenatal or postnatal PBDEs and total cognitive function scores at 4 years [79]. However, BDE-47 concentrations were low in the Menorca cohort, with a median of 0.12 ng/g lipid in child serum at 4 years [79]. Further, the Pregnancy, Infection, and Nutrition (PIN) Babies Study in North Carolina reported positive associations between PBDE concentrations measured in breastmilk and cognitive skills at 36 months [80]. Although, Adgent et al. [80] conclude that these positive associations may have been mitigated by the benefits of breastfeeding. Increased behavioral problems in children have also been observed with higher concentrations of PBDEs, particularly with externalizing and attention problems. In the CHAMACOS Study, prenatal and postnatal PBDE exposures were associated with attention problems in school-aged children [76]. In addition, concurrent concentrations in child serum were positively associated with more teacher-reported hyperactivity and attention problems at 7 years [76]. Increased hyperactivity problems in children at 5 years were also reported in the HOME Study with prenatal BDE-47 concentrations [78]. A cross-sectional study of children ages 9–11 years found positive associations between PBDEs and conduct problems, hostility, and aggression [81]. In contrast, null associations were reported by the Menorca birth cohort between prenatal and postnatal PBDEs and externalizing problems [79].

New studies are emerging on these and current-use FRs, different neurobehavioral outcomes, and in diverse study populations. This updated literature review focuses on recent findings published from 2015 onward on prenatal and postnatal exposures to historical (PBBs, PCBs), contemporary (PBDEs, TBBPA, HBCD), and current-use FRs (OPFRs, EH-TBB, BEH-TEBP) and several neurodevelopmental domains, including cognition (intelligence quotient), behavior (externalizing, internalizing, attention, social), and neuroimaging, in children up to 18 years of age.

Methods

We devised and executed a literature search strategy for PubMed on 11 December 2019. Search strings were developed that would address our population of interest (children), exposures of interest (FRs), and outcomes of interest (cognition, behavior, and neuroimaging). A combination of medical subject headings and free text words were used, with the exclusion on the publication dates that occurred prior to 2015. The specific search string utilized in PubMed was as follows: ("2015"[Date - Publication]: "2020"[Date - Publication]) AND ("Flame retardants" OR PBDEs OR PCBs OR PBBs OR TBBPA OR HBCD OR OPFRs OR EH-TBB OR BEH-TEBP OR BFRs) AND (IQ OR "Cognitive function" OR Behavior OR Neuroimaging OR "Brain imaging") AND Children. The search strategy was also limited to studies conducted on humans. Finally, we scanned references of the included studies to screen for any additional studies that were not retrieved by the initial literature search.

Results from PubMed were exported into an Excel file and screened for relevancy based on the title and abstract by two reviewers. Discrepancies between reviewers were marked and resolved by discussion. There was no limitation on the number of exposures examined within each study as some investigated the associations between several toxicants and neurodevelopment. Likewise, there was no limitation on the number of neurodevelopmental outcomes examined so long as one of the assessments aligned with the three domains selected for the present review. Studies that were not original research (e.g., review articles) or not written in English were excluded.

Data extraction from full-text documents was independently completed, with the following information recorded for each bibliographic citation: study type, publication year, geographical location, overall sample size, FR compound assessed, timing of FR quantification (prenatal [weeks], postnatal [days, weeks, months, years]) and corresponding biological (maternal or child serum, cord serum, breastmilk, urine) or environmental matrix (dust), neurobehavioral domains, age of assessment, and overall study findings.

Summary of Studies

The PubMed search retrieved 100 studies and hand searching bibliographies yielded two additional studies (Fig. 1). A total of 44 articles were considered relevant after title and abstract screening. Of these, we excluded 11 review articles and 1 non-English article. Full-text reviews for the remaining studies removed 3 additional articles based on irrelevant exposures and/or outcomes. A total of 29 epidemiological studies were identified (Table 1). Most epidemiological studies used a prospective cohort study design ($n = 26$), though there were a few cross-sectional studies ($n = 3$). Most studies ($n = 18$) examined prenatal exposures, while 5 examined postnatal exposures, and 6 investigated both pre-and postnatal concentrations. FRs evaluated in the studies include the following: PCBs ($n = 10$), PBDEs ($n = 18$), HBCD ($n = 2$), and OPFRs ($n = 4$). We did not identify any studies on PBBs, TBBPA, EH-TBB, or BEH-TEBP. Neurobehavioral outcomes assessed in the epidemiological studies, ranging from newborn to 15 years, were mainly behavior ($n = 25$), followed by intelligence quotient (IQ) ($n = 9$). Two studies have examined the relationship between FRs and neuroimaging.

Historical Flame Retardants (PCBs)

Cognition

In the Development at Adolescence and Chemical Exposure (DACE) Study, prenatal exposure to PCB-183 was associated with a higher risk of subclinical cognitive impairment (IQ ≤ 85), and PCB-105, -138, and -183 concentrations were inversely associated with verbal memory at ages 13–15 years [82•]. In the Norwegian Mother and Child Cohort Study (MoBa), the estimated maternal dietary exposure during pregnancy to dioxin-like PCBs or PCB-153 was associated with

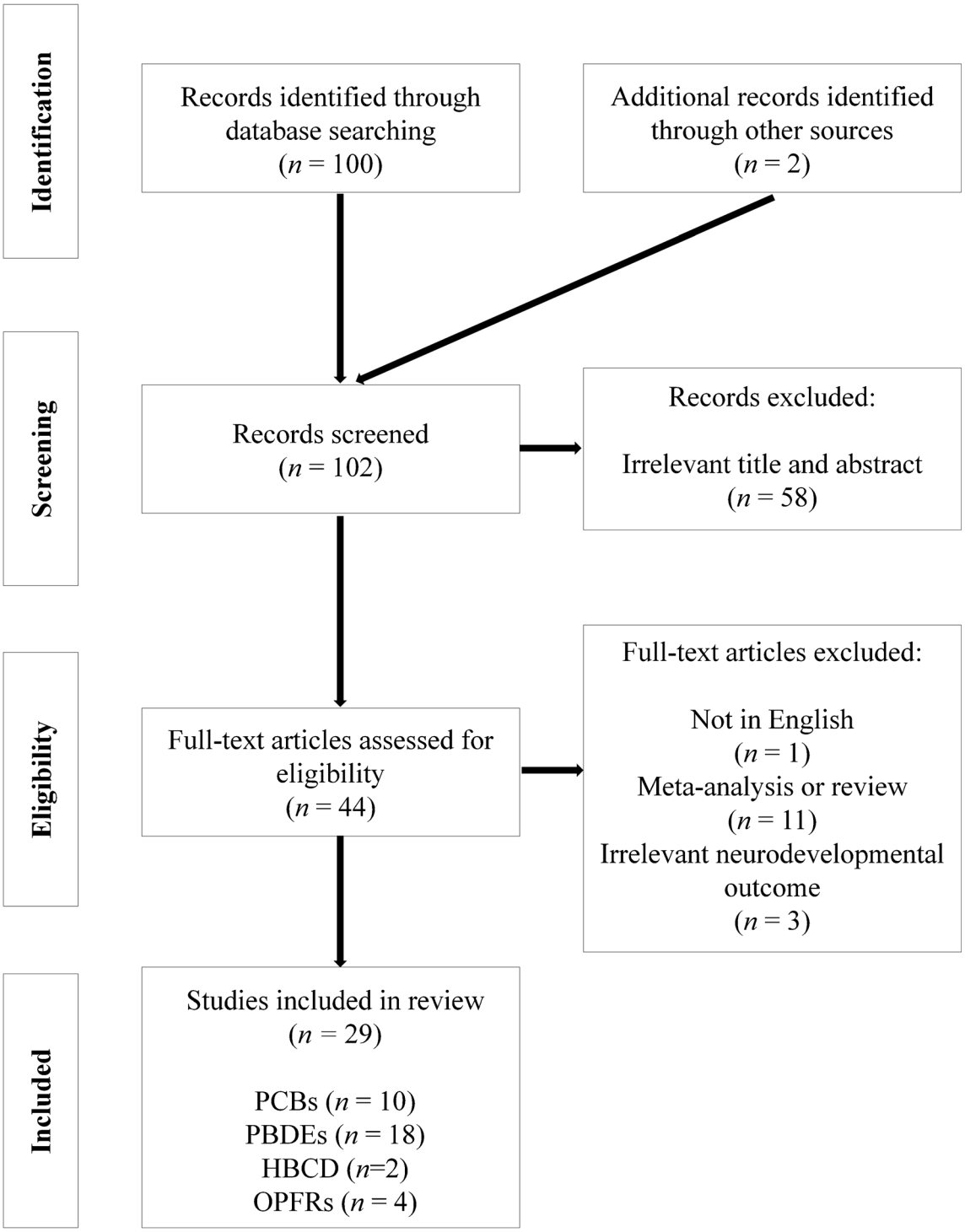

Fig. 1 Flow chart showing the process of literature search and study selection

Table 1 Characteristics of epidemiological studies examining flame retardants and cognition, behavior, and/or neuroimaging in children published from 2015 to 2020

First author (year), country	Study design		Sample size	Flame retardant assessment						Neurodevelopment assessment				Findings
	Prospective cohort	Cross-sectional		PCBs	PBDEs	HBCD	OPFRs	Timing	Matrix	Age	IQ	Behavior	Neuroimaging	
Cowell (2015), United States [101]	✓		210		✓			Delivery	Cord serum	3–7 y		✓		Positive associations were observed between cord BDE-47 and BDE-153 and attention problems at age 4 years. However, no significant associations were present between cord PBDEs and attention problems at age 6 years.
Ding (2015), China [104]	✓		232		✓			Delivery	Cord serum	1 y 2 y		✓		A 10-fold increase in cord BDE-47 was associated with a decrease of 1.89 points (95% CI − 3.75, − 0.03) in the social domain developmental quotient, indicating poorer social skills.
Donauer (2015), United States [96]	✓		349		✓			16 ± 3 w	Maternal serum	5 w		✓		Null associations were reported between prenatal PBDEs and neurobehavioral infant profiles at 5 weeks, including hypotonic and social/easygoing, and high arousal/difficult.
Neugebauer (2015), Germany [88]	✓		117	✓				32 w 2 w after delivery	Maternal serum Breast milk	8–9 y		✓		There was a positive association between maternal PCBs and omission error, and an inverse association between maternal and breast milk PCBs and ADHD-related behaviors.
Nowack (2015), Germany [91]	✓		116	✓				32 w	Maternal serum	9–10 y		✓		There was an inverse association between maternal PCB concentrations and Social Responsiveness Scale scores, mainly in girls.
Sagiv (2015), United States [102•]	✓		622		✓			26.7 ± 2.6 w Delivery 9 y	Maternal serum Cord serum Child serum	9 y 10.5 y 12 y		✓		Prenatal ∑PBDEs (BDE-47, -99, -100, and -153) were associated with poorer attention at ages 9–12 years, while no associations were observed between ∑PBDE concentrations in child serum and measures of attention in school-age children.
Sovcikova (2015), Slovakia [89]		✓	307	✓				8–9 y	Child serum	8–9 y		✓		Positive association between serum PCB concentrations and parameters μ and τ of the ex-Gaussian distribution of simple reaction time.
Verner (2015), United States [86]	✓		441	✓				Delivery 0–12 m	Cord serum Estimates for postnatal	8 y		✓		Positive associations between cord serum PCB-153 and ADHD-related behaviors in quantile regression at the 75th percentile. The association for postnatal PCB-153 was attenuated.

Table 1 (continued)

First author (year), country	Study design		Sample size	Flame retardant assessment						Neurodevelopment assessment				Findings
	Prospective cohort	Cross-sectional		PCBs	PBDEs	HBCD	OPFRs	Timing	Matrix	Age	IQ	Behavior	Neuroimaging	
Verner (2015), Canada [87]	✓		98	✓				Delivery	Cord plasma	5 y		✓		Null association between cord plasma PCB-153 and inattention, but estimated PCB-153 levels at 2 months were associated with increased duration of inattention.
Wang (2015), China [105]		✓	98		✓			4–5 y	House dust	4–5 y		✓		BDE-209 and total-BDEs (BDE-99, BDE-153, and BDE-209) were positively associated with depressive behavior problems and lower social development quotients.
Caspersen (2016), Norway [83]	✓		1024	✓				22 w	Food Frequency Questionnaire	3.5 y	✓	✓		Estimated PCB intake during pregnancy was related to lower language skills in girls, but not boys. There were null associations with ADHD, IQ, and executive function.
Forns (2016), Norway [99]	✓		548		✓			Median: 32 d	Breastmilk	12 m		✓		In a mixture model of 6 persistent organic pollutants that were selected by elastic net and Bayesian model averaging, null associations were noted between BDE-28 and BDE-47 with behavioral problems at 12 months.
Braun (2017), United States [92]	✓		346		✓			16 ± 3 w	Maternal serum	1–8 y	✓	✓		Prenatal BDE-47 was associated with lower MDI scores at ages 1–3 years and decreased FSIQ at ages 5 and 8 years. Positive associations were also reported between prenatal BDE-47 and externalizing behaviors.
Castorina (2017), United States [108••]	✓		310				✓	26 w	Maternal urine	7 y	✓	✓		Inverse associations between DPHP and Full-Scale IQ and working memory. Positive association between ip-PPP and hyperactivity scores.
Lipscomb (2017), United States [100•]		✓	72		✓		✓	3–5 y	Silicone passive sampler	3–5 y		✓		∑PBDEs (BDE-28, -33, -47, -49, -99, -153, and -154) were not associated with externalizing problems in preschool children, while there was a positive relationship with ∑OPFRs (TDCIPP, TPHP, TCPP, and TCEP).
Rosenquist (2017), Greenland and Ukraine [85]	✓		1018	✓				23–25 w First 12 months after delivery	Maternal serum Pharmacokinetic model for postnatal PCBs	5 and 9 y		✓		Pooled adjusted ORs between prenatal and postnatal PCB-153 and abnormal behavior scores for Greenland and Ukraine cohorts did not reveal a statistically significant relationship.

Table 1 (continued)

First author (year), country	Study design		Sample size	Flame retardant assessment						Neurodevelopment assessment				Findings
	Prospective cohort	Cross-sectional		PCBs	PBDEs	HBCD	OPFRs	Timing	Matrix	Age	IQ	Behavior	Neuroimaging	
Vuong (2017), United States [103]	✓		214		✓			16 ± 3 w 1, 2, 3, 5, 8 y	Maternal serum Child serum	8 y		✓		No statistically significant associations were reported between prenatal or postnatal PBDE concentrations and measures of inattention or impulsivity in children at age 8 years.
Vuong (2017), United States [93•]	✓		208		✓			1, 2, 3, 5, 8 y	Child serum	8 y	✓	✓		Postnatal PBDEs were associated with decreased FSIQ and increased hyperactivity and aggressive behaviors at age 8 years.
Zhang (2017), United States [94]	✓		239		✓			16 ± 3 w	Maternal serum	8 y	✓	✓		A 10-fold increase in prenatal ∑PBDEs was associated with a decrement of 5.3 points (95% CI − 10.6, − 0.02) in FSIQ. Prenatal BDE-153 were associated with increased externalizing problems in children at age 8 years.
Berghuis (2018), Denmark [82•]	✓		101	✓	✓	✓		35 w	Maternal serum	13–15 y	✓	✓		Prenatal HBCD was associated with decreased total intelligence in children 13–15 years. While PBDEs were not associated with cognition, BDE-153 was observed to decrease sustained auditory attention.
Kim (2018), South Korea [95]	✓		59 41		✓			Not specified	Maternal serum Breastmilk	13–24 m	✓	✓		Maternal serum BDE-47 was associated with more externalizing behaviors among infants. No associations were noted between PBDEs and MDI.
Oulhote (2018), United States [97]	✓		333		✓			6–13 w	Maternal serum	6.9 ± 0.9 m		✓		Increased concentrations of prenatal PBDEs were associated with more negative vocalizations in infants. Delayed physical reactivity was also noted with higher PBDEs, but only among boys.
Bernardo (2019), Canada [90]	✓		546	✓				First trimester	Maternal plasma	3–4 y		✓		The highest PCB-153 quartile was associated with increased risk of having a Social Responsiveness Scale score > 60.
de Water (2019), United States [107••]	✓		34		✓			12.2 ± 2.8 w	Maternal serum	5 y			✓	Prenatal PBDEs were associated with increased global efficiency in areas of the brain that are involved with visual attention at age 5 years. Increased global efficiency in this area of the brain is associated with more executive function problems.

Table 1 (continued)

First author (year), country	Study design		Sample size	Flame retardant assessment						Neurodevelopment assessment				Findings
	Prospective cohort	Cross-sectional		PCBs	PBDEs	HBCD	OPFRs	Timing	Matrix	Age	IQ	Behavior	Neuroimaging	
Doherty (2019), United States [109••]	✓		227 149				✓	27 w	Maternal urine	2–3 y	✓			Inverse associations between maternal ip-PPP concentrations and MSEL Cognitive Composite Scores and MB-CDI Vocabulary scores.
Doherty (2019), United States [110••]	✓		199				✓	27 w	Maternal urine	3 y		✓		Positive associations between maternal urinary BDCIPP concentrations and Behavioral Symptoms Index and Externalizing Problems. Inverse association between maternal urinary ip-PPP concentrations and Internalizing Problems.
Ji (2019), China [98]	✓		199 307		✓			Delivery	Cord serum	2 y 4 y		✓		Cord PBDEs were not associated with externalizing problems, but there was an increase in aggressive behaviors at age 2 years. Cord PBDEs were positively associated with emotional reactivity and internalizing behaviors, but only among girls.
Ruel (2019), Netherlands [84•]	✓		181	✓	✓	✓		35 w	Maternal serum	18 m 30 m	✓			Prenatal PCB-153 was associated with a delayed MDI score at 18 months. No associations were observed between PBDEs or HBCD and MDI.
Margolis (2020), United States [106••]	✓		33		✓			12.2 ± 2.8 w	Maternal serum	5 y			✓	Inverse associations were reported between prenatal PBDEs and global efficiency of the reading network. Increased global efficiency of the reading network was associated with improved word reading, suggesting prenatal PBDEs may be involved in reading development.

Abbreviations: *BDCIPP* bis(1,3-dichloro-2-propyl) phosphate, *d* days, *DPHP* diphenyl phosphate, *ip-PPP* isopropyl-phenyl phenyl phosphate, *m* months, *MB-CDI* MacArthur-Bates Communicative Development Inventories, *MDI* mental development index, *MSEL* Mullen Scales of Early Learning, *TCEP* tris(2-chloroethyl) phosphate, *TCPP* tris(1-chloro-2-propyl), *TDCIPP* tris(1,3-dichloro-2-propyl) phosphate, *TPHP* tri-phenylphosphate, *w* weeks, *y* years

reduced language skills in girls at age 3.5 years, but not IQ [83]. Using two cohorts in the Netherlands (Risk of Endocrine Contaminants on Human Health [RENCO] Study and the Groningen Infant Comparison of Exposure-Effect Pathways to Improve the Assessment of Human Health Risks of Complex Environmental Mixtures of Organohalogens [GIC] Study), Ruel et al. observed a significant association between prenatal PCB-153 concentrations and having a delayed mental development index (MDI) score at age 18 months [84•].

Behavior

ADHD-related behaviors have been examined in several studies. In the Inuit and European (INUENDO) birth cohort, pooled estimates for mother-child pairs from Greenland and Ukraine indicated no statistically significant relationship between concentrations of prenatal and postnatal PCB-153 and abnormal behavior scores at ages 5–9 years [85]. In contrast, cord serum PCB-153 concentrations were significantly associated with increased ADHD behaviors at age 8 years; postnatal exposures had weaker associations [86]. Another study in Inuit preschoolers identified an association between PCB-153 concentrations at 2 months, but not cord plasma concentrations, and inattention at age 5 years [87]. In the Duisburg Birth Cohort Study, prenatal exposure to PCBs was related to increased omission errors on a computer-based test battery of attention performance (KITAP), but reduced ADHD behaviors among children at ages 8–9 years [88]. The MoBa Study did not find associations of estimated prenatal exposure to dioxin-like PCBs or PCB-153 with ADHD and executive function at age 3.5 years [83]. A cross-sectional study in a PC-polluted region in Slovakia found that serum concentrations were related to longer simple reaction time at ages 8–9 years [89]. Two studies examining prenatal PCB exposure and Social Responsiveness Scale (SRS) scores, indicative of more autistic behaviors, had conflicting findings [90, 91]. Specifically, an inverse association was reported between prenatal PCB concentrations among girls at ages 9–10 years, while a positive association was observed among children at ages 3–4 years [90, 91].

Contemporary Flame Retardants (PBDEs and HBCD)

Cognition

In the HOME Study, investigators reported adverse associations between prenatal and postnatal concentrations of PBDEs and full-scale IQ (FSIQ) in children [92,93•,94]. A 10-fold increase in prenatal ∑PBDEs (BDE-47, -99, -100, and -153) was associated with a 5.3-point decrease (95% confidence interval [CI] − 10.6, − 0.02) in FSIQ at age 8 years [94]. Braun et al. [92] further examined the persistence of prenatal PBDEs' role in longitudinal patterns of child cognition. Prenatal BDE-47 was associated with lower mental development index (MDI) at ages 1–3 years and FSIQ at ages 5 and 8 years. In addition, child serum concentrations of PBDEs, quantified at ages 1, 2, 3, 5, and 8 years, were associated with lower FSIQ at age 8 years [93•]. Decrements in FSIQ were noted with higher BDE-153 concentrations measured at multiple time points during childhood [93•]. In contrast, the DACE Study reported null associations between prenatal PBDEs (BDE-47, -99, -100, -153, and -154) and the risk of subclinical cognitive impairment (IQ < 85) in adolescents at ages 13–15 years, but BDE-154 and HBCD were associated with lower verbal memory and total intelligence in continuous outcome analysis, respectively [82•]. In a prospective cohort in the Netherlands, Ruel et al. reported no associations between PBDEs or HBCD measured in maternal serum at 35-week gestation and MDI scores at 18 and 30 months [83]. In the Children's Health and Environmental Chemicals in Korean (CHECK) Study, maternal serum PBDEs were not associated with MDI at 13–24 months [95]. Findings between PBDE concentrations measured in breastmilk yielded similar null findings with MDI scores at 13–24 months [95].

Behavior

While prenatal PBDEs were not associated with neurobehavioral infant profiles at 5 weeks in the HOME Study [92], Oulhote et al. [97] reported that infants enrolled in the Maternal-Infant Research on Environmental Chemicals (MIREC) cohort displayed more negative vocalizations at 6.9 ± 0.9 months, including incidences of crying and screaming, with increased concentrations of prenatal PBDEs. Poorer emotional reactivity at ages 2 and 4 years was additionally reported in the Shanghai-Minhang Birth Cohort Study with higher concentrations of cord serum PBDEs [98].

Positive associations were additionally reported between prenatal PBDEs and externalizing problems from early childhood to age 8 years in the HOME Study [92, 94]. A 10-fold increase in BDE-153 was associated with a 3.9-point increase in Externalizing Problems score at age 8 years [94]. Similar findings were reported by Kim et al. [95] in the CHECK Study, with increased maternal serum BDE-47 associated with more externalizing behaviors in children at 13–24 months. Findings regarding postnatal PBDEs and externalizing behaviors are inconsistent. In the South Korean cohort, breastmilk PBDEs were not associated with externalizing problems in infants [95]. In addition, Forns et al. [99] utilized a multi-pollutant model to examine six persistent organic pollutant concentrations measured during infancy and behavioral problems at 12 months and reported no statistically significant relationships between breastmilk concentrations of BDE-28 or BDE-47 and behavioral problems. A cross-sectional study

of 72 children between ages 3–5 years also reported null findings between PBDEs, quantified via a silicone passive sampler that was worn for 7 days, and externalizing behaviors [100•]. In contrast, the HOME Study found associations between PBDEs and increased externalizing behaviors (hyperactivity and aggressive behaviors) at age 8 years [93•].

A handful of studies have examined PBDEs and childhood attention, though conclusions were discordant among cohort studies. Prenatal BDE-47 and BDE-153 were associated with more attention problems at age 4 years, though findings were no longer statistically significant when children were 6 years in the New York City cohort [101]. However, maternal serum BDE-153 was associated with poorer attention in adolescents aged 13–15 years in a Danish cohort [82•]. In the CHAMACOS Study, prenatal PBDEs were associated with poorer attention in children ages 9–12 years, while no statistically significant relationship was observed with child serum PBDEs [102•]. In the HOME Study, findings were suggestive of a potential relationship between prenatal and concurrent PBDE concentrations and inattention in children at age 8 years [103].

Few epidemiological studies have investigated PBDEs' relationship with social skills and internalizing behaviors. Cord serum BDE-47 was associated with poorer social skills at 1–2 years in a prospective birth cohort in rural China [104]. A statistically significant relationship was also observed in the Shanghai-Minhang Birth Cohort between cord PBDEs and internalizing behaviors, but this association was only present among girls ages 2 and 4 years [98]. In a cross-sectional study of PBDE household dust levels from urban dwellings in Nanjing, China, BDE-209 and total-BDEs (BDE-99, BDE-153, and BDE-209) were associated with poorer social skills and more depressive behaviors at ages 4–5 years [105].

Neuroimaging

Two preliminary epidemiological studies utilizing participants from the ongoing birth cohort, Endocrine Disruption in Pregnant Women: Thyroid Disruption and Infant Development Study, investigated prenatal PBDEs and the brain's intrinsic functional network organization involved with executive function and reading development [106••, 107••]. Resting-state functional magnetic resonance imaging (fMRI) was used to examine whether prenatal PBDEs were associated with the intrinsic functional network at age 5 years in a sample of 33–34 children [106••, 107••]. Prenatal PBDEs were associated with increased global efficiency in areas of the brain that are involved with visual attention [107••]. Children with increased global efficiency in this area of the brain were reported to experience more executive function problems. Margolis et al. [106••] reported inverse associations between prenatal PBDEs and global efficiency of the reading network, indicating poorer word reading. While there was no statistically significant association between prenatal PBDEs and reading skills in this study, the findings suggest that prenatal PBDEs play a role in altering network integration, which may result in downstream reading problems [106••].

Neuroimaging studies investigating PBDEs would enhance our understanding of the long-term neurodevelopment effects of PBDEs that may not be evident at earlier ages. These preliminary neuroimaging studies provide findings that indicate PBDEs may be involved in altering the brain's network architecture and intrinsic connectivity.

Current-Use Flame Retardants (OPFRs)

Cognition

Maternal urinary concentrations of diphenyl phosphate (DPHP), a metabolite of TPHP, were inversely associated with FSIQ (− 2.9 points, 95% CI: − 6.3, 0.5 for a 10-fold exposure increase) and working memory (− 3.9 points, 95% CI: − 7.3, − 0.5 for a 10-fold exposure increase) at age 7 years in the CHAMACOS cohort [108••]. In the third phase of the Pregnancy, Infection, and Nutrition (PIN3) Study, maternal urinary concentrations of isopropyl-phenyl phenyl phosphate (ip-PPP), a metabolite of mono-IT), but not metabolites of TDCIPP or TPHP, were inversely associated with Composite, Fine Motor, and Expressive Language scores from the Mullen Scales of Early Learning (MSEL) as well as the Vocabulary score from the MacArthur-Bates Communicative Development Inventories (MB-CDI) at ages 2–3 years [109••].

Behavior

In the CHAMACOS cohort, maternal urinary concentrations of ip-PPP were positively associated with Hyperactivity scores in the mother-reported Behavior Assessment System for Children-2 (BASC-2), but not teacher reports. Metabolites of TDCIPP and TPHP were not associated with BASC-2 scores or ADHD Index assessed by Conners' ADHD/DSM-IV Scales assessed at age 7 years [108••]. In the PIN3 Study, maternal urinary concentrations of bis(1,3-dichloro-2-propyl) phosphate (BDCIPP), a metabolite of TDCIPP, were positively associated with Behavioral Symptoms Index and Externalizing Problems scores assessed by BASC-2 at age 3 years. Higher ip-PPP concentrations, however, were associated with lower Internalizing Problems scores [100•]. Another cross-sectional study using a silicone wrist band to assess OPFR exposure identified less responsible behavior and more externalizing behavior problems associated with exposure at ages 3–5 years [100•].

Recommendations

Overall, findings from epidemiological studies within the past 5 years demonstrate that PBDEs have potential neurotoxic effects, particularly with exposures occurring during gestational development. Epidemiological studies from the United States provide evidence that supports prenatal and postnatal PBDE concentrations may adversely impact childhood intelligence, with findings suggesting that prenatal PBDEs' neurotoxicity may persist throughout childhood [92,93•,94]. However, cohort studies from Denmark and South Korea present null results. Discrepancies may be due to differences in the body burden of PBDEs between countries. In the HOME Study, prenatal BDE-47 had a median (IQR) of 19.1 (11–34.5) ng/g lipid compared to 0.9 (0.5–1.3) ng/g lipid in the DACE Study, 1.1 (<LOQ-2.1) ng/g lipid in the CHECK Study, and 0.8 (0.5–1.3) ng/g lipid in the RENCO and GIC Studies [82•, 84•, 111].

Recent epidemiological findings provide additional evidence supporting the hypothesis that prenatal PBDEs are associated with externalizing behaviors. However, the role of postnatal PBDEs is still unclear. Only the HOME Study reported positive associations with externalizing behaviors. Other studies investigating this relationship measured PBDEs at one time point shortly after birth in breastmilk samples or during childhood via a personal silicone passive sampler. Differences in exposure assessment methods and timing may have contributed to the discrepant findings. With regard to PBDEs and attention problems, the findings were varied. Although there is some evidence to suggest that prenatal PBDEs may be associated with more attention problems in children, there is limited evidence on postnatal exposures. Lastly, despite the limited number of studies, suggestive evidence indicates exposure to PBDEs is associated with elevated internalizing behaviors and impaired social skills. Epidemiological findings regarding current-use OPFRs are limited, but provide suggestive evidence of a relationship with neurodevelopment in children. A greater understanding of FR neurotoxicity can be achieved if future studies focus on current-use FRs as limited research thus far has examined pre- and postnatal concentrations of OPFRs and neurodevelopment. Further, the National Academies of Sciences, Engineering, and Medicine (NASEM) have called for the evaluation of OPFRs, putting forth a scoping plan for toxicity assessment [112•]. Secondly, very few studies investigating FR neurotoxicity have utilized advanced statistical multi-pollutant models, taking into account the totality of FR exposures. Historical and contemporary FRs have long biological half-lives. Thus, it would be prudent to examine the total impact of FR exposures on cognition and behavior in children. In addition, limited studies have explored potential sexual dimorphism and even fewer have employed neuroimaging to study FR neurotoxicity.

Current-Use Flame Retardants

OPFR production has increased to 341,000 tons worldwide, more than tripling from 1992 to 2007 [113]. In the US, OPFR production increased from 14,000 tons annually during the mid-1980s to almost 40,000 tons in 2012 [114]. OPFRs have been detected in household dust, cars, air conditioner filters, baby products, and furniture in several countries, including the US, Kuwait, New Zealand, Pakistan, Saudi Arabia, and Sweden [115–121]. Since OPFRs have a low vapor pressure and are hydrophobic [122, 123], they tend to partition into organic matter, such as indoor dust, which is a major source of human exposure [12, 124]. OPFR diester metabolites are now universally detected in urine samples [27, 125, 126], and children have almost 5 times higher urine levels of BDCIPP compared to their mothers [127]. There is sufficient evidence from toxicological studies to warrant concerns regarding OPFRs' impact on neurodevelopment [128]. As such, future epidemiological studies should investigate whether OPFRs are associated with cognitive and behavioral development, focusing on both prenatal and postnatal exposures. Delayed action regarding removal of PBDEs from the market (i.e., taking over 40 years) resulted in widespread and persistent human exposures. Epidemiological studies investigating OPFR neurotoxicity are necessary so that the similar scenario is not repeated.

Associations between OPFRs and neurodevelopment may be sexually dimorphic, but few epidemiological studies have assessed whether effect modification by sex is present [108••,109••,110••]. Sex may also modify OPFR neurotoxicity as there is evidence that OPFR exposure alters thyroid hormones in a sex-dependent measure. TDCIPP and TPHP exposure in adult zebrafish was reported to significantly decrease plasma triiodothyronine and thyroxine in males, while increases were noted in females [129]. TPHP exposure was additionally observed to increase total thyroxine levels, particularly in women, in a sample of 51 office workers in the Boston, MA area [130]. Further, OPFR bioaccumulation was shown to differ sexually in crucian carp, with female eggs having a higher perfusion rate of tri-*n*-butyl phosphate (TNBP) compared to male gonad concentrations [131].

Cumulative Assessment of FRs Using Multi-pollutant Models

Currently, no epidemiological study has investigated the full extent of all FR exposures, including historical, contemporary, and current-use FRs, on children's neurodevelopment. Given that most past-use FRs have long half-lives, each compound may act alone or in conjunction with other neurotoxicants to impact brain development. Several advanced mixture models are available to estimate individual and aggregate exposures, identify important mixture components, determine whether

non-monotonic relationships exist, and assess whether interactions are present between chemicals [132]. However, no epidemiological study has used advanced statistical methods to evaluate mixtures of FRs. While some studies examined chemical mixtures, they did not comprehensively examine FR compounds [94, 99, 106••, 107••]. Therefore, given the abundance of toxicological evidence to support the neurotoxicity of FRs, it is pertinent that future epidemiological studies comprehensively estimate associations of FR compounds taking into account potential additive, synergistic, and antagonistic effects.

Assessment of Neurodevelopmental Effects Utilizing Neuroimaging

Neuroimaging could contribute to our ability to investigate FR neurotoxicity by providing a method to examine brain structure and functionality, thus enhancing causal inference and identifying potential biological pathways altered by different FRs. This application advances our understanding by providing an assessment of developmental trajectories of cognition and behavior in children that cannot be achieved via traditional methods of assessment [133]. The field of pediatric neuroimaging is growing, and epidemiological studies examining FR neurotoxicity have begun to apply these techniques to further understand the potential downstream neurodevelopmental effects that may not be evident with assessments using neurodevelopmental batteries. To date, only two preliminary studies have applied neuroimaging to examine PBDE neurotoxicity; both studies yielded interesting findings despite small sample sizes [106••, 107••]. Neuroimaging has challenges that contribute to its application, including high costs, limited availability in some countries, practical difficulties, such as claustrophobia and motion, especially in young children, and differences in protocols which limit the ability to pool data. Despite this, there is immense promise in the knowledge and mechanistic insights that can be garnered, specifically regarding brain plasticity and developmental trajectories [134].

Conclusions

In summary, continuing studies on historically used FRs still reveal long-term adverse impacts of PCB exposures decades after the ban. Recently published studies on PBDE neurotoxicity confirm prenatal exposures are associated with poorer cognition and more externalizing problems in children. Evidence from epidemiological studies indicates that PBDEs may impact attention, internalizing behaviors, and social skills. PBDEs may also alter the intrinsic functional network organization of the brain, resulting in downstream effects on various neurodevelopmental domains, such as reading and executive function. Limited and inconsistent conclusions from epidemiological studies examining postnatal PBDEs make it difficult to conclude that exposures during childhood are as detrimental as those occurring during gestation. Limited studies on OPFRs have indicated an adverse impact on child cognitive function, hyperactivity, and externalizing behaviors, calling for more research on this class of FRs and child neurobehavioral development.

However, there is sufficient evidence to justify that a coordinated global effort be taken to reduce FR exposure in humans, because sensitive life stages for brain development should be protected. Further, the fire safety benefit of incorporating FRs in consumer products is questionable [135]. California revised the 1975 flammability standard, Technical Bulletin (TB 117) with TB117-2013. This update replaces the open flame test with the smolder test, which allows furniture to meet fire safety standards without the need of adding FRs, suggesting that these chemicals may not be needed. The phase-out of PBDEs was an important step in decreasing exposure to these neurotoxicants. However, PBDEs remain an important public health problem even though it has been over a decade after its removal from the market. OPFRs are rapidly following its predecessor by making their presence in environmental and human samples universally known. While epidemiological studies are still investigating OPFR neurotoxicity, delaying mitigating actions for several decades—as was done with PBDEs—is an injustice to children's health and will likely result in another regrettable substitution.

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Compliance with Ethical Standards

Human and Animal Rights All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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