ANNUAL REVIEWS

Annual Review of Physiology

Gestational Exposure to Common Endocrine Disrupting Chemicals and Their Impact on Neurodevelopment and Behavior

Dinushan Nesan[1,2,3] and Deborah M. Kurrasch[1,2,3]

[1]Department of Medical Genetics, University of Calgary, Calgary, Alberta T2N 4N1, Canada; email: dnesan@gmail.com, kurrasch@ucalgary.ca

[2]Alberta Children's Hospital Research Institute, University of Calgary, Calgary, Alberta T2N 4N1, Canada

[3]Hotchkiss Brain Institute, University of Calgary, Calgary, Alberta T2N 4N1, Canada

Annu. Rev. Physiol. 2020. 82:177–202

First published as a Review in Advance on November 18, 2019

The *Annual Review of Physiology* is online at physiol.annualreviews.org

https://doi.org/10.1146/annurev-physiol-021119-034555

Keywords

endocrine disruption, brain, bisphenol A, polychlorinated biphenyls, organophosphates, polybrominated diphenyl ethers

Abstract

Endocrine disrupting chemicals are common in our environment and act on hormone systems and signaling pathways to alter physiological homeostasis. Gestational exposure can disrupt developmental programs, permanently altering tissues with impacts lasting into adulthood. The brain is a critical target for developmental endocrine disruption, resulting in altered neuroendocrine control of hormonal signaling, altered neurotransmitter control of nervous system function, and fundamental changes in behaviors such as learning, memory, and social interactions. Human cohort studies reveal correlations between maternal/fetal exposure to endocrine disruptors and incidence of neurodevelopmental disorders. Here, we summarize the major literature findings of endocrine disruption of neurodevelopment and concomitant changes in behavior by four major endocrine disruptor classes:

bisphenol A, polychlorinated biphenyls, organophosphates, and polybrominated diphenyl ethers. We specifically review studies of gestational and/or lactational exposure to understand the effects of early life exposure to these compounds and summarize animal studies that help explain human correlative data.

INTRODUCTION

Endocrine disrupting chemicals (EDCs) have rapidly become a priority area for researchers and health regulators around the world. An EDC is defined by the US Environmental Protection Agency (EPA) as "an exogenous agent that interferes with the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body that are responsible for the maintenance of homeostasis, reproduction, development, and/or behavior" (1, p. 1) and by the Endocrine Society as "an exogenous chemical, or mixture of chemicals, that interferes with any aspect of hormone action" (2, p. E3). These definitions are broad and, as such, can be applied to an overwhelming number of compounds. To date, scientific investigation has generally focused on EDCs that act directly on nuclear hormone receptors and mimic or antagonize the effects of endogenous circulating hormones, although the field is expanding to include agents that interact with proteins that have more indirect effects on hormonal systems. Over the last few decades, public awareness of compounds such as bisphenol A (BPA), dioxins, organophosphate pesticides, and flame retardants has grown significantly, such that today many consumers are at least educated on the chemicals found in various products even if they continue to buy them. Despite consensus across the scientific community of the adverse effects of many EDCs, government regulatory bodies have been slow to restrict their use. The reasons for moderate regulation are varied and generally involve differences in how data are collected, analyzed, and interpreted.

Although ingestion is the most common route of exposure for humans and animals—mainly via contaminated drinking water—EDCs can also be inhaled (e.g., airborne organophosphate pesticides) or absorbed through the skin (e.g., BPA on thermal paper) (3–5). Most relevant to this review, EDCs can cross the placenta to expose the developing fetus or be transferred during lactation. Indeed, gestational and early life exposure to various EDCs has been repeatedly correlated with increased risk of neurodevelopmental disorders in humans. Here, we describe studies that have similar findings across different animal models and compare and contrast them with human studies to provide an effective understanding of the state of the scientific literature on the disruptive effects of gestational exposure to EDCs on the developing brain.

The brain is a frequently reported target of developmental disruption by EDCs, with alterations in synaptic connectivity, neurotransmitter or neuropeptide expression, and neuronal differentiation commonly influenced by gestational EDC exposure (6, 7). In addition, lasting changes to behavior, learning, memory, and potential effects that can be transmitted transgenerationally and/or epigenetically from a single exposure are also well documented (8). Given that the neuroendocrine hypothalamus is particularly sensitive to EDCs, the potential for lifelong alterations in endocrine signaling is also a likely outcome from gestational exposure to these chemicals (6). Fetal and/or newborn exposure to EDCs via placental transport or lactation is of particular concern, as the developing brain is in a state of rapid growth, with neurogenesis, gliogenesis, neuronal differentiation and migration, synaptogenesis, and synaptic pruning all taking place during relatively short temporal windows. Errors during these times will have lasting impacts on activity, behavior, learning and memory capacity, and other factors that can impact health, fitness, and quality of life.

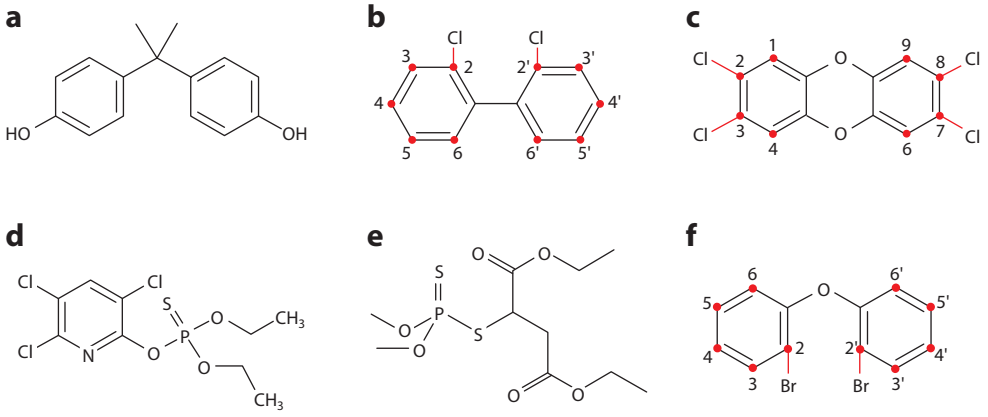


Figure 1

Chemical structures of the endocrine disrupting chemicals summarized in this review: (*a*) bisphenol A, (*b*) polychlorinated biphenyls (PCBs), (*c*) dioxin, (*d*) chlorpyrifos, (*e*) malathion, and (*f*) polybrominated diphenyl ethers (PBDEs). For PCBs, dioxin, and PBDEs, representative minimally substituted congeners are pictured. Red dots indicate potential alternate/additional substitution sites, and red lines indicate bonds to chlorine (*b*,*c*) or bromine (*f*) atoms that can be found at different or additional positions in other congeners.

Given the rising public awareness of EDCs combined with the correlations of human developmental neurodevelopmental disorders with early life exposure, here we collate the effects of four major EDC classes: BPA, polychlorinated biphenyls and dioxins, organophosphates, and polybrominated diphenyl ethers. These are arguably the four most well-known and best-studied classes of EDCs, and therefore findings have the highest chance of revealing potential trends. In this review, we have collected and grouped similar studies to capture the relative consensus in the scientific community, in hopes of simplifying complex literature and perhaps providing a basis for future work by researchers as well as information for those seeking to further improve regulatory guidelines.

BISPHENOL A

BPA is arguably the most well-studied EDC and likely the best publicized to the lay public. It is a plasticizer used to make the flexible plastics found in food containers, medical tubing, the lining of aluminum cans, and thermal receipt paper and many other consumer goods. BPA crosses the placental barrier freely during pregnancy (9, 10) and has been detected in human embryos as early as 1.5 months postconception (11). Its structure consists of two benzene rings joined by a central carbon with a hydroxyl group substituted on each ring (**Figure 1*a***). BPA was originally identified as an estrogenic compound acting through estrogen receptors (ERs) -α and -β and estrogen-related receptor (ERR)-γ (12–14), although now it is also recognized as modulating thyroid receptors (TRs) -α and -β (15) and the androgen receptor (AR) (16). BPA can also act via nongenomic intracellular signaling by binding membrane ERs such as GPR30 (17) and has been identified as a putative glucocorticoid receptor agonist (18). BPA exhibits a nonmonotonic U-shaped dose curve (19), with relatively high and low doses tending to exhibit more pronounced effects than median doses.

Bisphenol A Disrupts the Developing Brain

Prenatal exposure to BPA alters a number of neurodevelopmental processes, leading to lasting changes in the developing brain. Given that BPA is considered a "messy" EDC (e.g., has multiple

protein targets), it is not surprising that gestational BPA-mediated neural disruptions tend to be variable and region specific. For example, gestational exposure to BPA downregulates key neurodevelopmental transcription factors, including *Sox2* and *Pax6* (20), which mediate neural stem cell activation (21) and developmental regionalization of the brain (22). Moreover, BPA can influence the timing and duration of neurogenesis—the birth of neurons—specifically by altering neural stem cell proliferation and differentiation (see **Supplemental Figure 1** for schematic putative BPA mechanisms on neural stem cells). In fact, low-dose gestational BPA exposure accelerates the onset of hypothalamic neurogenesis in both zebrafish (23) and mice (D. Nesan, D. Kurrasch, unpublished data). In the hippocampus, higher doses of BPA exposure decrease neurogenesis in vivo and in neuronal culture (24). The hypothalamus and the hippocampus appear to be areas of particular vulnerability to BPA action. For example, ERβ expression in the hippocampus is reduced after prenatal BPA exposure (25), and sexually dimorphic ER expression is altered in the hypothalamus (26) in rats exposed during gestation to BPA.

Supplemental Material >

Alterations in hippocampal dendrites are also frequently reported in BPA studies. Indeed, gestational BPA exposure reduces spine density and branching of hippocampal CA1 neurons in mice (27) and decreases spine synapses in rhesus macaques (28). The dendritic regulator, *Arc*, is also downregulated following BPA exposure (29) and, perhaps tellingly, the dendritic cytoarchitecture is altered in cerebellar Purkinje cells (30) and in the prefrontal cortex following juvenile or adult BPA exposure (31, 32). Moreover, both data-mining analysis and separate validation indicate that zebrafish embryos exposed to BPA display reduced expression of *Sp4*, a gene involved in both hippocampal and cerebellar dendritic patterning (33–35), perhaps offering a potential mechanism for the decreases in observed arborization.

Gestational BPA exposure can also affect tyrosine hydroxylase (TH)-immunoreactive neurons, with reduced expression in the substantia nigra, the locus coeruleus, the periventricular preoptic hypothalamus, and midbrain regions (28, 36–38), although some of these effects are sex specific. Moreover, in addition to ERs, other hormone receptors are altered in BPA-exposed animals, such as the cerebellar somatostatin receptor subtype sst_2 (39) and cortical and cerebellar retinoic acid receptors (40). Beyond hormone receptors, other neuroendocrine targets of gestational BPA exposure include brain aromatase in zebrafish models (23), and neonatal BPA exposure alters kisspeptin expression and fiber density in rodents (41). Combined, gestational BPA can bind to various receptors and proteins found throughout the developing brain and can lead to changes in neurodevelopment.

Early Bisphenol A Exposure Impacts Behavior

Consistent with the widespread impact of gestational BPA exposure on key brain regions, including the cerebellum, hippocampus, and hypothalamus, lasting alterations in behavior are also observed. Indeed, in numerous models, across multiple generations, and over a variety of tests, behavioral perturbations are commonly observed in animals exposed to BPA in utero. Many of these studies arise from a desire to determine causality of the associations observed in humans. For example, in cohort studies, early life BPA exposure is associated with increased externalizing behaviors in two-year-old girls (42), increased opposition behaviors and aggression in school-aged boys (43, 44), increased anxiety and depressive symptoms in three-year-old girls (45), and increased attention deficit/hyperactivity disorder symptoms in four-year-old boys and girls (46). All of these behaviors (and more) have been assessed in BPA-exposed animal models.

The most commonly reported behavior in BPA-exposed animal studies is hyperactivity. For example, exposure to nanomolar dosages of BPA in zebrafish embryos causes increased total movement by larval stages (23). In mice, gestational BPA exposure increases spontaneous activity in

females nine months of age (47) and, in rats, gestational and lactational BPA exposure causes 4-week-old males to be hyperactive in open field tests (48). Anxiety-like behaviors are also reported in gestational BPA-exposed mice (49) and rats (50), as measured using the elevated plus-maze, open field test, and dark-light transition tasks. Depressive behaviors, commonly measured by the forced swim test, are likewise increased following in utero BPA exposure (51, 52).

Sociosexual behaviors are also commonly disrupted in rodents after early life BPA exposure, although the studies tend to use varied assessments and end points, making it challenging to identify trends. For example, play behavior is reduced in female rats exposed to BPA during gestation and lactation, leading to reduced play and social grooming with males (53). In contrast, a change in gender-specific sexual behavior is observed in gestationally exposed animals, with females more receptive and males more defensive and less interested (54). This finding is supported by reports in juvenile mice, whereby BPA-exposed males exhibit more solitary investigative behaviors and females more social interests (55).

Finally, gestational BPA exposure also impairs learning, but with contrasting sex-specific effects. For example, one study reports that only female rats exposed to BPA in utero exhibit an impaired performance in a water maze learning test (56). In other reports, only male rats experience learning and memory impairments (29, 57).

Altogether, a striking similarity exists between the observations of the effects of gestational BPA exposure in rodents and zebrafish and the effects seen in children with relatively high prenatal/perinatal exposure to BPA, although caution is needed when translating animal model findings to human behavioral patterns. Furthermore, when considering the findings that gestational BPA exposure alters the neural development of key brain regions, the consensus in the field is clear that the brain, specifically the hippocampal and hypothalamic regions, is a sensitive target for developmental endocrine disruption by BPA.

POLYCHLORINATED BIPHENYLS AND DIOXINS

Polychlorinated biphenyls (PCBs) are a class of endocrine disrupting compounds originally produced for manufacturing uses such as mechanical coolants, hydraulic fluids, lubricants, and carbonless copy papers, among others. PCBs all share a common dual-benzene (biphenyl) ring structure that can be variably substituted with chlorines (**Figure 1*b***). Despite a ban on their production in the United States and other Western countries starting in the 1970s, PCBs are highly stable and tend to persist in the environment. Indeed, PCBs have been found in remote regions far from production sources because they tend to bioaccumulate in migratory animals and can thereby be spread to distant food chains and environments. PCBs are classed as either coplanar or noncoplanar, depending on whether the benzene rings lie in the same plane. Coplanar PCBs are often referred to as dioxin-like PCBs, as they tend to exert similar effects as dioxins because both EDCs act through the aryl hydrocarbon receptor (AhR) (58). Noncoplanar PCBs tend to be less neurotoxic, requiring much higher doses for adverse effects, although some chemicals do alter neurotransmitter expression at lower levels. Mechanistically, PCBs act through a variety of pathways. Depending on the specific congeners studied, PCBs can be either estrogenic, antiestrogenic (59), or antiandrogenic (60).

Dioxins are structurally similar to coplanar PCBs with two benzene rings, except the dioxin rings are linked by central oxygen molecules that are not present in PCBs (**Figure 1*c***) (61). The archetypal dioxin is 2,3,7,8-tetrachlorodibenzodioxin (TCDD), often just referred to as dioxin. Dioxins are primarily produced in industrial combustion reactions, such as incinerators, but are also created as by-products of herbicide production and chlorine bleaching of paper products. A similar class of EDCs is furans, which are not discussed here but are often characterized alongside

dioxins because they have similar effects and mechanisms of action. As stated above, dioxins bind AhR, and AhR agonists cause antiestrogenic effects (62) with significant effects on sex steroids and reproductive functions such as ovarian follicle development and ovulation (58).

Both PCBs and dioxins are lipophilic, and human exposure is predominantly via diet, with PCB half-lives ranging from 10 to 15 years and dioxins from 5 to 15 years (63, 64). Given their persistence in the environment and their widespread effects, decades of research have produced a large body of literature describing the impact of PCBs and dioxins on human health; however, only a subset of that literature examines the risk of maternal-fetal transfer and actions on the developing brain and behavior. Below, we summarize the disruptive effects of gestational PCB and dioxin exposure on neurodevelopment.

Polychlorinated Biphenyls and Dioxins Disrupt Neuroendocrine Signaling and Other Brain Functions

PCBs and dioxins readily cross the placenta and can be found in lactation samples, and given their persistence in adult human fat, there is a high likelihood of fetal exposure during gestation (65, 66). One of the most explored neurodevelopmental phenotypes from gestational PCB exposure is changes to brain thyroid hormone levels. Fetal exposure to different PCB mixtures results in lowered thyroid hormone expression in the juvenile rat brain, including a reduction in triiodothyronine (T3) and thyroxine (T4) expression and an increase in the conversion of T3 to T4 (67). Likewise, a reduction of circulating levels of T3 and T4 is found in rodents exposed to PCB or dioxins gestationally (68, 69). Thyroid hormone metabolism is also affected in gestationally PCB-exposed rats, with reduced deiodinase enzyme expression preventing T4 to T3 conversion. Moreover, peripheral hepatic glucuronidation of T4 is increased, causing a decrease in circulating T4 (67) and likely responsible for the lowered brain T4 observed in other studies. Additionally, gestational PCB exposure causes thyroid structural changes that mimic those found in pups chronically exposed to increased thyroid stimulating hormone levels, indicating a potential neuroendocrine effect of PCBs (68). It should be noted that although PCBs are structurally similar to thyroid hormones and cause widespread alterations in thyroid hormone expression and metabolism, PCBs do not bind to TRs (70).

There are indications that the neuroendocrine system also is a target of gestational PCB exposure and, indeed, the hypothalamus appears to be a region of vulnerability. Developmental exposure to a mixture of PCBs [commercially available as Aroclor (A) 1221, which contains lightly chlorinated PCBs that are commonly found in humans] lowers ERβ expression in the anteroventral periventricular nucleus of female rats. It also sex-specifically alters expression of genes, including brain-derived neurotrophic factor (BDNF), GABAβ receptors 1 and 2, kisspeptin receptor, and NMDA receptor subunits in the preoptic area of the hypothalamus, suggesting that gestational PCB exposure masculinizes the brain of female rats (71, 72). The loss of BDNF in male rats is of particular interest, as BDNF regulates sensory neuron development and its reduced expression causes aggression and other behavioral disruptions (73, 74). Moreover, BDNF expression also is altered following short-term PCB exposure later in life (75), further illustrating a link between BDNF and PCBs. Interestingly, the expression of BDNF itself is regulated by thyroid hormone (76), potentially linking the thyroid disruption described above following gestational PCB exposure with neuroendocrine dysfunction. A final neuroendocrine target of gestational PCBs is brain aromatase, expression of which can change depending on the administered PCB mixture (77, 78). Meanwhile, a single dose of dioxins at gestational day (GD)15 to pregnant dams was sufficient to significantly impair release of gonadotropin-releasing hormone in male offspring (79), likely contributing to the reduction in downstream hormones produced from the pituitary and gonads (80).

Neurotransmitter signaling is also affected by gestational PCB exposure. For example, fetal exposure to PCBs alters prefrontal cortex dopamine expression in a congener-specific manner, with coplanar compounds increasing and noncoplanar PCBs decreasing dopamine levels (81). Moreover, serotonin levels are increased in response to gestational exposure to A1254 (82). Finally, hippocampal cholinergic nicotinic receptors are downregulated after gestational PCB exposure, although the technique used in the study only looked at binding capacity as opposed to expression itself. A single dose of dioxin on GD15 was found to reduce neural activity in the somatosensory cortex along with a reduction in glutamate and NMDA receptor subunits (83), while a single dose at GD18 impairs glutamate transport in the cortex alongside general cell death (84). Additionally, the astrocytes marker glial fibrillary acidic protein (GFAP) was increased in the cerebellum and olfactory tract following fetal exposure to PCBs in rats, whereas the neuronal marker synaptophysin was decreased in the olfactory tract, prefrontal cortex, and striatum, but neither GFAP nor synaptophysin was impacted in the hippocampus (85). This apparent increase in astrocytes is of interest because the cerebellum appears to be a functional target of PCB action, but assessment of cerebellar morphology revealed few to no defects after A1254 exposure (86). There has also been a report of general delay in fetal brain development with prolonged low-dose gestational dioxin exposure (as opposed to the higher single dose that most studies use), resulting in lowered fetal brain forebrain weight (87). Taken together, these studies make clear that gestational PCB or dioxin exposure has lasting effects on a variety of neural systems.

Polychlorinated Biphenyls and Dioxins Alter Sexual Behaviors and Cognitive Function

A series of cohort studies has correlated behavioral deficits in children following fetal exposure to PCBs. For example, a Dutch study found reduced cognitive function in nine-year-olds exposed to PCBs during gestation (88). Moreover, studies from children cohorts in Michigan and North Carolina found correlations between higher gestational and lactational PCB exposure and lower psychomotor scores in six- and twelve-month-old children (89), reduced performance in visual memory tests in seven-month-olds (90), and deficits in short-term memory at four years of age (91). Meanwhile a series of studies from a cohort of children living near a dioxin-contaminated site in Vietnam has provided correlations between perinatal exposure via breast milk and reduced newborn head circumference (92), impaired neurodevelopment at four months old based on lower cognitive and fine motor domains on the Bayley Scales of Infant and Toddler Development (BSID) (93), increased autistic traits (94), and impaired motor coordination and cognitive function (95) in three-year-olds. Together these human studies provide compelling evidence that gestational exposure to PCBs and dioxins can lead to lasting behavioral and cognitive defects.

To provide supporting evidence and mechanistic understanding for these human associations, animal studies have been employed, with the primary focus on coplanar PCBs that are more commonly found in human tissues. Globally, studies reveal learning deficits in mice exposed to PCBs in utero, although a variety of congeners have been tested with varying and sometimes confounding results. For example, exposure to ortho-substituted PCBs or dioxin disrupts spatial learning in rats (69, 96, 97), whereas coplanar PCBs alter spatial or passive avoidance learning (98), and dioxin impairs active avoidance learning (87). In contrast, under certain conditions gestational PCB exposure can improve working memory (99). Furthermore, both dioxin-like and nondioxin-like PCB exposure can impair learning ability in a Y-maze task, but only in three-month-old mice and not at 7–8 months (100). Learning effects of gestational and lactational exposure to ortho-substituted PCBs are sex specific, with both male and female rats experiencing learning deficits in a Y-maze discrimination task, although the alterations appear to be fundamentally different, with

PCB-exposed males learning poorly based on previous experience and females exhibiting impaired learning of new associations (101). Meanwhile, examination of other nondioxin-like PCBs shows congener-specific effects, with developmental exposure to PCBs 138 or 180 impairing learning in a Y-maze test, while PCB 52 affects motor coordination. These findings from rat studies are reinforced in other model animals, as PCB-exposed mice exhibit learning and memory deficits (102) and maternally exposed nonhuman primates underperform on spatial learning tasks (103). Finally, there is some evidence that learning deficits may be sex specific, which is supported by the estrogenic properties and brain-masculinizing effects of PCBs on neurodevelopmental processes in rodent studies. Although sex differences are not found in human cohorts, assessing boys and girls separately might be beneficial in future studies.

Locomotor function and activity are also frequently measured end points in gestational PCB-exposed animals, but as with learning, the combination of different exposure times and varied uses of PCB congeners and mixtures makes for a complex body of literature that is in some cases complementary and in others contradictory. For example, righting and startle reflexes in rat pups exposed to PCBs or dioxin during gestation are impaired across multiple studies (87, 104, 105); however, other experiments showed no alteration in these reflexes (106, 107). Moreover, more complex behaviors such as swimming (107) and cliff avoidance (104) are delayed in rats exposed to gestational PCBs. Assessments of locomotor activity in rats show similar mixed findings, with some demonstrating hyperactivity (108–110) and others showing no change in activity (107, 111). Additionally, a pair of studies shows no change in activity in one-month-old mice gestationally exposed to PCBs; one study shows hyperactivity at two months (104) but the other shows a decrease in activity by three months (112), which serves to illustrate the challenges of determining the exact outcomes of gestational PCB exposure. Complex locomotor tests also show similar mixed findings, with grip strength decreased (108) or unchanged (104, 111) following fetal PCB exposure. In addition, rotor rod measurements of walking capacity are impaired by gestational and lactational exposure to A1254 (105, 113) but actually improved following a short gestational exposure to PCB118 (104). Altogether, this lack of consensus indicates that PCB neurodevelopmental disruption is highly dependent on the specific congeners tested, the length and dose of exposure, and likely the rodent strain and/or environmental conditions. Nonetheless, collectively these data show that gestational exposure to select PCBs can disrupt a variety of behavioral characteristics, including learning, memory, and fine motor control, whereas exposure to other PCBs causes few if any defects.

Multiple studies have reported alterations in sociosexual behavior from gestational or lactational dioxin exposure, including reduced social interaction in rats (110) and impaired sexual behavior (80) after a single dose at GD15. A slightly lower dose, also at GD15, was found to result in demasculinized sexual behaviors in male rats (114). Finally, these effects are found in nonhuman primates as well, as repeated doses during gestation and lactation altered social behavior in rhesus monkeys (115). Given the effects on multiple species, the evidence indicates that gestational dioxin exposure is a likely cause of impaired sociosexual behavior.

ORGANOPHOSPHATES

Organophosphates are a group of EDCs commonly found in pesticides and herbicides. They share a common structure, including a central phosphate atom double bonded to one oxygen atom and single bonded to three more. These single-bonded oxygen atoms can have varied substitutions depending on the specific organophosphate. Organophosphates are widely used in North America for agricultural pest control and by some cities for insect management programs. All organophosphates target the acetylcholinesterase (AChe) enzyme and inhibit its ability to break down the

neurotransmitter acetylcholine (ACh). Inhibited ACh turnover causes increased binding of ACh at synapses that can result in a variety of symptoms, including seizures, muscle paralysis, and suffocation due to lung failure. Organophosphates can be classified as reversible, quasi-reversible, or irreversible depending on their duration of efficacy and their ability to be readily broken down to release AChe. Reversible agents tend to be used in pharmaceuticals to treat conditions such as myasthenia gravis, neuromuscular block, and glaucoma. Quasi-reversible and irreversible agents are used as pesticides or as nerve agents in chemical weapons. Because all organophosphates share a common central mechanism, findings from individual molecules can be extrapolated to the class as a whole. Thus, herein we focus on two major organophosphate compounds: chlorpyrifos and malathion (see **Figure 1*d*** and ***e*** for structures).

We focus on these two compounds because they are the most abundant organophosphates in the environment, with nearly all US wheat-based products contaminated with chlorpyrifos and/or malathion (116). Malathion is among the most commonly used organophosphates in the United States, a position it has held since 2007 (117). Additionally, malathion is of particular interest because despite classification as moderately toxic by the EPA (118), it has metabolites and impurities, such as malaoxon and isomalathion, that are up to 1,000-fold more toxic (119, 120). Chlorpyrifos is also classified as moderately toxic by the EPA (118) and moderately hazardous by the World Health Organization (121). Chlorpyrifos was a target of the EPA's attempt in 2000 to reduce pesticide exposure, and manufacturers have since agreed to remove it from residential products. Interestingly, chlorpyrifos was recently the subject of intense court battles seeking to permanently ban its use in all applications given its harmful effects, particularly on children. Chlorpyrifos would not be the first organophosphate to be removed from use given that parathion was banned in the early 2000s due to potent toxicity to nontarget organisms (122). Exposure to organophosphates occurs through multiple routes, with inhalation and skin absorption the most common and ingestion from contaminated food products or from water also frequent. Fetal and newborn exposure to organophosphates occurs by both transplacental transport and lactation (123, 124). Here, we examine the known effects of these two predominant organophosphate compounds on neurodevelopment and behavior.

Organophosphates Disrupt Neurodevelopment and Neurotransmitter Signaling

Because organophosphates are primarily AChe inhibitors, the most reported neural end point is the measurement of brain cholinesterase activity. Predictably, gestational exposure to organophosphates inhibits AChe activity, with both chlorpyrifos (125–127) and malathion (128, 129) affecting AChe function. However, the effect of these two organophosphates on fetal AChe is always lower than their inhibition of maternal AChe (125, 126, 130), suggesting protective mechanisms at the placental level. In contrast, lactational exposure to malathion causes similar inhibition of AChe as is found in the adult brain exposed directly (128), consistent with the notion that the placenta is a unique barrier.

Gestational organophosphate exposure also perturbs other aspects of ACh signaling in newborn and juvenile rat pups, including reduced activity of the ACh synthetic enzyme choline acetyltransferase, reduced muscarinic and vesicular acetylcholine receptor expressions (127), and muscarinic receptor binding (125). Again, differences between dam and fetal AChe sensitivity to these organophosphates indicate potential placental protection (130). Most of these effects appear to persist into adulthood, with hippocampal cholinergic nerve impulse activity and muscarinic receptor binding decreased in adolescent and adult rats exposed to gestational chlorpyrifos. Moreover, chlorpyrifos exposure in utero causes the expression of choline acetyltransferase to increase, and these mice exhibit disrupted neurodevelopment with altered expression of biomarkers for cell

size, number, and density, as well as a loss of neurite projections (131, 132). Forebrain volume also is reduced in guinea pigs following gestational chlorpyrifos exposure (133). These findings raise the possibility that decreased regional brain volume may occur via organophosphate action on developing neural progenitors, which would explain the lowered overall cell density and number in various parts of the brain. Indeed, there is evidence that organophosphates target developing neurons and glia beyond their effects on AChe. For example, gestational chlorpyrifos exposure causes a reduction in biomarkers for oligodendrocytes, neurons, and axon bodies in juvenile females only (134). Interestingly, postnatal chlorpyrifos exposure had a similar effect but it was not restricted to females only, supporting the idea that the placenta might offer fetal protection from organophosphate exposure perhaps in a sex-specific manner. Peak gliogenesis (postnatal days 11–14 in rats) might represent a window of vulnerability to chlorpyrifos because GFAP expression is disrupted in both males and females, indicating altered astrocyte development (135, 136). Moreover, studies in neural stem cells indicate that malathion affects cell proliferation and differentiation (137), which could be the initial source of these widespread alterations of cell number, size, and type observed in developing organophosphate-exposed rodent brains. Of particular note, multiple groups have highlighted the striatum as the region with the largest effects (135, 138), indicating that the striatum might be particularly vulnerable to organophosphate exposure, although the underlying mechanisms remain unknown.

ACh is not the only neurotransmitter affected by developmental organophosphate exposure, as changes in dopamine and serotonin signaling have also been reported. In fact, gestational chlorpyrifos exposure in rodents is more impactful on serotonergic systems than postnatal exposure, causing alterations in serotonin receptor and transporter expression in juvenile rats (139). These effects persist into adulthood, with altered serotonin turnover observed in two-month-old rats after late gestation (but not postnatal) exposure to chlorpyrifos (140). Similarly, dopamine content is decreased in the hippocampus and cerebral cortex of juvenile rats after gestational exposure to chlorpyrifos, with permanent region-specific effects reported depending on if the exposure was early (GD 7.5–11.5, more hippocampal effect) or mid- (GD 13–17, more cortical effect) gestation (141). Although gestational organophosphate exposure is more consequential than postnatal exposure on serotoninergic pathways, this observation is not true for dopamine receptors. In fact, a marked loss of dopaminergic neurons in the substantia nigra occurs after postnatal (days 11–14) exposure, which persists into adulthood (142). Moreover, gestational exposure to chlorpyrifos results in increased presynaptic activity of both serotonin and dopamine in adolescent rats (143), demonstrating the lasting effects of organophosphates in the fetal brain. Organophosphates may also affect intracellular signaling cascades in the developing brain. For example, short-term gestational or postnatal exposure to organophosphates can change adenylyl cyclase signaling in adult rat brains (144), underscoring the lasting effects of developmental exposure to organophosphates. Combined, these data demonstrate that gestational organophosphate exposure can affect neurotransmitter and signaling systems during neural development.

Unlike PCBs and BPA, organophosphates have not been found to strongly disrupt neuroendocrine function, although extensive studies have not been conducted. A recent report found that gestational and lactational exposure to chlorpyrifos increases hypothalamic ERβ, decreases amygdala oxytocin receptor expression in males, and increases amygdala vasopressin 1a receptor expression in both sexes (145). Moreover, oxytocin levels increase, and male-only vasopressin expression decreases in the hypothalamus after late gestational and/or postnatal chlorpyrifos exposure. Gestational exposure to chlorpyrifos can also lower thyroid hormone content in adult mice (146), potentially impacting learning, memory, and social behaviors. Finally, both chlorpyrifos and malathion exposure in utero increases oxidative stress (147, 148), though it is unclear whether it contributes to the observed neurotoxic effects of organophosphates.

Organophosphates Disrupt a Wide Variety of Behaviors and Reflexes

Although numerous studies have explored the consequences of organophosphate exposures in human populations (149), only a limited subset has examined pregnant mothers and the neurodevelopmental outcomes in their offspring. In a cohort of 30 Chinese infants, cord blood chlorpyrifos concentration was associated with poorer visual acuity and motor function at 9 months of age (150, 151). In a larger study, prenatal organophosphate exposure correlated with a lower social developmental quotient (as measured by Gesell Developmental Schedules), whereas postnatal exposure was associated with a higher adaptive developmental quotient (152). In a cohort of Latino-American families from California [the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) cohort], higher levels of maternal urinary organophosphate metabolites correlated with increases in abnormal reflexes in newborns as per the Brazelton Neonatal Behavioral Assessment Scale (153); lower scores on the Mental Development Index (but not on the Psychomotor Development Index) of the BSID at two years of age (154); and lower measures of working memory, processing speed, verbal comprehension, perceptual reasoning, and IQ in 7-year-olds as measured by the Wechsler Intelligence Scale for Children (155). A second cohort of inner-city families from New York City [the Columbia Center for Children's Environmental Health (CCCEH) Mothers and Newborns cohort] also used the BSID and found that high levels of chlorpyrifos in umbilical cord blood are correlated with significantly lower scores on both the Mental and Psychomotor Developmental Indexes at 3 years old (156) and lower working memory and IQ scores at 7 years, again measured by the Wechsler Intelligence Scale (157). And finally, a study of 350 mother/infant pairs from Cincinnati [the Health Outcomes and Measures of the Environment Study (HOMES) cohort] found no correlation between higher maternal urinary organophosphate metabolite concentration and altered neurobehavior in 5-week-old infants (158). Despite some divergent findings, the overall consensus from these studies is that maternal exposure, especially at the relatively high levels observed in farmworker families or others of low socioeconomic status, correlates readily with reduced cognitive function as well as potential effects on early reflexes and social interaction.

In animal models, multiple studies show that gestational organophosphate exposure reduces learning ability, though the effects are nuanced. For example, sex-specific learning deficiencies following late gestational chlorpyrifos exposure occur in female mice as measured by a foraging behavior maze (146) in female rats in multiple maze tests (159) and in both sexes after early gestation exposure using a radial maze (160). In contrast, male guinea pigs exposed during late gestation exhibit lower performance in spatial navigation and learning in water maze trials (161), indicating some species specificity in organophosphate effects. Gestational organophosphate exposure also affects early reflexes, including impaired righting reflex and cliff avoidance in rats (125) as well as general hyporeflexia and reduced ultrasonic vocalization (162).

Social interactions are also perturbed following gestational organophosphate exposure in animal models. In mice, mid-gestation chlorpyrifos exposure increases social investigation time of a novel animal in females only (163), whereas combined gestational and lactational chlorpyrifos exposure causes sex-specific effects, with males exhibiting increased investigation of unfamiliar social stimuli and females displaying delayed social investigation and lower reaction to novel stimuli (145). Animal behavioral testing has also uncovered changes in activity levels and anxiety in gestationally exposed animals, although these phenotypes have not been reported in human cohorts. The findings in organophosphate-exposed rodents are mixed, however. For example, gestational and lactational malathion exposure reduces locomotor activity specifically in male rats (164). In contrast, early postnatal exposure to chlorpyrifos increases activity in both sexes in mice (165) and rats (160), whereas late gestational and/or lactational organophosphate exposure causes no alteration in activity in mice (148) or guinea pigs (161). Similarly, multiple studies show increases

in anxiogenic behaviors in mice exposed prenatally and lactationally to chlorpyrifos (166, 167) and malathion (148, 164). In rats, late gestational chlorpyrifos exposure induces anxiety-like behaviors in males only (168), but in contrast, this same exposure can also decrease anxiety (165) as can a postnatal dosing to mimic lactational exposure (169). Taken together, behavioral studies in rodents and other animal models reinforce the human cohort studies, whereby gestational and lactational exposure impairs learning, cognition, and sociability, and provides evidence that more complex traits should be explored as these cohorts age, especially signs of hyperactivity or anxiety.

POLYBROMINATED DIPHENYL ETHERS

Polybrominated diphenyl ethers (PBDEs) are a class of EDCs used primarily as flame retardants. The structure of PBDEs is two benzene rings each connected via an ether bond to a central oxygen atom (**Figure 1*f***). The benzene rings are substituted at one or more sites with bromine atoms, with a fully substituted PBDE having 10 bromines (decabromodiphenyl ether). PBDEs are generally classified by the number of bromines they contain: monoPBDEs have a single bromine substitution, diPBDEs have two bromines, triPBDEs have three, and so on. The lower the number of bromines, the more distinct the molecules within a given class due to the number of possible substitution sites available for diversification. In total there are 209 different PBDE congeners. Lower-brominated PBDEs tend to bioaccumulate more readily, although all PBDEs are lipophilic and will readily concentrate in fat stores. Although commercial mixtures tend to be labeled by their most common class, they are nonetheless complex mixtures due to contamination during production. For example, commercial pentabromodiphenyl generally contains tri-, tetra-, and hexaPBDEs as well. Based on human exposure studies, tetra-, penta-, and hexaPBDEs are the most common congeners found in bodily tissues. Concerns regarding toxicity have led to the banning of both penta- and octaPBDEs from production in the United States and Europe (170). In general, PBDEs are highly resistant to degradation, in the environment and in the body, leading to their persistence and bioaccumulation despite recent measures to limit their production (171). The most common PBDE exposure routes are ingestion and inhalation (170), and maternal-fetal transfer occurs readily across the placenta and via lactation (172, 173). There is still some debate as to the mechanisms underlying PBDE endocrine disruption, although both in vitro and in vivo evidence shows that they can act as ER (174) and TR agonists (175) as well as AR antagonists (176, 177). Despite the lack of mechanistic clarity, numerous studies, including from government labs such as the EPA, have identified the brain as a specifically vulnerable developmental target of PBDE toxicity (178, 179).

Polybrominated Diphenyl Ethers Are Neurotoxic and Disrupt Neuroendocrine and Neurotransmitter Targets

The effects of gestational PBDE exposure on thyroid hormone levels are among the most well-characterized and frequent effects reported in the literature. Pre- and/or postnatal PBDE exposure reduces circulating thyroid hormone concentrations in mice (180), rats (181, 182), human fetal cord blood (183), and young children (184). Gestational PBDE exposure also reduces thyroid weight in female rats (185), increases thyroid growth in male rats (186), and alters thyroid cell growth in both sexes (182), with human cohort analysis suggesting that these thyroid hormone and physiological changes are independent from PBDE action on hypothalamic thyroid-stimulating hormone release (187). Despite unclear mechanisms of PBDE action, thyroid hormones are well known to mediate multiple neurodevelopmental processes, including proliferation, differentiation, migration, and myelination (188). These effects alone can cause potent neurodevelopment disruption and, indeed, prenatal and/or postnatal PBDE exposure disrupts neuronal maturation

and cell cytoskeletal development (189), alters neurogenesis and synaptogenesis (190), and impairs oligodendrocyte development (182). The hippocampus is resistant to neurogenic or gliogenic disruption (186), but regions such as the corpus callosum and cingulate cortex are apparent targets (182).

In the hippocampus, nonthyroid effects also are observed following pre- or postnatal PBDE exposure, including a reduction in nicotinic receptor expression (191), an increase in muscarinic receptor expression (192), increases in neuronal apoptosis and autophagy (193), and increases in measures of oxidative stress (194). In fact, gestational PBDE exposure has significant disruptive effects on the cholinergic signaling system more broadly (195), as alterations are also demonstrated in the cortex (192), even though changes in gene expression might be minimal (196).

In contrast to other EDCs, limited evidence links gestational PBDE exposure to defects in neuroendocrine function beyond the indirect effects of thyroid hormone signaling. For example, alterations of gene expression in sexually dimorphic hypothalamic regions occur following fetal PBDE exposure (197), although circulating hormone levels from peripheral sources are also decreased in male rats (198) along with other effects on secondary sex characteristics such as delayed pubertal onset and reduced spermatogenesis (198, 199). It is unclear whether these effects are due to direct PBDE neuroendocrine disruption or via action on peripheral targets, although even if indirect, there is the potential for disruptions at the level of the hypothalamus due to feedback regulation by circulating hormones. Additionally, prenatal PBDE exposure increases signaling through the glutamate-nitric oxide-cGMP pathway in the cerebellum (200) and impairs synaptic plasticity in the dentate gyrus (201), illustrating how neurodevelopmental changes may impact behaviors.

Early Polybrominated Diphenyl Ether Exposure Leads to Numerous Human Behavioral Deficits that Are Reflected in Animal Models

Several reports from human cohort studies suggest that fetal PBDE exposure affects behavioral outcomes in children and adolescents. Extensive findings have come from behavioral testing of children from the HOMES cohort of 349 mother/infant pairs from Cincinnati. Although maternal PBDE exposure was not correlated with any alterations in infant neurobehavior at five weeks of age (202), there were significant behavioral defects as the children grew, especially once they reached school age. For example, children from the HOMES cohort aged 5–8 years old exhibited correlations between maternal PBDE exposure and reduced behavioral regulation and executive function (203), poorer reading scores, lower full-scale IQ, and increased externalizing behaviors (204), as well as poorer performance on attention and impulse control, with boys more affected than girls (205). Interestingly, PBDE exposure correlated with improved visual spatial learning in these children (206).

Additional cohort studies support some of these findings. For example, a cohort of 232 Chinese mother/infant pairs shows no impairment in neurobehavior as per the Gesell Developmental Schedules in one-year-olds, but by two years this gestational PBDE exposure can correlate with lowered language and social domain developmental quotients (207), indicating that defects tend to manifest as children age. However, a study of Spanish children indicates that lactational exposure may be specifically damaging for infants, as increased colostrum PBDE content was correlated with poorer neurodevelopment in children aged 12–18 months as per the BSID (208). These effects were found at a younger age than in any other report. Analysis of the CHAMACOS cohort of Latino-American California families associated gestational PBDE exposure with impaired attention, fine motor control, and cognitive measurements in children at 5 and 7 years old (209) and poorer attention and executive function in children aged 9–12 (210). Results from the CCCEH cohort, which primarily consists of African-American and Dominican families, show that prenatal PBDE exposure correlates with a variety of neurodevelopmental deficits as

measured on the BSID and the Wechsler Preschool and Primary Scale of Intelligence from ages 1–6, including lower psychomotor and mental developmental index scores and reductions in full-scale, verbal, and performance IQ depending on age (211). Other reports from this cohort associate prenatal PBDE exposure with impaired attention in children of both sexes at age 4 (212) and reduced working memory among girls aged 9–14 (213).

Animal models appear to support the human cohort studies and show that behavioral effects occur later in life with possible additional defects occurring with increasing lactational exposure. We could find no reports of gestational-only exposure affecting early reflexes, but studies with postnatal or a combination of gestational and lactational PBDE exposure did reveal impaired sensorimotor responses and spontaneous locomotor activity in immature mice, indicative of developmental delay (180, 214), delayed negative geotaxis, and cliff avoidance reflexes in juvenile rats (194). Hyperactivity was a commonly reported phenotype of PBDE-exposed mice (195, 214) and in some cases was only found in male mice (180) and rats (199). Alternatively, a separate study shows more nuanced results, with perinatal PBDE exposure leading to hyperactivity in adolescent mice and hypoactivity in adults (214). Overall, data show that gestational and/or lactational PBDE exposure can cause changes in activity; however, the specific effects are variable and may depend on dose, congener, and length of exposure, as there are also reports that show few if any neurobehavioral defects (181, 196). Additionally, studies of mice exposed to a direct postnatal dose, proposed to be analogous to lactation-specific exposure, show a marked lack of spontaneous behavior in adulthood (191, 195).

There is also an effort to use rodent assays to understand the observed human behavioral deficits in attention and impulse control in PBDE-exposed children. Tests using the Morris water maze in gestational PBDE-exposed rats show deficits in learning and memory (193). This effect also occurs when a direct dose is administered to postnatal pups (185, 191). Additionally, as observed with other EDCs, gestational PBDE exposure can feminize some sex-specific behaviors, with male-specific saccharine preference increasing to levels approaching what is normally found in females (198). Taken together, PBDE-correlated human behavioral deficits in attention, cognition, and executive function are at least partially reflected in animal models, but more work is needed to reach consensus given the variabilities related to dose, congener, and exposure windows. In light of the prominence of PBDE usage and their tendency to bioaccumulate, it is imperative that we work to elucidate the mechanisms of neurodevelopmental disruption by individual PBDE congeners and perhaps more importantly by commercially available mixtures.

CONCLUSIONS

In this review we have discussed reported findings on the neurodevelopmental impairments caused by gestational and lactational exposure to four major classes of EDCs, namely BPA, PCBs and dioxin, organophosphates, and PBDEs. By incorporating human cohort analyses, we have presented the literature consensus on how behavioral outcomes are altered by early life exposure to these compounds (detailed in **Supplemental Table 1**), backed by studies from as many relevant animal models as are available. Although we have presented some evidence from class-specific mixtures, e.g., PCB mixture A1254 or groups of PBDE congeners such as Firemaster 550, we have ignored the more complex mixtures that combine two or more EDC classes themselves. This is not because there is a dearth of these studies. On the contrary, there are researchers attempting to model complex mixtures to increase the relevancy of their findings. After all, no pregnant mother is exposed to just BPA, for example, and unexpected synergistic interactions can exist between these compounds, as they often share common target pathways. However, the complexity of these mixtures leads to a convulsion of the findings, making their comparison beyond the scope of this

Supplemental Material >

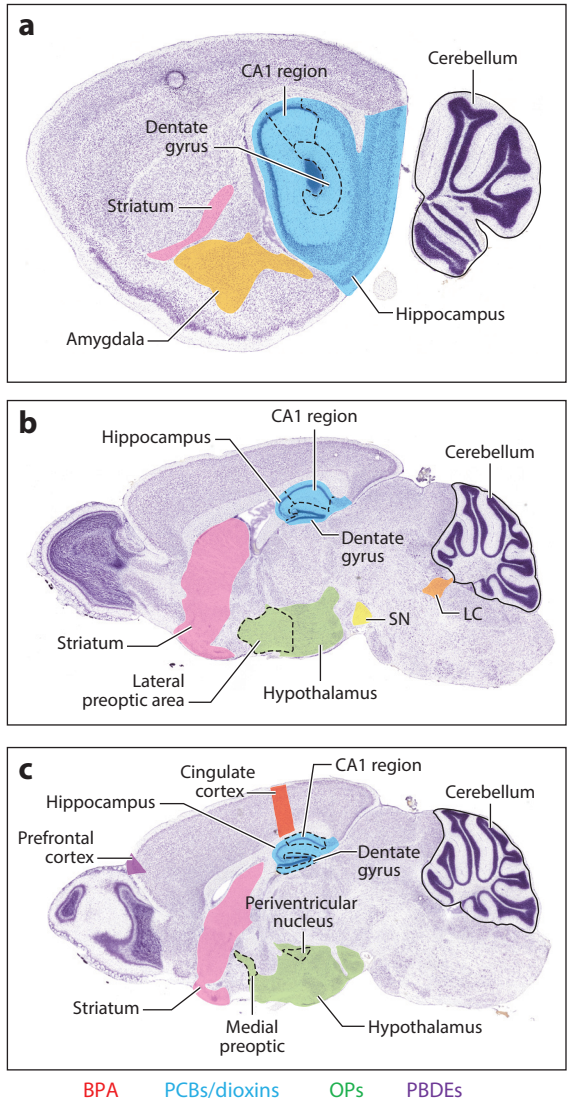
Amygdala
- ⬇ Estrogen receptor
- ⬇ Oxytocin
- ⬆ Vasopressin receptor 1a

Hippocampus
- Altered CA1 dendrite morphology
- Decreased neurogenesis
- ⬆ Serotonin
- ⬇ Cholinergic nicotinic receptors
- ⬇ Cholinergic nerve activity
- ⬇ Dopamine
- ⬇ Nicotinic receptors
- ⬇ Muscarinic receptors
- ⬆ Neuron apoptosis

Substantia nigra
- ⬇ TH+ neurons
- ⬇ Dopaminergic neurons

Locus coeruleus
- ⬇ TH+ neurons

Prefrontal cortex
- ⬇ Retinoic acid receptors
- ⬆ Serotonin
- Altered dopamine



Striatum
- Altered cell morphology
- ⬇ Synaptophysin

Cerebellum
- ⬇ Somatostatin sst_2 receptor
- ⬇ Retinoic acid receptor
- ⬇ GFAP
- ⬇ Dopamine
- ⬆ Glutamate/NO/cGMP signaling
- Impaired dentate gyrus
- Synaptic plasticity

Hypothalamus
- Accelerated neurogenesis
- ⬇ PVN estrogen receptor
- ⬇ Preoptic estrogen receptor
- ⬇ TH+ neurons
- ⬇ AVPV estrogen receptor β
- ⬇ GnRH release
- Altered preoptic gene expression
- ⬆ Estrogen receptor β
- ⬆ Oxytocin
- ⬇ Male-specific vasopressin

Cingulate cortex
- Altered neurogenesis
- ⬇ Oligodendrocytes

Figure 2

Summary of region-specific gestational and/or lactational effects of EDCs in the brain, using the mouse brain as a reference. Three sagittal sections are shown from lateral to medial: (*a*) lateral 3.325 mm, (*b*) lateral 1.10 mm, and (*c*) lateral 0.675 mm (all measured from midline). Specific regions of interest are shaded in different colors, whereas subdivisions are outlined with black dotted lines. Effects of each EDC class on these highlighted regions are noted and color coded. Initial Nissl stained images adapted from the Allen Mouse Brain Atlas (215). Abbreviations: AVPV, anteroventral periventricular; BPA, bisphenol A; cGMP, guanosine 3′, 5′-cyclic monophosphate; EDC, endocrine disrupting chemical; GFAP, glial fibrillary acidic protein; GnRH, gonadotropin-releasing hormone; NO, nitric oxide; OP, organophosphate; PBDE, polybrominated diphenyl ether; PCB, polychlorinated biphenyl; PVN, paraventricular nucleus; TH, tyrosine hydroxylase.

review. However, the study of complex mixtures is key to the future of EDC research and the isolated findings we have grouped here can help to inform future work.

Additionally, we have tried to highlight and reinforce regions of the brain that we find to be particularly susceptible to neurodevelopmental disruption (see **Figure 2** and further details in **Supplemental Table 2**). We repeatedly discussed effects on the hippocampus, the cerebral

Supplemental Material >

cortex, and the hypothalamus and noted them as targets of specific vulnerability to EDC disruption. We present these regions and their governed behaviors such as learning and memory, sensorimotor control, and sexual and social interactions as useful end points for future EDC experiments. Altogether, this review reinforces the consensus from the scientific community that the developing brain is an especially vulnerable target for EDCs and that these compounds exist in our environment and in our food, resulting in risks to pregnant mothers and infants. The body of literature discussed herein suggests that better government regulation is warranted, as is more research into how these effects in utero can be minimized.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

LITERATURE CITED

1. US Environ. Prot. Agency. 1997. *Special report on environmental endocrine disruption: an effects assessment and analysis*. Rep., EPA/630/R-96/012, US Environ. Prot. Agency, Washington, DC. **https://archive.epa.gov/raf/web/pdf/endocrine.pdf**
2. Gore AC, Chappell VA, Fenton SE, Flaws JA, Nadal A, et al. 2015. EDC-2: The Endocrine Society's second Scientific Statement on endocrine-disrupting chemicals. *Endocr. Rev.* 36:E1–150
3. Falconer IR, Chapman HF, Moore MR, Ranmuthugala G. 2006. Endocrine-disrupting compounds: a review of their challenge to sustainable and safe water supply and water reuse. *Environ. Toxicol.* 21:181–91
4. Rubin BS. 2011. Bisphenol A: an endocrine disruptor with widespread exposure and multiple effects. *J. Steroid Biochem. Mol. Biol.* 127:27–34
5. Rudel RA, Perovich LJ. 2009. Endocrine disrupting chemicals in indoor and outdoor air. *Atmos. Environ.* 43:170–81
6. Gore AC. 2010. Neuroendocrine targets of endocrine disruptors. *Hormones* 9:16–27
7. Patisaul HB, Polston EK. 2008. Influence of endocrine active compounds on the developing rodent brain. *Brain Res. Rev.* 57:352–62
8. Clotfelter ED, Bell AM, Levering KR. 2004. The role of animal behaviour in the study of endocrine-disrupting chemicals. *Anim. Behav.* 68:665–76
9. Balakrishnan B, Thorstensen E, Ponnampalam A, Mitchell MD. 2011. Passage of 4-nonylphenol across the human placenta. *Placenta* 32:788–92
10. Wan Y, Choi K, Kim S, Ji K, Chang H, et al. 2010. Hydroxylated polybrominated diphenyl ethers and bisphenol A in pregnant women and their matching fetuses: placental transfer and potential risks. *Environ. Sci. Technol.* 44:5233–39
11. Chen M, Fan Z, Zhao F, Gao F, Mu D, et al. 2016. Occurrence and maternal transfer of chlorinated bisphenol A and nonylphenol in pregnant women and their matching embryos. *Environ. Sci. Technol.* 50:970–77
12. Gould JC, Leonard LS, Maness SC, Wagner BL, Conner K, et al. 1998. Bisphenol A interacts with the estrogen receptor α in a distinct manner from estradiol. *Mol. Cell. Endocrinol.* 142:203–14
13. Tohmé M, Prudhomme SM, Boulahtouf A, Samarut E, Brunet F, et al. 2014. Estrogen-related receptor γ is an in vivo receptor of bisphenol A. *FASEB J.* 28:3124–33
14. Kuiper GG, Lemmen JG, Carlsson B, Corton JC, Safe SH, et al. 1998. Interaction of estrogenic chemicals and phytoestrogens with estrogen receptor β. *Endocrinology* 139:4252–63
15. Moriyama K, Tagami T, Akamizu T, Usui T, Saijo M, et al. 2002. Thyroid hormone action is disrupted by bisphenol A as an antagonist. *J. Clin. Endocrinol. Metab.* 87:5185–90
16. Lee HJ. 2003. Antiandrogenic effects of bisphenol A and nonylphenol on the function of androgen receptor. *Toxicol. Sci.* 75:40–46

17. Alonso-Magdalena P, Laribi O, Ropero AB, Fuentes E, Ripoll C, et al. 2005. Low doses of bisphenol A and diethylstilbestrol impair Ca^{2+} signals in pancreatic α-cells through a nonclassical membrane estrogen receptor within intact islets of Langerhans. *Environ. Health Perspect.* 113:969–77
18. Prasanth GK, Divya LM, Sadasivan C. 2010. Bisphenol-A can bind to human glucocorticoid receptor as an agonist: an in silico study. *J. Appl. Toxicol.* 30:769–74
19. Vandenberg LN. 2013. Non-monotonic dose responses in studies of endocrine disrupting chemicals: bisphenol A as a case study. *Dose-Response* 12:259–76
20. Yang C-W, Chou W-C, Chen K-H, Cheng A-L, Mao I-F, et al. 2014. Visualized gene network reveals the novel target transcripts Sox2 and Pax6 of neuronal development in trans-placental exposure to bisphenol A. *PLOS ONE* 9:e100576
21. Ellis P, Fagan BM, Magness ST, Hutton S, Taranova O, et al. 2004. SOX2, a persistent marker for multipotential neural stem cells derived from embryonic stem cells, the embryo or the adult. *Dev. Neurosci.* 26:148–65
22. Haubst N, Berger J, Radjendirane V, Graw J, Favor J, et al. 2004. Molecular dissection of Pax6 function: the specific roles of the paired domain and homeodomain in brain development. *Development* 131:6131–40
23. Kinch CD, Ibhazehiebo K, Jeong J-H, Habibi HR, Kurrasch DM. 2015. Low-dose exposure to bisphenol A and replacement bisphenol S induces precocious hypothalamic neurogenesis in embryonic zebrafish. *PNAS* 112:1475–80
24. Kim K, Son TG, Park HR, Kim SJ, Kim HS, et al. 2009. Potencies of bisphenol A on the neuronal differentiation and hippocampal neurogenesis. *J. Toxicol. Environ. Health A* 72:1343–51
25. Xu X-h, Zhang J, Wang Y-M, Ye Y-P, Luo Q-Q. 2010. Perinatal exposure to bisphenol-A impairs learning-memory by concomitant down-regulation of *N*-methyl-D-aspartate receptors of hippocampus in male offspring mice. *Horm. Behav.* 58:326–33
26. Cao J, Rebuli ME, Rogers J, Todd KL, Leyrer SM, et al. 2013. Prenatal bisphenol A exposure alters sex-specific estrogen receptor expression in the neonatal rat hypothalamus and amygdala. *Toxicol. Sci.* 133:157–73
27. Kimura E, Matsuyoshi C, Miyazaki W, Benner S, Hosokawa M, et al. 2015. Prenatal exposure to bisphenol A impacts neuronal morphology in the hippocampal CA1 region in developing and aged mice. *Arch. Toxicol.* 90:691–700
28. Elsworth JD, Jentsch JD, VandeVoort CA, Roth RH, Redmond DE, Leranth C. 2013. Prenatal exposure to bisphenol A impacts midbrain dopamine neurons and hippocampal spine synapses in non-human primates. *Neurotoxicology* 35:113–20
29. Liu Z-H, Ding J-J, Yang Q-Q, Song H-Z, Chen X-T, et al. 2016. Early developmental bisphenol-A exposure sex-independently impairs spatial memory by remodeling hippocampal dendritic architecture and synaptic transmission in rats. *Sci. Rep.* 6:32492
30. Shikimi H, Sakamoto H, Mezaki Y, Ukena K, Tsutsui K. 2004. Dendritic growth in response to environmental estrogens in the developing Purkinje cell in rats. *Neurosci. Lett.* 364:114–18
31. Bowman RE, Luine V, Khandaker H, Villafane JJ, Frankfurt M. 2014. Adolescent bisphenol-A exposure decreases dendritic spine density: role of sex and age. *Synapse* 68:498–507
32. Eilam-Stock T, Serrano P, Frankfurt M, Luine V. 2012. Bisphenol-A impairs memory and reduces dendritic spine density in adult male rats. *Behav. Neurosci.* 126:175–85
33. Lam SH, Hlaing MM, Zhang X, Yan C, Duan Z, et al. 2011. Toxicogenomic and phenotypic analyses of bisphenol-A early-life exposure toxicity in zebrafish. *PLOS ONE* 6:e28273
34. Ramos B, Gaudillière B, Bonni A, Gill G. 2007. Transcription factor Sp4 regulates dendritic patterning during cerebellar maturation. *PNAS* 104:9882–87
35. Zhou X, Qyang Y, Kelsoe JR, Masliah E, Geyer MA. 2007. Impaired postnatal development of hippocampal dentate gyrus in *Sp4* null mutant mice. *Genes Brain Behav.* 6:269–76
36. Tando S, Itoh K, Yaoi T, Ikeda J, Fujiwara Y, Fushiki S. 2007. Effects of pre- and neonatal exposure to bisphenol A on murine brain development. *Brain Dev.* 29:352–56
37. Tando S, Itoh K, Yaoi T, Ogi H, Goto S, et al. 2014. Bisphenol A exposure disrupts the development of the locus coeruleus-noradrenergic system in mice. *Neuropathology* 34:527–34

38. Rubin BS, Lenkowski JR, Schaeberle CM, Vandenberg LN, Ronsheim PM, Soto AM. 2006. Evidence of altered brain sexual differentiation in mice exposed perinatally to low, environmentally relevant levels of bisphenol A. *Endocrinology* 147:3681–91
39. Facciolo RM, Alo R, Madeo M, Canonaco M, Dessi-Fulgheri F. 2002. Early cerebral activities of the environmental estrogen bisphenol A appear to act via the somatostatin receptor subtype sst_2. *Environ. Health Perspect.* 110(Suppl. 3):397–402
40. Nishizawa H, Manabe N, Morita M, Sugimoto M, Imanishi S, Miyamoto H. 2003. Effects of in utero exposure to bisphenol A on expression of RARα and RXRα mRNAs in murine embryos. *J. Reprod. Dev.* 49:539–45
41. Patisaul HB, Todd KL, Mickens JA, Adewale HB. 2009. Impact of neonatal exposure to the ERα agonist PPT, bisphenol-A or phytoestrogens on hypothalamic kisspeptin fiber density in male and female rats. *Neurotoxicology* 30:350–57
42. Braun JM, Yolton K, Dietrich KN, Hornung R, Ye X, et al. 2009. Prenatal bisphenol A exposure and early childhood behavior. *Environ. Health Perspect.* 117:1945–52
43. Evans SF, Kobrosly RW, Barrett ES, Thurston SW, Calafat AM, et al. 2014. Prenatal bisphenol A exposure and maternally reported behavior in boys and girls. *Neurotoxicology* 45:91–99
44. Perera F, Vishnevetsky J, Herbstman JB, Calafat AM, Xiong W, et al. 2012. Prenatal bisphenol A exposure and child behavior in an inner-city cohort. *Environ. Health Perspect.* 120:1190–94
45. Braun JM, Kalkbrenner AE, Calafat AM, Yolton K, Ye X, et al. 2011. Impact of early-life bisphenol A exposure on behavior and executive function in children. *Pediatrics* 128:873–82
46. Casas M, Forns J, Martínez D, Avella-García C, Valvi D, et al. 2015. Exposure to bisphenol A during pregnancy and child neuropsychological development in the INMA-Sabadell cohort. *Environ. Res.* 142:671–79
47. Anderson OS, Peterson KE, Sanchez BN, Zhang Z, Mancuso P, Dolinoy DC. 2013. Perinatal bisphenol A exposure promotes hyperactivity, lean body composition, and hormonal responses across the murine life course. *FASEB J.* 27:1784–92
48. Zhou R, Bai Y, Yang R, Zhu Y, Chi X, et al. 2011. Abnormal synaptic plasticity in basolateral amygdala may account for hyperactivity and attention-deficit in male rat exposed perinatally to low-dose bisphenol-A. *Neuropharmacology* 60:789–98
49. Nakamura K, Itoh K, Dai H, Han L, Wang X, et al. 2012. Prenatal and lactational exposure to low-doses of bisphenol A alters adult mice behavior. *Brain Dev*. 34:57–63
50. Fujimoto T, Kubo K, Aou S. 2006. Prenatal exposure to bisphenol A impairs sexual differentiation of exploratory behavior and increases depression-like behavior in rats. *Brain Res*. 1068:49–55
51. Ohtani N, Iwano H, Suda K, Tsuji E, Tanemura K, et al. 2017. Adverse effects of maternal exposure to bisphenol F on the anxiety- and depression-like behavior of offspring. *J. Vet. Med. Sci.* 79:432–39
52. Xu X, Hong X, Xie L, Li T, Yang Y, et al. 2012. Gestational and lactational exposure to bisphenol-A affects anxiety- and depression-like behaviors in mice. *Horm. Behav.* 62:480–90
53. Porrini S, Belloni V, Seta DD, Farabollini F, Giannelli G, Dessì-Fulgheri F. 2005. Early exposure to a low dose of bisphenol A affects socio-sexual behavior of juvenile female rats. *Brain Res. Bull.* 65:261–66
54. Farabollini F, Porrini S, Della Seta D. 2002. Effects of perinatal exposure to bisphenol A on sociosexual behavior of female and male rats. *Environ. Health Perspect.* 110(Suppl. 3):409–14
55. Wolstenholme JT, Taylor JA, Shetty SRJ, Edwards M, Connelly JJ, Rissman EF. 2011. Gestational exposure to low dose bisphenol A alters social behavior in juvenile mice. *PLOS ONE* 6:e25448
56. Hass U, Christiansen S, Boberg J, Rasmussen MG, Mandrup K, Axelstad M. 2016. Low-dose effect of developmental bisphenol A exposure on sperm count and behaviour in rats. *Andrology* 4:594–607
57. Xu X, Liu Y, Sadamatsu M, Tsutsumi S, Akaike M, et al. 2007. Perinatal bisphenol A affects the behavior and SRC-1 expression of male pups but does not influence on the thyroid hormone receptors and its responsive gene. *Neurosci. Res.* 58:149–55
58. Craig ZR, Wang W, Flaws JA. 2011. Endocrine-disrupting chemicals in ovarian function: effects on steroidogenesis, metabolism and nuclear receptor signaling. *Reproduction* 142:633–46
59. Jansen HT, Cooke PS, Porcelli J, Liu TC, Hansen LG. 1993. Estrogenic and antiestrogenic actions of PCBs in the female rat: in vitro and in vivo studies. *Reprod. Toxicol.* 7:237–48

60. Bonefeld-Jorgensen EC, Andersen HR, Rasmussen TH, Vinggaard AM. 2001. Effect of highly bioaccumulated polychlorinated biphenyl congeners on estrogen and androgen receptor activity. *Toxicology* 158:141–53
61. Mandal PK. 2005. Dioxin: a review of its environmental effects and its aryl hydrocarbon receptor biology. *J. Comp. Physiol. B* 175:221–30
62. Safe S, Wang F, Porter W, Duan R, McDougal A. 1998. Ah receptor agonists as endocrine disruptors: antiestrogenic activity and mechanisms. *Toxicol. Lett.* 102–103:343–47
63. Ritter R, Scheringer M, MacLeod M, Moeckel C, Jones KC, Hungerbuhler K. 2011. Intrinsic human elimination half-lives of polychlorinated biphenyls derived from the temporal evolution of cross-sectional biomonitoring data from the United Kingdom. *Environ. Health Perspect.* 119:225–31
64. Milbrath MO, Wenger Y, Chang CW, Emond C, Garabrant D, et al. 2009. Apparent half-lives of dioxins, furans, and polychlorinated biphenyls as a function of age, body fat, smoking status, and breast-feeding. *Environ. Health Perspect.* 117:417–25
65. Lancz K, Murinova L, Patayova H, Drobna B, Wimmerova S, et al. 2015. Ratio of cord to maternal serum PCB concentrations in relation to their congener-specific physicochemical properties. *Int. J. Hyg. Environ. Health* 218:91–98
66. Vizcaino E, Grimalt JO, Fernandez-Somoano A, Tardon A. 2014. Transport of persistent organic pollutants across the human placenta. *Environ. Int.* 65:107–15
67. Morse DC, Groen D, Veerman M, van Amerongen CJ, Koeter HB, et al. 1993. Interference of polychlorinated biphenyls in hepatic and brain thyroid hormone metabolism in fetal and neonatal rats. *Toxicol. Appl. Pharmacol.* 122:27–33
68. Ness DK, Schantz SL, Moshtaghian J, Hansen LG. 1993. Effects of perinatal exposure to specific PCB congeners on thyroid hormone concentrations and thyroid histology in the rat. *Toxicol. Lett.* 68:311–23
69. Schantz SL, Seo B-W, Moshtaghian J, Amin S. 1997. Developmental exposure to polychlorinated biphenyls or dioxin: do changes in thyroid function mediate effects on spatial learning? *Am. Zool.* 37:399–408
70. Gauger KJ, Kato Y, Haraguchi K, Lehmler HJ, Robertson LW, et al. 2004. Polychlorinated biphenyls (PCBs) exert thyroid hormone-like effects in the fetal rat brain but do not bind to thyroid hormone receptors. *Environ. Health Perspect.* 112:516–23
71. Dickerson SM, Cunningham SL, Patisaul HB, Woller MJ, Gore AC. 2011. Endocrine disruption of brain sexual differentiation by developmental PCB exposure. *Endocrinology* 152:581–94
72. Walker DM, Goetz BM, Gore AC. 2014. Dynamic postnatal developmental and sex-specific neuroendocrine effects of prenatal polychlorinated biphenyls in rats. *Mol. Endocrinol.* 28:99–115
73. Ernfors P, Lee KF, Jaenisch R. 1994. Mice lacking brain-derived neurotrophic factor develop with sensory deficits. *Nature* 368:147–50
74. Jones KR, Farinas I, Backus C, Reichardt LF. 1994. Targeted disruption of the BDNF gene perturbs brain and sensory neuron development but not motor neuron development. *Cell* 76:989–99
75. Bavithra S, Sugantha Priya E, Selvakumar K, Krishnamoorthy G, Arunakaran J. 2015. Effect of melatonin on glutamate: BDNF signaling in the cerebral cortex of polychlorinated biphenyls (PCBs)-exposed adult male rats. *Neurochem. Res.* 40:1858–69
76. Giordano T, Pan JB, Casuto D, Watanabe S, Arneric SP. 1992. Thyroid hormone regulation of NGF, NT-3 and BDNF RNA in the adult rat brain. *Brain Res. Mol. Brain Res.* 16:239–45
77. Hany J, Lilienthal H, Sarasin A, Roth-Harer A, Fastabend A, et al. 1999. Developmental exposure of rats to a reconstituted PCB mixture or Aroclor 1254: effects on organ weights, aromatase activity, sex hormone levels, and sweet preference behavior. *Toxicol. Appl. Pharmacol.* 158:231–43
78. Colciago A, Casati L, Mornati O, Vergoni AV, Santagostino A, et al. 2009. Chronic treatment with polychlorinated biphenyls (PCB) during pregnancy and lactation in the rat: Part 2: Effects on reproductive parameters, on sex behavior, on memory retention and on hypothalamic expression of aromatase and 5alpha-reductases in the offspring. *Toxicol. Appl. Pharmacol.* 239:46–54
79. Clements RJ, Lawrence RC, Blank JL. 2009. Effects of intrauterine 2,3,7,8-tetrachlorodibenzo-p-dioxin on the development and function of the gonadotrophin releasing hormone neuronal system in the male rat. *Reprod. Toxicol.* 28:38–45

80. Takeda T, Matsumoto Y, Koga T, Mutoh J, Nishimura Y, et al. 2009. Maternal exposure to dioxin disrupts gonadotropin production in fetal rats and imprints defects in sexual behavior. *J. Pharmacol. Exp. Ther.* 329:1091–99
81. Seegal RF, Brosch KO, Okoniewski RJ. 2005. Coplanar PCB congeners increase uterine weight and frontal cortical dopamine in the developing rat: implications for developmental neurotoxicity. *Toxicol. Sci.* 86:125–31
82. Morse DC, Seegal RF, Borsch KO, Brouwer A. 1996. Long-term alterations in regional brain serotonin metabolism following maternal polychlorinated biphenyl exposure in the rat. *Neurotoxicology* 17:631–38
83. Hood DB, Woods L, Brown L, Johnson S, Ebner FF. 2006. Gestational 2,3,7,8-tetrachlorodibenzo-*p*-dioxin exposure effects on sensory cortex function. *Neurotoxicology* 27:1032–42
84. Tomasini MC, Beggiato S, Ferraro L, Tanganelli S, Marani L, et al. 2012. Prenatal exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin produces alterations in cortical neuron development and a long-term dysfunction of glutamate transmission in rat cerebral cortex. *Neurochem. Int.* 61:759–66
85. Morse DC, Plug A, Wesseling W, van den Berg KJ, Brouwer A. 1996. Persistent alterations in regional brain glial fibrillary acidic protein and synaptophysin levels following pre- and postnatal polychlorinated biphenyl exposure. *Toxicol. Appl. Pharmacol.* 139:252–61
86. Roegge CS, Morris JR, Villareal S, Wang VC, Powers BE, et al. 2006. Purkinje cell and cerebellar effects following developmental exposure to PCBs and/or MeHg. *Neurotoxicol. Teratol.* 28:74–85
87. Nishijo M, Kuriwaki J, Hori E, Tawara K, Nakagawa H, Nishijo H. 2007. Effects of maternal exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin on fetal brain growth and motor and behavioral development in offspring rats. *Toxicol. Lett.* 173:41–47
88. Vreugdenhil HJ, Mulder PG, Emmen HH, Weisglas-Kuperus N. 2004. Effects of perinatal exposure to PCBs on neuropsychological functions in the Rotterdam cohort at 9 years of age. *Neuropsychology* 18:185–93
89. Gladen BC, Rogan WJ, Hardy P, Thullen J, Tingelstad J, Tully M. 1988. Development after exposure to polychlorinated biphenyls and dichlorodiphenyl dichloroethene transplacentally and through human milk. *J. Pediatr.* 113:991–95
90. Jacobson SW, Fein GG, Jacobson JL, Schwartz PM, Dowler JK. 1985. The effect of intrauterine PCB exposure on visual recognition memory. *Child Dev.* 56:853–60
91. Jacobson JL, Jacobson SW, Humphrey HE. 1990. Effects of in utero exposure to polychlorinated biphenyls and related contaminants on cognitive functioning in young children. *J. Pediatr.* 116:38–45
92. Nishijo M, Tawara K, Nakagawa H, Honda R, Kido T, et al. 2008. 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in maternal breast milk and newborn head circumference. *J. Expo. Sci. Environ. Epidemiol.* 18:246–51
93. Tai PT, Nishijo M, Anh NT, Maruzeni S, Nakagawa H, et al. 2013. Dioxin exposure in breast milk and infant neurodevelopment in Vietnam. *Occup. Environ. Med.* 70:656–62
94. Nishijo M, Pham TT, Nguyen AT, Tran NN, Nakagawa H, et al. 2014. 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in breast milk increases autistic traits of 3-year-old children in Vietnam. *Mol. Psychiatry* 19:1220–26
95. Tran NN, Pham TT, Ozawa K, Nishijo M, Nguyen AT, et al. 2016. Impacts of perinatal dioxin exposure on motor coordination and higher cognitive development in Vietnamese preschool children: a five-year follow-up. *PLOS ONE* 11:e0147655
96. Schantz SL, Moshtaghian J, Ness DK. 1995. Spatial learning deficits in adult rats exposed to ortho-substituted PCB congeners during gestation and lactation. *Fundam. Appl. Toxicol.* 26:117–26
97. Seo BW, Sparks AJ, Medora K, Amin S, Schantz SL. 1999. Learning and memory in rats gestationally and lactationally exposed to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). *Neurotoxicol. Teratol.* 21:231–39
98. Weinand-Harer A, Lilienthal H, Bucholski KA, Winneke G. 1997. Behavioral effects of maternal exposure to an ortho-chlorinated or a coplanar PCB congener in rats. *Environ. Toxicol. Pharmacol.* 3:97–103

99. Schantz SL, Seo BW, Moshtaghian J, Peterson RE, Moore RW. 1996. Effects of gestational and lactational exposure to TCDD or coplanar PCBs on spatial learning. *Neurotoxicol. Teratol.* 18:305–13
100. Piedrafita B, Erceg S, Cauli O, Monfort P, Felipo V. 2008. Developmental exposure to polychlorinated biphenyls PCB153 or PCB126 impairs learning ability in young but not in adult rats. *Eur. J. Neurosci.* 27:177–82
101. Widholm JJ, Clarkson GB, Strupp BJ, Crofton KM, Seegal RF, Schantz SL. 2001. Spatial reversal learning in Aroclor 1254-exposed rats: sex-specific deficits in associative ability and inhibitory control. *Toxicol. Appl. Pharmacol.* 174:188–98
102. Curran CP, Nebert DW, Genter MB, Patel KV, Schaefer TL, et al. 2011. *In utero* and lactational exposure to PCBs in mice: adult offspring show altered learning and memory depending on *Cyp1a2* and *Ahr* genotypes. *Environ. Health Perspect.* 119:1286–93
103. Schantz SL, Levin ED, Bowman RE, Heironimus MP, Laughlin NK. 1989. Effects of perinatal PCB exposure on discrimination-reversal learning in monkeys. *Neurotoxicol. Teratol.* 11:243–50
104. Kuriyama SN, Chahoud I. 2004. In utero exposure to low-dose 2,3′,4,4′,5-pentachlorobiphenyl (PCB 118) impairs male fertility and alters neurobehavior in rat offspring. *Toxicology* 202:185–97
105. Nguon K, Baxter MG, Sajdel-Sulkowska EM. 2005. Perinatal exposure to polychlorinated biphenyls differentially affects cerebellar development and motor functions in male and female rat neonates. *Cerebellum* 4:112–22
106. Rice DC. 1999. Effect of exposure to 3,3′,4,4′,5-pentachlorobiphenyl (PCB 126) throughout gestation and lactation on development and spatial delayed alternation performance in rats. *Neurotoxicol. Teratol.* 21:59–69
107. Pantaleoni GC, Fanini D, Sponta AM, Palumbo G, Giorgi R, Adams PM. 1988. Effects of maternal exposure to polychlorobiphenyls (PCBs) on F1 generation behavior in the rat. *Fundam. Appl. Toxicol.* 11:440–49
108. Agrawal AK, Tilson HA, Bondy SC. 1981. 3,4,3′,4′-Tetrachlorobiphenyl given to mice prenatally produces long-term decreases in striatal dopamine and receptor binding sites in the caudate nucleus. *Toxicol. Lett.* 7:417–24
109. Tilson HA, Davis GJ, McLachlan JA, Lucier GW. 1979. The effects of polychlorinated biphenyls given prenatally on the neurobehavioral development of mice. *Environ. Res.* 18:466–74
110. Nguyen AT, Nishijo M, Hori E, Nguyen NM, Pham TT, et al. 2013. Influence of maternal exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin on socioemotional behaviors in offspring rats. *Environ. Health Insights* 7. **https://doi.org/10.4137/ehi.s10346**
111. Bushnell PJ, Moser VC, MacPhail RC, Oshiro WM, Derr-Yellin EC, et al. 2002. Neurobehavioral assessments of rats perinatally exposed to a commercial mixture of polychlorinated biphenyls. *Toxicol. Sci.* 68:109–20
112. Schantz SL, Seo BW, Wong PW, Pessah IN. 1997. Long-term effects of developmental exposure to 2,2′,3,5′,6-pentachlorobiphenyl (PCB 95) on locomotor activity, spatial learning and memory and brain ryanodine binding. *Neurotoxicology* 18:457–67
113. Roegge CS, Wang VC, Powers BE, Klintsova AY, Villareal S, et al. 2004. Motor impairment in rats exposed to PCBs and methylmercury during early development. *Toxicol. Sci.* 77:315–24
114. Bjerke DL, Brown TJ, MacLusky NJ, Hochberg RB, Peterson RE. 1994. Partial demasculinization and feminization of sex behavior in male rats by in utero and lactational exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin is not associated with alterations in estrogen receptor binding or volumes of sexually differentiated brain nuclei. *Toxicol. Appl. Pharmacol.* 127:258–67
115. Negishi T, Shimomura H, Koyama T, Kawasaki K, Ishii Y, et al. 2006. Gestational and lactational exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin affects social behaviors between developing rhesus monkeys (*Macaca mulatta*). *Toxicol. Lett.* 160:233–44
116. Sullivan PJ, Clark JJJ, Agardy FJ, Rosenfeld PF. 2007. Synthetic chemicals in a balanced diet. In *Toxic Legacy: Synthetic Toxins in the Food, Water and Air of American Cities*, ed. SJ Sullivan, JJJ Clark, FJ Hardy, PF Rosenfeld, pp. 37–87. Burlington, MA: Academic
117. Bonner MR, Coble J, Blair A, Beane Freeman LE, Hoppin JA, et al. 2007. Malathion exposure and the incidence of cancer in the agricultural health study. *Am. J. Epidemiol.* 166:1023–34

118. Roberts JR, Reigart JR. 2013. Organophosphate insecticides. In *Recognition and Management of Pesticide Poisonings*, ed. JR Roberts, JR Reigart, pp 43–55. Washington, DC: US Environ. Prot. Agency. **https://www.epa.gov/sites/production/files/documents/rmpp_6thed_ch5_organophosphates.pdf**
119. Aldridge WN, Miles JW, Mount DL, Verschoyle RD. 1979. The toxicological properties of impurities in malathion. *Arch. Toxicol.* 42:95–106
120. Kralj MB, Černigoj U, Franko M, Trebše P. 2007. Comparison of photocatalysis and photolysis of malathion, isomalathion, malaoxon, and commercial malathion—products and toxicity studies. *Water Res.* 41:4504–14
121. World Health Organ. 2010. *The WHO recommended classification of pesticides by hazard and guidelines to classification 2009*. Rep., Int. Prog. Chem. Safety, World Health Organ., Geneva. **https://www.who.int/foodsafety/publications/classification-pesticides/en/**
122. Brouwer A, Ahlborg UG, van Leeuwen FX, Feeley MM. 1998. Report of the WHO working group on the assessment of health risks for human infants from exposure to PCDDs, PCDFs and PCBs. *Chemosphere* 37:1627–43
123. Jajoo M, Saxena S, Pandey M. 2010. Transplacentally acquired organophosphorus poisoning in a newborn: case report. *Ann. Trop. Paediatr.* 30:137–39
124. Eskenazi B, Bradman A, Castorina R. 1999. Exposures of children to organophosphate pesticides and their potential adverse health effects. *Environ. Health Perspect.* 107(Suppl. 3):409–19
125. Chanda SM, Pope CN. 1996. Neurochemical and neurobehavioral effects of repeated gestational exposure to chlorpyrifos in maternal and developing rats. *Pharmacol. Biochem. Behav.* 53:771–76
126. Lassiter TL, Barone S Jr., Moser VC, Padilla S. 1999. Gestational exposure to chlorpyrifos: dose response profiles for cholinesterase and carboxylesterase activity. *Toxicol. Sci.* 52:92–100
127. Richardson JR, Chambers JE. 2004. Neurochemical effects of repeated gestational exposure to chlorpyrifos in developing rats. *Toxicol. Sci.* 77:83–90
128. da Silva AP, Meotti FC, Santos AR, Farina M. 2006. Lactational exposure to malathion inhibits brain acetylcholinesterase in mice. *Neurotoxicology* 27:1101–5
129. Selmi S, El-Fazaa S, Gharbi N. 2012. Oxidative stress and cholinesterase inhibition in plasma, erythrocyte and brain of rats' pups following lactational exposure to malathion. *Environ. Toxicol. Pharmacol.* 34:753–60
130. Chanda SM, Harp P, Liu J, Pope CN. 1995. Comparative developmental and maternal neurotoxicity following acute gestational exposure to chlorpyrifos in rats. *J. Toxicol. Environ. Health* 44:189–202
131. Qiao D, Seidler FJ, Abreu-Villaça Y, Tate CA, Cousins MM, Slotkin TA. 2004. Chlorpyrifos exposure during neurulation: cholinergic synaptic dysfunction and cellular alterations in brain regions at adolescence and adulthood. *Dev. Brain Res.* 148:43–52
132. Qiao D, Seidler FJ, Tate CA, Cousins MM, Slotkin TA. 2003. Fetal chlorpyrifos exposure: adverse effects on brain cell development and cholinergic biomarkers emerge postnatally and continue into adolescence and adulthood. *Environ. Health Perspect.* 111:536–44
133. Mullins RJ, Xu S, Pereira EF, Pescrille JD, Todd SW, et al. 2015. Prenatal exposure of guinea pigs to the organophosphorus pesticide chlorpyrifos disrupts the structural and functional integrity of the brain. *Neurotoxicology* 48:9–20
134. Garcia SJ, Seidler FJ, Slotkin TA. 2003. Developmental neurotoxicity elicited by prenatal or postnatal chlorpyrifos exposure: effects on neurospecific proteins indicate changing vulnerabilities. *Environ. Health Perspect.* 111:297–303
135. Garcia SJ, Seidler FJ, Qiao D, Slotkin TA. 2002. Chlorpyrifos targets developing glia: effects on glial fibrillary acidic protein. *Brain Res. Dev. Brain Res.* 133:151–61
136. Garcia SJ, Seidler FJ, Slotkin TA. 2005. Developmental neurotoxicity of chlorpyrifos: targeting glial cells. *Environ. Toxicol. Pharmacol.* 19:455–61
137. Salama M, Lotfy A, Fathy K, Makar M, El-Emam M, et al. 2015. Developmental neurotoxic effects of malathion on 3D neurosphere system. *Appl. Transl. Genom.* 7:13–18
138. Roy TS, Seidler FJ, Slotkin TA. 2004. Morphologic effects of subtoxic neonatal chlorpyrifos exposure in developing rat brain: regionally selective alterations in neurons and glia. *Brain Res. Dev. Brain Res.* 148:197–206

139. Aldridge JE, Seidler FJ, Meyer A, Thillai I, Slotkin TA. 2003. Serotonergic systems targeted by developmental exposure to chlorpyrifos: effects during different critical periods. *Environ. Health Perspect.* 111:1736–43
140. Aldridge JE, Meyer A, Seidler FJ, Slotkin TA. 2005. Alterations in central nervous system serotonergic and dopaminergic synaptic activity in adulthood after prenatal or neonatal chlorpyrifos exposure. *Environ. Health Perspect.* 113:1027–31
141. Chen XP, Wang X, Dong JY. 2011. Different reaction patterns of dopamine content to prenatal exposure to chlorpyrifos in different periods. *J. Appl. Toxicol.* 31:355–59
142. Zhang J, Dai H, Deng Y, Tian J, Zhang C, et al. 2015. Neonatal chlorpyrifos exposure induces loss of dopaminergic neurons in young adult rats. *Toxicology* 336:17–25
143. Slotkin TA, Seidler FJ. 2007. Prenatal chlorpyrifos exposure elicits presynaptic serotonergic and dopaminergic hyperactivity at adolescence: critical periods for regional and sex-selective effects. *Reprod. Toxicol.* 23:421–27
144. Meyer A, Seidler FJ, Aldridge JE, Tate CA, Cousins MM, Slotkin TA. 2004. Critical periods for chlorpyrifos-induced developmental neurotoxicity: alterations in adenylyl cyclase signaling in adult rat brain regions after gestational or neonatal exposure. *Environ. Health Perspect.* 112:295–301
145. Venerosi A, Tait S, Stecca L, Chiarotti F, De Felice A, et al. 2015. Effects of maternal chlorpyrifos diet on social investigation and brain neuroendocrine markers in the offspring—a mouse study. *Environ. Health* 14:32
146. Haviland JA, Butz DE, Porter WP. 2010. Long-term sex selective hormonal and behavior alterations in mice exposed to low doses of chlorpyrifos in utero. *Reprod. Toxicol.* 29:74–79
147. De Felice A, Greco A, Calamandrei G, Minghetti L. 2016. Prenatal exposure to the organophosphate insecticide chlorpyrifos enhances brain oxidative stress and prostaglandin E2 synthesis in a mouse model of idiopathic autism. *J. Neuroinflamm.* 13:149
148. Ouardi FZ, Anarghou H, Malqui H, Ouasmi N, Chigr M, et al. 2019. Gestational and lactational exposure to malathion affects antioxidant status and neurobehavior in mice pups and offspring. *J. Mol. Neurosci.* 69:17–27
149. Eaton DL, Daroff RB, Autrup H, Bridges J, Buffler P, et al. 2008. Review of the toxicology of chlorpyrifos with an emphasis on human exposure and neurodevelopment. *Crit. Rev. Toxicol.* 38(Suppl. 2):1–125
150. Silver MK, Shao J, Ji C, Zhu B, Xu L, et al. 2018. Prenatal organophosphate insecticide exposure and infant sensory function. *Int. J. Hyg. Environ. Health* 221:469–78
151. Silver MK, Shao J, Zhu B, Chen M, Xia Y, et al. 2017. Prenatal naled and chlorpyrifos exposure is associated with deficits in infant motor function in a cohort of Chinese infants. *Environ. Int.* 106:248–56
152. Wang Y, Zhang Y, Ji L, Hu Y, Zhang J, et al. 2017. Prenatal and postnatal exposure to organophosphate pesticides and childhood neurodevelopment in Shandong, China. *Environ. Int.* 108:119–26
153. Young JG, Eskenazi B, Gladstone EA, Bradman A, Pedersen L, et al. 2005. Association between in utero organophosphate pesticide exposure and abnormal reflexes in neonates. *Neurotoxicology* 26:199–209
154. Eskenazi B, Marks AR, Bradman A, Harley K, Barr DB, et al. 2007. Organophosphate pesticide exposure and neurodevelopment in young Mexican-American children. *Environ. Health Perspect.* 115:792–98
155. Bouchard MF, Chevrier J, Harley KG, Kogut K, Vedar M, et al. 2011. Prenatal exposure to organophosphate pesticides and IQ in 7-year-old children. *Environ. Health Perspect.* 119:1189–95
156. Rauh VA, Garfinkel R, Perera FP, Andrews HF, Hoepner L, et al. 2006. Impact of prenatal chlorpyrifos exposure on neurodevelopment in the first 3 years of life among inner-city children. *Pediatrics* 118:e1845–59
157. Rauh V, Arunajadai S, Horton M, Perera F, Hoepner L, et al. 2011. Seven-year neurodevelopmental scores and prenatal exposure to chlorpyrifos, a common agricultural pesticide. *Environ. Health Perspect.* 119:1196–201
158. Yolton K, Xu Y, Sucharew H, Succop P, Altaye M, et al. 2013. Impact of low-level gestational exposure to organophosphate pesticides on neurobehavior in early infancy: a prospective study. *Environ. Health* 12:79
159. Levin ED, Addy N, Baruah A, Elias A, Christopher NC, et al. 2002. Prenatal chlorpyrifos exposure in rats causes persistent behavioral alterations. *Neurotoxicol. Teratol.* 24:733–41

160. Icenogle LM, Christopher NC, Blackwelder WP, Caldwell DP, Qiao D, et al. 2004. Behavioral alterations in adolescent and adult rats caused by a brief subtoxic exposure to chlorpyrifos during neurulation. *Neurotoxicol. Teratol.* 26:95–101
161. Mamczarz J, Pescrille JD, Gavrushenko L, Burke RD, Fawcett WP, et al. 2016. Spatial learning impairment in prepubertal guinea pigs prenatally exposed to the organophosphorus pesticide chlorpyrifos: toxicological implications. *Neurotoxicology* 56:17–28
162. Venerosi A, Ricceri L, Scattoni ML, Calamandrei G. 2009. Prenatal chlorpyrifos exposure alters motor behavior and ultrasonic vocalization in CD-1 mouse pups. *Environ. Health* 8:12
163. De Felice A, Venerosi A, Ricceri L, Sabbioni M, Scattoni ML, et al. 2014. Sex-dimorphic effects of gestational exposure to the organophosphate insecticide chlorpyrifos on social investigation in mice. *Neurotoxicol. Teratol.* 46:32–39
164. N'Go PK, Azzaoui F-Z, Ahami AOT, Soro PR, Najimi M, Chigr F. 2013. Developmental effects of Malathion exposure on locomotor activity and anxiety-like behavior in Wistar rat. *Health* 5:603–11
165. Ricceri L, Venerosi A, Capone F, Cometa MF, Lorenzini P, et al. 2006. Developmental neurotoxicity of organophosphorous pesticides: fetal and neonatal exposure to chlorpyrifos alters sex-specific behaviors at adulthood in mice. *Toxicol. Sci.* 93:105–13
166. Venerosi A, Ricceri L, Rungi A, Sanghez V, Calamandrei G. 2010. Gestational exposure to the organophosphate chlorpyrifos alters social-emotional behaviour and impairs responsiveness to the serotonin transporter inhibitor fluvoxamine in mice. *Psychopharmacology* 208:99–107
167. Braquenier JB, Quertemont E, Tirelli E, Plumier JC. 2010. Anxiety in adult female mice following perinatal exposure to chlorpyrifos. *Neurotoxicol. Teratol.* 32:234–39
168. Silva JG, Boareto AC, Schreiber AK, Redivo DD, Gambeta E, et al. 2017. Chlorpyrifos induces anxiety-like behavior in offspring rats exposed during pregnancy. *Neurosci. Lett.* 641:94–100
169. Carr RL, Armstrong NH, Buchanan AT, Eells JB, Mohammed AN, et al. 2017. Decreased anxiety in juvenile rats following exposure to low levels of chlorpyrifos during development. *Neurotoxicology* 59:183–90
170. Costa LG, Giordano G, Tagliaferri S, Caglieri A, Mutti A. 2008. Polybrominated diphenyl ether (PBDE) flame retardants: environmental contamination, human body burden and potential adverse health effects. *Acta Biomed.* 79:172–83
171. Darnerud PO, Eriksen GS, Johannesson T, Larsen PB, Viluksela M. 2001. Polybrominated diphenyl ethers: occurrence, dietary exposure, and toxicology. *Environ. Health Perspect.* 109(Suppl. 1):49–68
172. Hooper K, McDonald TA. 2000. The PBDEs: an emerging environmental challenge and another reason for breast-milk monitoring programs. *Environ. Health Perspect.* 108:387–92
173. Phillips AL, Chen A, Rock KD, Horman B, Patisaul HB, Stapleton HM. 2016. Transplacental and lactational transfer of Firemaster® 550 components in dosed Wistar rats. *Toxicol. Sci.* 153:246–57
174. Meerts IA, Letcher RJ, Hoving S, Marsh G, Bergman A, et al. 2001. In vitro estrogenicity of polybrominated diphenyl ethers, hydroxylated PDBEs, and polybrominated bisphenol A compounds. *Environ. Health Perspect.* 109:399–407
175. Ren XM, Guo LH, Gao Y, Zhang BT, Wan B. 2013. Hydroxylated polybrominated diphenyl ethers exhibit different activities on thyroid hormone receptors depending on their degree of bromination. *Toxicol. Appl. Pharmacol.* 268:256–63
176. Stoker TE, Cooper RL, Lambright CS, Wilson VS, Furr J, Gray LE. 2005. In vivo and in vitro anti-androgenic effects of DE-71, a commercial polybrominated diphenyl ether (PBDE) mixture. *Toxicol. Appl. Pharmacol.* 207:78–88
177. Yang W, Mu Y, Giesy JP, Zhang A, Yu H. 2009. Anti-androgen activity of polybrominated diphenyl ethers determined by comparative molecular similarity indices and molecular docking. *Chemosphere* 75:1159–64
178. Costa LG, Giordano G. 2011. Is decabromodiphenyl ether (BDE-209) a developmental neurotoxicant? *Neurotoxicology* 32:9–24
179. Szabo DT, Richardson VM, Ross DG, Diliberto JJ, Kodavanti PR, Birnbaum LS. 2009. Effects of perinatal PBDE exposure on hepatic phase I, phase II, phase III, and deiodinase 1 gene expression involved in thyroid hormone metabolism in male rat pups. *Toxicol. Sci.* 107:27–39

180. Rice DC, Reeve EA, Herlihy A, Zoeller RT, Thompson WD, Markowski VP. 2007. Developmental delays and locomotor activity in the C57BL6/J mouse following neonatal exposure to the fully-brominated PBDE, decabromodiphenyl ether. *Neurotoxicol. Teratol.* 29:511–20
181. Kodavanti PR, Coburn CG, Moser VC, MacPhail RC, Fenton SE, et al. 2010. Developmental exposure to a commercial PBDE mixture, DE-71: neurobehavioral, hormonal, and reproductive effects. *Toxicol. Sci.* 116:297–312
182. Fujimoto H, Woo GH, Inoue K, Takahashi M, Hirose M, et al. 2011. Impaired oligodendroglial development by decabromodiphenyl ether in rat offspring after maternal exposure from mid-gestation through lactation. *Reprod. Toxicol.* 31:86–94
183. Lin SM, Chen FA, Huang YF, Hsing LL, Chen LL, et al. 2011. Negative associations between PBDE levels and thyroid hormones in cord blood. *Int. J. Hyg. Environ. Health* 214:115–20
184. Vuong AM, Braun JM, Webster GM, Zoeller RT, Hoofnagle AN, et al. 2018. Polybrominated diphenyl ether (PBDE) exposures and thyroid hormones in children at age 3 years. *Environ. Int.* 117:339–47
185. He P, Wang A, Niu Q, Guo L, Xia T, Chen X. 2011. Toxic effect of PBDE-47 on thyroid development, learning, and memory, and the interaction between PBDE-47 and PCB153 that enhances toxicity in rats. *Toxicol. Ind. Health* 27:279–88
186. Kim TH, Lee YJ, Lee E, Kim MS, Kwack SJ, et al. 2009. Effects of gestational exposure to decabromodiphenyl ether on reproductive parameters, thyroid hormone levels, and neuronal development in Sprague-Dawley rats offspring. *J. Toxicol. Environ. Health A* 72:1296–303
187. Chevrier J, Harley KG, Bradman A, Sjodin A, Eskenazi B. 2011. Prenatal exposure to polybrominated diphenyl ether flame retardants and neonatal thyroid-stimulating hormone levels in the CHAMACOS study. *Am. J. Epidemiol.* 174:1166–74
188. Bernal J. 2005. Thyroid hormones and brain development. *Vitam. Horm.* 71:95–122
189. Alm H, Kultima K, Scholz B, Nilsson A, Andren PE, et al. 2008. Exposure to brominated flame retardant PBDE-99 affects cytoskeletal protein expression in the neonatal mouse cerebral cortex. *Neurotoxicology* 29:628–37
190. Viberg H, Eriksson P. 2011. Differences in neonatal neurotoxicity of brominated flame retardants, PBDE 99 and TBBPA, in mice. *Toxicology* 289:59–65
191. Viberg H. 2003. Neonatal exposure to polybrominated diphenyl ether (PBDE 153) disrupts spontaneous behaviour, impairs learning and memory, and decreases hippocampal cholinergic receptors in adult mice. *Toxicol. Appl. Pharmacol.* 192:95–106
192. Hallgren S, Fredriksson A, Viberg H. 2015. More signs of neurotoxicity of surfactants and flame retardants—neonatal PFOS and PBDE 99 cause transcriptional alterations in cholinergic genes in the mouse CNS. *Environ. Toxicol. Pharmacol.* 40:409–16
193. Sun W, Du L, Tang W, Kuang L, Du P, et al. 2017. PBDE-209 exposure damages learning and memory ability in rats potentially through increased autophagy and apoptosis in the hippocampus neuron. *Environ. Toxicol. Pharmacol.* 50:151–58
194. Cheng J, Gu J, Ma J, Chen X, Zhang M, Wang W. 2009. Neurobehavioural effects, redox responses and tissue distribution in rat offspring developmental exposure to BDE-99. *Chemosphere* 75:963–68
195. Johansson N, Viberg H, Fredriksson A, Eriksson P. 2008. Neonatal exposure to deca-brominated diphenyl ether (PBDE 209) causes dose-response changes in spontaneous behaviour and cholinergic susceptibility in adult mice. *Neurotoxicology* 29:911–19
196. Haave M, Folven KI, Carroll T, Glover C, Heegaard E, et al. 2011. Cerebral gene expression and neurobehavioural development after perinatal exposure to an environmentally relevant polybrominated diphenylether (BDE47). *Cell Biol. Toxicol.* 27:343–61
197. Faass O, Ceccatelli R, Schlumpf M, Lichtensteiger W. 2013. Developmental effects of perinatal exposure to PBDE and PCB on gene expression in sexually dimorphic rat brain regions and female sexual behavior. *Gen. Comp. Endocrinol.* 188:232–41
198. Lilienthal H, Hack A, Roth-Harer A, Grande SW, Talsness CE. 2006. Effects of developmental exposure to 2,2,4,4,5-pentabromodiphenyl ether (PBDE-99) on sex steroids, sexual development, and sexually dimorphic behavior in rats. *Environ. Health Perspect.* 114:194–201

199. Kuriyama SN, Talsness CE, Grote K, Chahoud I. 2005. Developmental exposure to low dose PBDE 99: effects on male fertility and neurobehavior in rat offspring. *Environ. Health Perspect.* 113:149–54
200. Llansola M, Erceg S, Monfort P, Montoliu C, Felipo V. 2007. Prenatal exposure to polybrominated diphenylether 99 enhances the function of the glutamate-nitric oxide-cGMP pathway in brain in vivo and in cultured neurons. *Eur. J. Neurosci.* 25:373–79
201. Xing T, Chen L, Tao Y, Wang M, Chen J, Ruan DY. 2009. Effects of decabrominated diphenyl ether (PBDE 209) exposure at different developmental periods on synaptic plasticity in the dentate gyrus of adult rats in vivo. *Toxicol. Sci.* 110:401–10
202. Donauer S, Chen A, Xu Y, Calafat AM, Sjodin A, Yolton K. 2015. Prenatal exposure to polybrominated diphenyl ethers and polyfluoroalkyl chemicals and infant neurobehavior. *J. Pediatr.* 166:736–42
203. Vuong AM, Yolton K, Webster GM, Sjodin A, Calafat AM, et al. 2016. Prenatal polybrominated diphenyl ether and perfluoroalkyl substance exposures and executive function in school-age children. *Environ. Res.* 147:556–64
204. Zhang H, Yolton K, Webster GM, Sjodin A, Calafat AM, et al. 2017. Prenatal PBDE and PCB exposures and reading, cognition, and externalizing behavior in children. *Environ. Health Perspect.* 125:746–52
205. Vuong AM, Yolton K, Poston KL, Xie C, Webster GM, et al. 2017. Prenatal and postnatal polybrominated diphenyl ether (PBDE) exposure and measures of inattention and impulsivity in children. *Neurotoxicol. Teratol.* 64:20–28
206. Vuong AM, Braun JM, Yolton K, Xie C, Webster GM, et al. 2017. Prenatal and postnatal polybrominated diphenyl ether exposure and visual spatial abilities in children. *Environ. Res.* 153:83–92
207. Ding G, Yu J, Cui C, Chen L, Gao Y, et al. 2015. Association between prenatal exposure to polybrominated diphenyl ethers and young children's neurodevelopment in China. *Environ. Res.* 142:104–11
208. Gascon M, Fort M, Martinez D, Carsin AE, Forns J, et al. 2012. Polybrominated diphenyl ethers (PBDEs) in breast milk and neuropsychological development in infants. *Environ. Health Perspect.* 120:1760–65
209. Eskenazi B, Chevrier J, Rauch SA, Kogut K, Harley KG, et al. 2013. In utero and childhood polybrominated diphenyl ether (PBDE) exposures and neurodevelopment in the CHAMACOS study. *Environ. Health Perspect.* 121:257–62
210. Sagiv SK, Kogut K, Gaspar FW, Gunier RB, Harley KG, et al. 2015. Prenatal and childhood polybrominated diphenyl ether (PBDE) exposure and attention and executive function at 9–12 years of age. *Neurotoxicol. Teratol.* 52:151–61
211. Herbstman JB, Sjodin A, Kurzon M, Lederman SA, Jones RS, et al. 2010. Prenatal exposure to PBDEs and neurodevelopment. *Environ. Health Perspect.* 118:712–19
212. Cowell WJ, Lederman SA, Sjodin A, Jones R, Wang S, et al. 2015. Prenatal exposure to polybrominated diphenyl ethers and child attention problems at 3–7 years. *Neurotoxicol. Teratol.* 52:143–50
213. Cowell WJ, Margolis A, Rauh VA, Sjodin A, Jones R, et al. 2018. Associations between prenatal and childhood PBDE exposure and early adolescent visual, verbal and working memory. *Environ. Int.* 118:9–16
214. Branchi I, Alleva E, Costa LG. 2002. Effects of perinatal exposure to a polybrominated diphenyl ether (PBDE 99) on mouse neurobehavioural development. *Neurotoxicology* 23:375–84
215. Lein ES, Hawrylycz MJ, Ao N, Ayres M, Bensinger A, et al. 2006. Genome-wide atlas of gene expression in the adult mouse brain. *Nature* 445:168–76