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Thyroid-disrupting chemicals and brain development: an update

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Abstract

This review covers recent findings on the main categories of thyroid hormone–disrupting chemicals and their effects on brain development. We draw mostly on epidemiological and experimental data published in the last decade. For each chemical class considered, we deal with not only the thyroid hormone–disrupting effects but also briefly mention the main mechanisms by which the same chemicals could modify estrogen and/or androgen signalling, thereby exacerbating adverse effects on endocrine-dependent developmental programmes. Further, we emphasize recent data showing how maternal thyroid hormone signalling during early pregnancy affects not only offspring IQ, but also neurodevelopmental disease risk. These recent findings add to established knowledge on the crucial importance of iodine and thyroid hormone for optimal brain development. We propose that prenatal exposure to mixtures of thyroid hormone–disrupting chemicals provides a plausible biological mechanism contributing to current increases in the incidence of neurodevelopmental disease and IQ loss.

Key Words

- thyroid
- endocrine disruptors
- neuroendocrinology

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Introduction

Thyroid hormone (TH) is essential for normal brain development where it influences, during specific temporal windows, neurogenesis, neuronal migration, neuronal and glial cell differentiation, myelination and synaptogenesis. These TH-dependent processes are crucial during early gestation and postnatal development, and then continue, albeit at reduced rates, throughout adulthood. During the first 10–12 weeks of gestation, the foetus relies entirely on maternal TH. Hence, severe maternal TH deficiency adversely affects offspring neurodevelopment (1, 2). Recent epidemiological evidence suggests that even more moderate forms of maternal thyroid dysfunction may affect child cognitive development and increase the risk of neurodevelopmental disorders (3, 4, 5, 6). Therefore, it is important to gain a better understanding of early thyroid dysfunction on offspring neurodevelopment (1, 7).

Another major cause of thyroid dysfunction can be the presence of thyroid hormone-disrupting chemicals in the maternal and fetal environment. Endocrine-disrupting compounds (EDCs) are xenobiotics that modulate hormonal homeostasis thereby inducing adverse effects (8). Numerous EDCs identified to date contain a halogen group substitution with chlorine and bromine. Interestingly, THs are the only complex halogenated (iodine) molecules produced by and necessary for vertebrate homeostasis, making TH physiology highly vulnerable to EDCs. Halogen-substituted phenolic moieties can mimic natural THs and thereby interact with multiple aspects of hormone production, feedback, distribution, entry into cells, intracellular metabolism (deiodination, conjugation) of THs, as well as at the level of receptors, as antagonists or analogues.

The aim of this review is to provide an update on how different chemicals in the environment can disrupt thyroid signalling and thereby affect brain development. A number of previous reviews have addressed certain

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aspects of this question. Notably, in 1998, Brucker-Davis and colleagues (9) reviewed the different classes of chemicals that could affect thyroid signalling and Zoeller and Crofton (10) underlined how endocrine disruption affected early brain development. A decade later the situation was updated by Crofton (11) and by Boas and colleagues (12).

No new major classes of TH-disrupting chemicals have been characterised since the last review appeared. However, within classes certain novel compounds have attracted attention. Most often these new compounds have been introduced to replace a similar chemical for which adverse effects were reported. This has led to many examples of 'regrettable substitutions' within classes, cases of which are described below. Thus, our focus remains on perchlorate, phenols, pesticides, polychlorinated biphenyls (PCBs), poly brominated flame retardants, perfluorinated compounds (PFCs) and phthalates (Fig. 1). Many of these substances are classed as persistent organic pollutants (POPs) and were banned decades ago yet they remain environmentally relevant due to their previous high production volumes and exceptionally long half-lives.

Perchlorate

Perchlorate is a well-characterised inhibitor of the sodium-iodide symporter (NIS) that is expressed in the basal membrane of thyroid follicular cells and is critical for iodide uptake (13). Two other NIS inhibitor classes, nitrates and thiocyanates, are found at significant levels in human fluids, but in molar terms, they are respectively 240 and 15 times less active than perchlorate (14). However, their environmental levels are such that their combined effects should be more often taken into account (15, 16).

Given first, its wide-ranging uses as an oxidant in products ranging from in rocket fuel to airbags and second, its high stability, perchlorate contamination is widespread. Epidemiological data show that despite its short half-life (<8 h in humans), continual exposure means that the chemical is virtually ubiquitous in the US population (17). Epidemiological evidence showed that perchlorate levels were associated with TSH in women, and this association was stronger in women with <100 µg/L urinary iodine (18). The relationship was even greater in women who smoke, related to the fact that cigarette smoke is a source of thiocyanate.

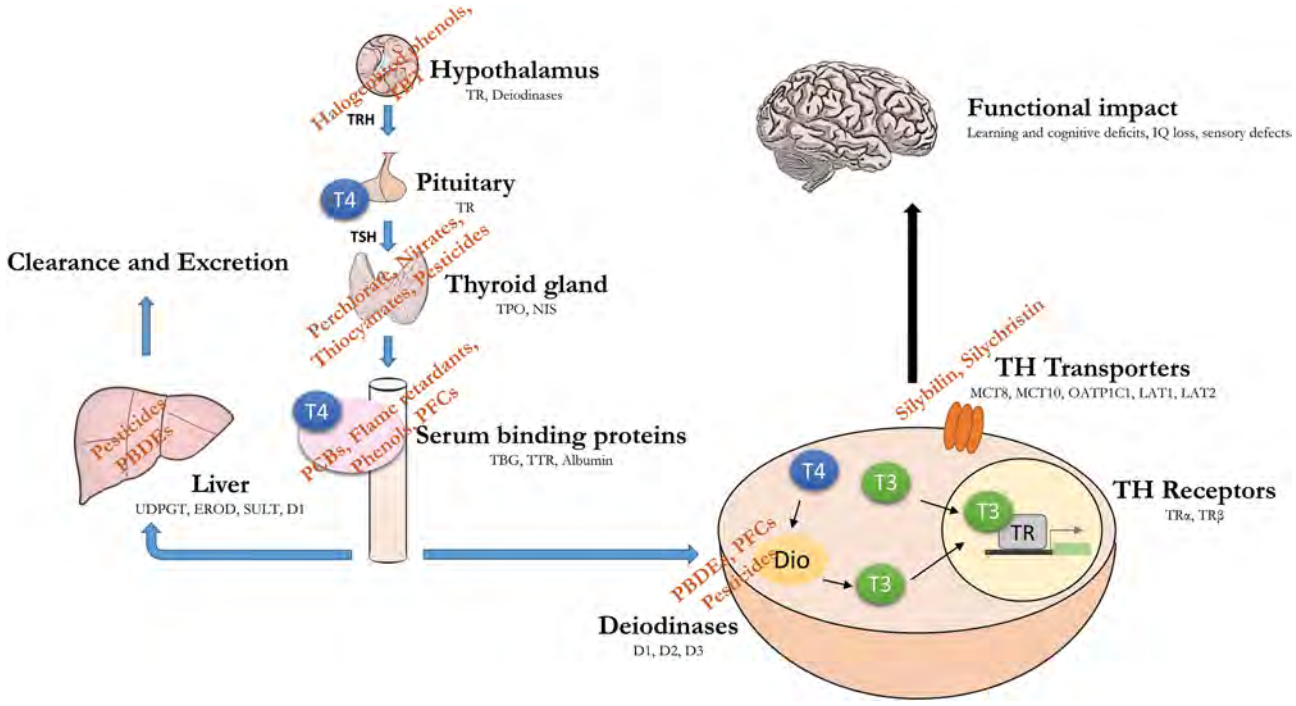

Figure 1
Endocrine-disrupting chemicals (EDCs) act at multiple levels of the hypothalamus–pituitary–thyroid (HPT) axis. Environmental chemicals have the potential to disrupt the HPT axis, alone or in combination. Given the crucial role for thyroid hormone in brain development, such disruption can have a long-lasting functional impact, such as IQ loss and increased risk of neurodevelopmental disease (note: targets not drawn to scale).

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Furthermore, recent epidemiological data analysed pregnant women for their thyroid status and perchlorate levels (19). Offspring born to those women that were both borderline hypothyroid and hypothyroxinemic and had higher perchlorate levels had a higher risk of being in the lowest 10% for IQ scores. The adverse effect of perchlorate was not modified by thyroxine therapy (150 µg/day) during pregnancy. However, it is possible that the timing of replacement (after 12 weeks pregnancy) was too late to exert corrective effects. Other recent data also link maternal perchlorate exposure to modified thyroid function during pregnancy (20). Iodine has long been known to be required for TH synthesis and both iodine deficiency and maternal hypothyroidism are risk factors for decreased IQ and neurodevelopmental disease (21, 22). It is worth noting that in the study cited (20), a large proportion of the women (74%) had urinary iodine levels below the recommended median level (150 µg/L) for pregnancy, raising the question of whether iodine deficiency exacerbates the effects of perchlorate (and potentially other TH-disrupting chemicals). This question deserves far more research and needs to be taken into account in both epidemiological and experimental studies. Similarly, the presence of TH-disrupting chemicals has been identified as a confounder for epidemiological studies assessing effects of iodine supplementation during pregnancy (23).

Phenols

Two principal phenols are well-characterised TH disruptors, bisphenol A (BPA) and triclosan (TCS). Both have high production volumes and been so extensively used that they are now virtually ubiquitous contaminants of human fluids (24) and the environment (25).

Bisphenol A (BPA, 4,4′ isopropylidenediphenol)

BPA is an organic synthetic compound, first identified as a synthetic estrogen in 1930s (26). Current common uses of BPA are in plastic products such as water bottles and food containers, CDs, DVDs, safety equipment, thermal paper and medical devices. In the United States, France and Denmark, BPA is restricted for certain uses, such as baby bottles. More recently, since 2015, France banned the use of BPA in plastic food containers. The same year (2015), EFSA maintained their opinion delivered in 2013 that BPA poses no health risks, but the committee lowered the tolerable daily intake from 50 µg/kg bw/day to 4 µg/kg bw/day (27). Despite these recent restrictions, there is still widespread exposure to BPA in human populations (28). It is retained in humans and has been found in pregnant women's serum, placenta and breast milk (29, 30, 31, 32, 33, 34). As restrictions were increasingly placed on BPA use, a number of structural BPA analogues such as bisphenol S (BPS), bisphenol F (BPF) and bisphenol B (BPB) were marketed. These analogues are found now in considerable quantities in human urine (35, 36, 37, 38). These replacement chemicals are often described as 'regrettable substitutions' as their EDC-related effects are apparently no less than those of BPA, including effects on TH signalling (39, 40) and estrogen receptor (ER) signalling (41).

As BPA is primarily thought of as an estrogen disruptor but is also a TH modulator. EDC action across endocrine systems is to be expected as crosstalk exists at multiple levels: from different nuclear receptors (42) to individual target genes and networks to physiological systems. As BPA can interact with multiple nuclear hormone receptors including ER (43), estrogen-related receptors (ERR) (44), AR (45, 46) and thyroid hormone receptors (TR) (39, 47, 48), potential crosstalk needs to be considered at multiple levels.

BPA and ER interaction has been reviewed extensively elsewhere, for both classical and non-classical estrogen receptors (8, 49). As to TRs, some experimental studies show that BPA does not bind to TR based on a competitive TR-binding test (50, 51, 52), others show T_3-TR-mediated agonistic and antagonistic effects of BPA (48, 53, 54). More recently, binding affinities of BPA and its analogues BPF and BPS, with TR were calculated *in silico* and found to be roughly similar (55). When tested by a spectrum of *in vitro* and *in vivo* methods, all three analogues activated TH signalling in the absence of T_3 (39). The *in vitro* approaches included competitive binding assays, molecular docking and coactivator-binding assays, whereas the *in vivo* methodology exploited TH-response gene responses in *Pelophylax nigromaculatus* tadpoles.

In human epidemiology, studies have reported changes in TH parameters as a function of BPA exposure in adults (56, 57, 58, 59), including in pregnant women (60, 61, 62). In pregnant women, maternal BPA levels were inversely (62) or positively (60) associated with T_4 levels while two studies reported no association (61, 63). In humans, inverse associations of BPA with TSH have also been reported in both sexes (60) and in other cases, only in women (61). Yet another study reported a positive association (64). Such inconsistencies need to be examined notably for methodological differences between studies.

We now focus specifically on BPA and TH and neurodevelopment. Increased prenatal BPA exposure is implicated in several sex-specific changes in child behaviour (65, 66, 67, 68, 69, 70). Prenatal BPA exposure is linked to increased internalizing behaviours in boys (66, 67, 70) and increased risk of ADHD-related behaviour (65). In girls, prenatal BPA exposure has been associated with both internalising and externalising behaviours (66, 69), as well as poor executive function (68). It is possible that differences in the results are due to varying timing of sample collection, exposure and assessment among the studies. Studies on postnatal childhood BPA exposure and effects on neurodevelopment are even more inconsistent. Some studies report a positive association of BPA levels with ADHD-linked behaviours in both girls and boys (71), and anxious, depressive or aggressive behaviours in girls (66, 67, 72). Others report null association with childhood BPA exposure and neurodevelopmental outcomes (68, 73). Pubertal BPA exposure has also been associated with poorer cognitive performance in adolescence (74) and adulthood (75).

The lack of full endocrine profiles in these epidemiological studies makes it hard to pinpoint the exact mechanism linking endocrine disruption and neurodevelopmental outcome. Animal studies however can better define mode of action. Such studies link BPA levels with behavioural outcomes often associated with TH disruption including, hyperactivity (not sex specific) (76, 77), anxiety (78) and decreased motor activity (79). Prenatal BPA exposure in mice also results in mostly sex-specific changes in aggression and cognitive defects (80, 81, 82, 83, 84, 85). These sex-specific changes are not surprising due to the role of estrogen in differentiation of sexually dimorphic areas involved in behaviour and cognitive development (86). BPA exposure also causes epigenetic changes (methylation) on the *ER-α* gene in the cortex and hypothalamus of male and female mice and alters mRNA levels of DNA methyltransferases *DNMT1* and *DNMT3A* (78, 87). Interestingly, *DNMT3A* is a well-known TH-responsive gene, activated by liganded TRs (88, 89).

Halogenated BPAs include a bromine (Tetrabromobisphenol A, TBBPA) or chlorine (Tetrachlorobisphenol-A, TCBPA) substitute on the phenolic ring and are common flame retardants. TBBPA is currently the flame retardant with the highest production volume worldwide. It is found in printed electronic circuit boards and in plastics for electrical housings or piping. Due to its high production volume, toxicological effects attributed to TBBPA have been extensively reviewed by governments (90, 91, 92) and deemed to have no health hazard, risk or concerns to humans. However, Van der Ven and colleagues (93) assessing multiple *in vivo* studies on rats concluded that the margin of exposure for humans was only 2.6 and that TBBPA exposure was a matter of concern for authorities.

What is more, TBBPA has been established *in vitro* as neurotoxicant that disrupts multiple intracellular pathways including zinc and calcium homeostasis, inducing oxidative stress (94, 95, 96, 97) as well as acting as a partial $GABA_A$ agonist at 0.1 µM (98). So far, results for *in vivo* developmental toxicity are less consistent. The conclusions of Van der Ven *et al*. (93) for instance contrast with those of certain toxicologists (99, 100). Although Viberg and Eriksson (2011) reported more marked effects for PBDE 99 than TBBPA in neonatal mouse brain, they observed downregulation of a certain classes of nicotinic receptors in the frontal cortex with both chemicals (101). In our laboratory, studies on mice showed that gestational exposure to TBBPA decreased TRH receptor and melanocortin 4 receptor basal expression in pups, dramatically affecting T_3-induced repression of these genes (102).

Some studies have reported neural defects, including impaired motor function in zebrafish (103). Similarly, Nakajima and colleagues reported behavioural effects of TBBPA administration in adult mice and differential accumulation of the chemical according to brain region (104). Further, Lilienthal *et al*. noted increased latency of hearing responses in a rat one generation study (105). Interestingly, development of the inner ear is known to be a TH-dependent process (106).

Significant reduction in circulating T_4 is the most frequent phenotype seen across rodent studies as a function of TBBPA exposure (93, 107). T_4 reductions could occur through activation of UDP-glucuronosyltransferase, UGT, which increases metabolism of T_4 in the liver and subsequent reduction of serum T_4 levels (108). *In vitro*, TBBPA competes with binding of transthyretin (TTR) and interferes with T_3-dependent cell proliferation (109). In a fluorescent polarization assay, TBBPA was found to modulate both coactivator and co-repressor interactions with TR (110). TBBPA also shows TH-disrupting effects in amphibian models. In *Rana rugosa*, TBBPA displayed inhibitory effects on T_3-induced tail shortening (111) and in *Xenopus laevis*, TBBPA exerted antagonistic effects in the presence of high TH levels, but agonistic activity with low TH levels (112). TBBPA has also been demonstrated as a TH disruptor using both the amphibian metamorphosis assay (112, 113) and the *Xenopus* embryonic thyroid assay

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(XETA) (114). In the latter study, TBBPA was further found to alter expression of TH target genes implicated in neural stem cell function and differentiation. Whether such effects extend to other proliferative brain regions during development remains to be investigated (115).

In rats, TBBPA exposure increases estrogen levels (108) and uterine tumours (116), effects thought to be related to inhibition of liver estradiol sulfotransferase (109). The combined effects of TBBPA, increasing estrogen and antagonising TH signalling could well interact to modify genetic and cellular responses, as well as inducing longer-term adverse physiological responses governing reproduction.

Triclosan (TCS, 2,4,4-trichloro-hydroxy diphenyl ether)

Triclosan (TCS) is a widely used chlorinated phenolic antimicrobial and antifungal agent. It has been used for over 40 years as an antiseptic, disinfectant or preservative in medical and personal care products such as hand soaps and shampoos, mouthwash, toothpaste and cosmetics. While it has been banned from soaps and body washes in the United States, it is still extensively used in skin care products and toothpaste. TCS has a short half-life in humans, that is it is rapidly absorbed, metabolized and eliminated (primarily via urine) with a median excretion half-life of 11 h after oral intake (117). Despite this rapid clearance, the over use of products containing TCS maintain permanent, but varying exposure. The most likely sources in humans are ingestion and skin absorption. TCS has been found in the majority of urine samples obtained via population-based studies in North America (118, 119). TCS has also been detected in human milk and pregnant women's urine (120, 121, 122). EU has restricted TCS use as a preservative to a maximum concentration of 0.2% in mouthwashes and 0.3% in other categories (123). In the environment, TCS likely accumulates in sediments as it is a lipophilic compound with low aqueous solubility and is commonly found contaminant in solid and water compartments (124, 125).

Several animal studies have confirmed TCS to act as a TH-disruptive chemical. In pregnant rats, TCS decreases serum T_3 and T_4, disrupts pup sex ratio balance and lowers their body weights (126, 127, 128). TH disruption is also evident during weaning rats when their mothers are exposed to triclosan (126, 127). In mice, decreased levels of T_4 are also observed after a short-term oral exposure to triclosan (129, 130, 131). In amphibian models, the North American bullfrog (*Rana catesbeiana*) and *Xenopus laevis*, TCS exposure results in the disruption of TH-dependent metamorphosis, marked metabolic disorders of the liver and modulation of innate immunity (132, 133, 134).

In addition to TH, numerous studies report adverse effects of TCS exposure on reproductive organ development in male rats i.e., decreased testosterone and sperm production (135), and early age of pubertal onset in female mice (136). *In vitro* assays have confirmed TCS to act as an estrogen agonist using ERα and ERβ reporter gene assays (137, 138, 139) stimulate breast and ovarian cancer cell growth *in vitro* (140, 141) and magnifying the effects of ethinyl estradiol (136, 142). In rodent models, TCS, like TBBA (see above) inhibits estrogen sulfation by inhibiting sulfotransferases, thus preventing metabolism of estradiol into biologically inactive forms (143, 144, 145) thereby increasing circulating estrogen levels (143). Similar effects are seen in sheep (144). It is worth noting that these same sulfotransferases metabolise TH as well.

Epidemiological studies have investigated the short-term and long-term effect of TCS and TH parameters, with inconsistent findings (56, 146, 147, 148, 149, 150). Many report no significant disruptions in TH levels while some report only most marked effects (149, 151). Among the effects, some observe a positive association between TCS and total T_3 (149) in adolescents, while others report an inverse association between TCS and fT_3 (151) levels in pregnant women. A prospective study on prenatal TCS exposure recently reported reduced head circumference in boys but not girls (152).

Flavonoids

Flavonoids are phenols that occur as natural food items. Recent work identified the plant extract (*Silybum*) silymarin, and its derivatives silychristin and silybilin, as inhibitors of the membrane TH transporter, mct8 (*slc16a2*). Entry of both T_3 and T_4 into target cells is reduced (153). This feature highlights the possible, and little studied, effects of compounds that interact with membrane TH transporters.

Pesticides

Pesticide usage increased dramatically over the last century, arguably to keep up with the demands of a

growing population. However, many studies have shown that pesticide usage is excessive and that yields can be maintained even when halving pesticide use (154). Many pesticides exert toxicological effects, including on thyroid signalling. Notably, the European Food Safety Authority reported that of 287 pesticide files examined, 101 showed effects indicative of thyroid disruption (155). Even though many incriminated pesticides have now been banned, many of them are still in use in emerging economies. Further, many of these chemicals are persistent due to their long half-lives and remain in the environment long after their ban. Such pesticides are called legacy pesticides, with many being common environmental contaminants. Here, we choose a few examples of this latter category and some others that currently on the market, but are potentially problematic.

Dichlorodiphenyltrichloroethane (DDT)

Dichlorodiphenyltrichloroethane (DDT) is an organochlorine insecticide, first used in World War I to control malaria and typhus. Its initial notoriety arose due to widespread effects on wildlife described by Rachel Carlson in her 1962 book *Silent Spring* (156), notoriety that led to its ban in the United States by 1972 and worldwide by the Stockholm Convention on POPs later that decade. Despite the ban, it is still used in certain countries to fight against malaria and dengue fever (157). DDT, and its main metabolite dichlorodiphenyltrichloroethylene (DDE), are highly persistent, lipophilic compounds that bio-accumulate and are still found in significant amounts in the environment and in humans, including in pregnant women (158, 159, 160). Prenatal exposure to p,p′-DDT and p,p′-DDE has been associated with obesity (161, 162) and a significant reduction in children's psychomotor neurodevelopment (162, 163, 164, 165, 166, 167, 168), in some cases, in a sex-specific manner (162, 169, 170). The latter is not surprising as DDT binds to and activates ERs in both reproductive and other tissues including the brain (171, 172). On the other hand, DDE has been shown to inhibit androgens from binding to their receptors (173, 174). In adolescent boys, DDE is associated with increased testosterone (175) and decreased luteinizing hormone (176) while DDT is associated with decreases in both luteinizing hormone and testosterone (176). In women, *in utero* exposure to DDT, as judged by umbilical cord levels, has been associated with an increased risk of breast cancer later in life (177).

DDT and its metabolites have also been confirmed as TH-disrupting chemicals through human epidemiological studies (158, 178, 179, 180, 181). Studies have found negative association with DDE and total T_3 and T_4 levels (182, 183) and a positive association with TSH levels (183); suggesting an anti-thyroid effect. In contrast, recent studies found a positive association of DDE with total T_3 and T_4 levels, and a non-significant TSH reduction in floriculture workers (158, 179). These differences could be due to different levels of exposure and/or exposure to additional chemicals and characteristics of the populations studied, such as iodine or thyroid status and genetic factors.

In experimental studies, rats exposed to DDE exposure exhibit lower free T_4 levels. One target of DDT action on thyroid metabolism may be through the inhibition of TSH-stimulated intracellular accumulation of cyclic adenosine monophosphate (cAMP) by the action of DDT on the TSH receptor (184, 185, 186, 187). The highly lipophilic DDT may also interfere indirectly with the TSH receptor by altering the phosphor-lipid composition of the thyroid cell membrane, rendering the TSH receptor unable to internalise and instead be released extracellularly in vesicle forms in the presence of DDT (188). These vesicles have been suggested to initiate autoimmunity favouring the development of Graves' disease (184). Mice exposed to DDE also exhibit reduced expression of TTR and *Dio2* mRNA, which further explains the reduced free T_4 levels observed (189, 190). Increased expression of several hepatic enzymes can further contribute to TH degradation (190). Another study in mice reported that DDT exposure was associated with increased peripheral conversion of T_4 into T_3, reduced TSH levels and morphological changes in the thyroid gland typical of iodine deficiency (191).

Hexachlorobenzene (HCB)

Hexachlorobenzene (HCB) is an organochloride, used primarily as a fungicide for seeds and as a wood-preserving agent. It was banned globally in 1979 under the Stockholm Convention on POPs as a pesticide. Its current main source is through the industrial emission as a by-product of the manufacture of chlorinated solvents and pesticides. It is extremely lipophilic and accumulates in the environment. It gained prominence during late 1950s when accidentally over-treated HCB-treated seeds were consumed by the general public in Turkey. Affected individuals, primarily children, displayed changed porphyrin metabolism, leading to *porphyria cutanea tarda*, enlarged liver and thyroid gland and osteoporosis (192, 193). Similar effects have been observed in HCB-exposed rats (194) i.e. hepatic and thyroid neoplasms (195, 196, 197), porphyria (193, 198). Other epidemiological studies

have found associations between lower levels of HCB and decreased gestational length (199), poor social competence (200) and increased body weight during childhood (201). Studies on floriculture workers have further revealed an association between HCB with decreased levels of total T_4 (TT_4) (202) and TT_3 (203). In animal studies, HCB is known to disrupt progesterone and estradiol concentrations (204, 205, 206), impair reproductive efficiency (207, 208) and reduce neonatal viability and growth (209). It also disrupts levels of T_3 and T_4 (210, 211), leads to goitre (212) and hypothyroidism (213). Disruption of the TH axis may partly be due to HCB's action on the activity and expression of hepatic Dio1 and Dio2 enzymes, respectively (214). In rats, HCB has been shown to induce apoptosis in the thyroid cells, most likely due to action on mitochondria through oxidative stress (215, 216). There is also evidence that HCB may competitively inhibit binding of thyroxine to serum carrier proteins (214, 215). More investigations are required to elucidate the exact mechanisms of HCB on TH signalling.

Chlorpyrifos (CPF, O,O-diethyl O-(3,5,6-trichloro-2-pyridinyl) ester phosphorothioic acid)

Chlorpyrifos is a member of the organophosphate class of insecticides that target the central and peripheral nervous system specifically inhibiting the enzyme activity of acetylcholinesterase (217). It is currently one of the most widely used insecticides in the United States and other countries, to manage insect pests on agricultural crop. CPF applications were once particularly heavy in urban areas, where the exposed populations included pregnant women (218, 219). Interestingly, its ban in household use in 2001 allowed for a natural experiment within an ongoing birth cohort study at Columbia University. Before the ban, decreases in birth weight and length were observed in association with CPF in newborn cord blood. After the ban, these outcomes disappeared (220). This result has been observed more recently (221), a result that is not surprising as CPF readily crosses the placenta (222). Further studies have reported prenatal CPF exposure association with impaired cognition and motor function (223), attention-deficit hyperactive disorder (224), deficits in working memory and reduced IQ (225) and tremors during childhood (226). While some groups have considered that the levels of CPF in cord blood are too low to induce adverse effects (227, 228), one needs to take into account that the half-life of CPF is approximatively 27 h (229). Thus, the possibility of substantially higher *in utero* levels of CPF is considerable. Despite these studies and its recent thorough evaluation by the World Health Organization (WHO) and Danish Environmental Protection Agency finding, toxicological evidence to be strong and the epidemiological evidence to be of moderate-to-high quality, the EPA denied a recent petition for ban calling it 'crucial to U.S. agriculture' (230). Not surprisingly, given the well-demonstrated epidemiological data showing negative effects on brain development, this decision has been severely criticised (231).

Given the importance of TH to brain development, the neurological and impaired cognitive outcomes associated with CPF exposure could well have underlying thyroid hormone-dependent mechanisms. Two studies based on analysis of NHANES data from the years 1999–2002 describe significant associations between levels of chlorpyrifos metabolite, 3,5,6-trichloro-2-pyridinol (TCPY) and thyroid parameters, namely increased TT_4 in both males and females and decreased TSH levels in males, with increased TSH levels in females (232, 233).

In rat studies, a reduction in brain T_4 levels is seen following prenatal CPF exposure whereas postnatal exposure results in a transient elevation in young adulthood (234). Mice exposed to low-dose CPF display reduced serum T_4 levels and display altered thyroid follicular size, with an apparent higher vulnerability in males (235) and anxiety-like behaviour (236). Reduction of T_4 in response to CPF has also been observed in rats (237), whereas exposure to CPF's methyl counterpart (chlorpyrifos-methyl) results in reduced T_4 and increased TSH (hypothyroidism) (238). In our lab, CPF was shown to affect TH signalling using a transgenic reporter. Moreover, a short embryonic exposure impacts mature brain structure (Spirhanzlova P, Leemans M, Sébastien LE, Mughal BB, Wejaphikul K, Fini J-B, Visser T & Demeneix BA, unpublished observations).

As to the effects on ER and AR signalling, CPF has been found to interfere with the ERβ mRNA steady state level (239, 240) and exert an ERα-dependent estrogenic effect on cell proliferation *in vitro* (241) and *in vivo* (242). CPF also has anti-androgenic activity as Leydig cells from the rat exposed to CPF *in vitro* exhibit a significant decrease in testosterone biosynthesis (243). More epidemiological and experimental data are urgently needed as this pesticide is being assessed for renewal in the EU from 2019.

Other pesticides

As previously stated, more than a 100 of the 287 pesticides examined by European Food Safety Authority (EFSA) had features indicative of thyroid disruption (155).

In the recent review of chemicals that could be used as reference for thyroid disruption screening, Wegner and colleagues identified a number of phytopharmaceuticals or biocides with TH-disrupting activity (244). To cite a few, their list contained different classes of fungicides and organophosphates, along with a number of juvenile hormone analogues. Among the fungicides, figure the ethylene bisdithiocarbamates (EBDC) e.g. maneb, mancozeb, ziram, zineb. Their common degradation product, ethylene thiourea (ETU), in addition to being a type IIB carcinogen, interferes with iodide organification by inhibiting thyroid peroxidase (TPO) (245) thereby decreasing thyroidal production of T_3 and T_4 in experimental animals (246, 247). In addition, the animals exhibit increased thyroid/body weight ratio, histopathological changes and reduced serum protein-bound iodine (246). Recent epidemiological data further underlines the importance of iodine status and the effect of ETU on thyroid function (248). Another class of fungicides with TH-disrupting activity are the azoles. This class of fungicide can enhance TH hepatic metabolism through the induction of enzymes uridine diphosphate-glucuronosyl-transferase (UDPGT), thereby increasing biliary elimination of T_3 and T_4 (249). Reduction of TH level varies considerably depending on the class of azoles (250).

The organophosphate insecticide malathion is an acetylcholinesterase inhibitor, similar to CPF, widely used in North American agriculture and residential landscapes, and in public health pest control programmes such as residential mosquito eradication. It has also been characterised as an inhibitor of teleost TPO (251) and TTR (252, 253). Other authors have documented increased levels of T_3 and reduced T_4 as a function of malathion exposure (254, 255). As it is currently an approved insecticide in North America and Europe, it is important to note that it has been associated with a strongly increased risk of thyroid cancer in spouses of pesticide applicators (256).

Pyrethroids are synthetic organic insecticides similar to the natural pyrethrins produced by the flowers of chrysanthemums. Due to their high lipophilicity and persistence, they are prone to bioaccumulation. Further, toxicological studies have demonstrated their potential to disrupt the endocrine system and exert developmental toxicity (257). Permethrin (PM), one of the most heavily used synthetic pyrethroids, exerts estrogenic effect in zebrafish (258) while other pyrethroids have been demonstrated as interfering with TRs (259), TTR binding (260) and Dio1 inhibition (261, 262). Several rat studies also suggest that pyrethroid insecticides alter serum TH levels, mostly increasing total T_3 levels (255, 263, 264, 265).

Finally, a pyridine-based juvenile hormone analogue pesticide, Pyriproxyfen, has been suggested as a TH-active substance (244). This and other findings led us and colleagues to suspect it could be implicated in the increased incidence of Zika-induced microcephaly in north eastern Brazil (266), especially given its use at high levels in drinking water during the outbreak (266).

Polychlorinated biphenyls (PCBs)

PCBs are a class of organic man-made chemicals that were mass produced globally since the 1920s, until their commercial production ban in the United States in 1979. They were widely used as plasticizers, in hydraulic fluids, heat transfer fluids, lubricants and electrical equipment like capacitors and transformers. A total of 209 possible congeners exists, classed according to the number and position of chlorine atoms carried. PCBs can also be metabolized by hydroxylation to OH-PCBs. Due to their high chemical stability, PCBs do not readily break down and are still found in significant quantities throughout the environment and human fluids (267). PCBs and their metabolites are known to efficiently transfer from maternal to foetal blood via the placenta (268, 269) and to nursing children via milk (270, 271). Prenatal PCB exposure in human has been associated with increased risk of a number of TH-related disorders including, high BMI (272), IQ loss (273, 274, 275), cognitive defects (23, 273, 276, 277, 278), reduced visual recognition memory (274), attention and motor deficits (276, 279, 280, 281), increased risk of autism (282, 283) and ADHD (273, 284, 285). In PCB-exposed adults, an increased risk of cardiovascular disease has been reported (286), as has a slightly increased risk of thyroid autoimmunity in men (287, 288).

Due to their physiochemical properties, PCBs have long been suspected to act as TH and other steroidal hormone analogues (2, 289). Numerous publications covering both epidemiological and experimental studies have confirmed the association of hydroxylated and non-hydroxylated PCBs with decreased TH levels, T_4 (290, 291, 292) and T_3 (292, 293, 294, 295). In fact, serum hypothyroxinemia is the most frequently reported adverse health effect in human populations exposed to PCBs due to displacement of T_4 from TTR and subsequent increase of metabolism (296). PCBs in cord blood have also been linked with low thyroid-binding globulin (TBG) (293) and high TSH levels (297, 298). In contrast to the latter study, a recent analysis of

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three cohorts revealed slightly lower levels of TSH with PCB-153 exposure (299).

In experimental studies, PCB and their metabolites demonstrate a clear association with reduced TH levels in animal models (300, 301, 302) and induce long-term effects on behaviour and neurodevelopment (303, 304). More recent studies have highlighted other possible mechanisms of PCB action on additional TH axis components. TTR disruption may play a role in distribution of hydroxylated PCBs to the placenta and the brain as PCB metabolites are known competitors for TTR's T_4-binding pocket (296, 305). PCB exposure suppresses NIS expression (301) through the Akt/FoxO3a/NIS pathway (306, 307). NIS suppression may also be due to inflammation by PCB exposure. The PCB-induced AhR/JNK pathway stimulates the production of cytokines and thereby suppresses NIS expression (308). Hydroxylated PCBs may also inhibit SULT-catalysed THs sulfation (309). A more recent study on infants found further an association between PCBs in maternal blood with high T_3 and low rT_3 in cord serum indicating possible action on deiodinases (310). Finally, iodine status can have a major impact on the effect of PCB exposure (23). A pilot study found that PCB exposure lessens the benefits of iodine supplementation during pregnancy in a borderline iodine-deficient group and higher PCB levels have a negative impact on the neurocognitive development of the offspring.

The importance of other endocrine systems especially the sex hormones must not be overlooked as many sexually dimorphic changes due to gestational PCB exposure have been reported. Gestationally PCB-exposed females pups display increased birth weight, higher locomotor behaviours, higher corticosterone concentrations while the males display increased anogenital distances (311, 312). Certain PCB metabolites have been shown to interact with the ERs acting either as agonists or antagonists (313, 314). On the other hand, one PCB metabolite (PCB104) exhibits both, AR antagonistic and ER agonist properties (315). PCBs may also induce estrogenicity indirectly through inhibition of the estrogen sulfotransferase (316).

Polybrominated flame retardants

PBDEs are widely used flame retardants being used in furniture, carpets, automobiles, electrical appliances and flame-retardant fabrics. PBDEs are lipophilic in nature and as they are not chemically bound to the substrate, they easily accumulate in the environment. High levels are found in diverse situations from house dust (317) to river sediments (318). There are 209 congeners of PBDEs, due to the different possible bromine substitutions on the biphenyl backbone. Similar to PCBs, hydroxylated PBDEs (OH-PBDEs) add to the complexity of chemical interactions and stability. Production and usage of the less brominated PBDEs were banned in Europe in 2004, and more recently extended to BDE-209 (or deca-BDE). As BDE-209, is the most highly brominated compound (10 bromines), it is easily broken down into less brominated congeners (318). However, general levels of PBDE are increasing despite the ban (see for instance: (319)). In the United States, despite similar restrictions and phase out of deca-PBDE at the end of 2013 (except for certain uses) the entire population have detectable levels of at least one PBDE congener in their blood (320).

As PBDEs are persistent, PBDE congeners are still found in significant amounts in the placenta (321), fetal blood (322), and breast milk (323). Early exposure of PBDEs has also been associated with decreased IQ, diminished language and reading abilities, increased problems with hyperactivity and attention, and poorer executive function in children (324, 325, 326, 327, 328, 329, 330, 331, 332). Among these, two studies further observed sex-specific differences. Vuong *et al.* reported significantly poorer executive function among boys with higher concurrent BDE-153 and no associations in girls, while Sagiv *et al.*, observed poorer executive function in girls with higher 4 PBDE (BDE-47, -99, -100, -153) concentrations, but not in boys (327, 333). These sex-specific differences need to be investigated further as other studies have revealed no statistically significant sex interactions (328, 329).

The biological mechanism for sex differences in PBDE exposure-related neurotoxicity remains unknown. These behavioural changes are not surprising as PBDEs are well known to pass the blood–brain barrier, accumulate in the central nervous system and induce developmental neurotoxicity (334). Neonatal rodents exposed to PBDEs exhibit behavioural changes (335, 336, 337, 338), with reduced hippocampal long-term potentiation, modified intracellular calcium homeostasis (339), oxidative stress (340) and reduced postsynaptic protein levels in the hippocampus (341). Poorer attention and executive function suggests that PBDEs may also target the prefrontal cortex region of the brain (342, 343).

The precise mechanism of PBDE action at a molecular level, still remains to be elucidated. Clearly, one plausible action of PBDEs is through its disruption of TH availability. Several epidemiological studies have reported increased TSH levels, lower total T_4 and, in some studies greater

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free T_3 levels in humans, including children (295, 344, 345, 346, 347, 348, 349). These TH parameters are not always consistent and the differences in findings may be due to the median levels of PBDEs as demonstrated by a meta-analysis (350). High levels of PBDEs were positively correlated with TSH/T_4 levels while low PBDE levels were negatively associated. Decreased levels of T_4 are, however, the most consistently observed adverse effect observed in populations, as a function of PBDE exposure. Decreased circulating TH levels have also been observed in experimental studies on rodents, fish and birds after exposure to perinatal PBDE (340, 351, 352, 353, 354). Further, PBDE congeners have been tested for their agonist and antagonist properties against TRs. Using a reporter gene assay, PBDE congeners, including hydroxylated compounds, inhibited TR-mediated transcription at varying concentrations (355, 356, 357, 358, 359). The antagonist action of PBDEs on TR is further evident through its effect on purkinje cell dendrite arborisation and neural progenitor cell differentiation into the oligodendrocyte lineage (360, 361). In contrast, several hydroxylated PBDEs have been reported to act as agonists on TH-dependent transcription (355). Recently, using zebrafish knock down model of TRβ, the developmental toxicity of PBDE was demonstrated (362).

Several hydroxylated PBDE congeners have been shown to bind to and alter T_4 binding to the two TH distributor proteins, TBG and TTR (363, 364). The displacement of T_4 from TTR and TBG, may lead to its increased glucuronidation, followed by decrease in circulating T_4 and hence higher TSH. PBDEs and hydroxylated metabolites alter DIO2 activity in different astrocyte cell lines (365). BDE-99 decreased DIO2 activity by up to 80% while 3-OH-BDE-47, 6-OH-BDE-47, and 5-OH-BDE-99 also decreased DIO2 activity by 45–80%. Multiple mechanisms appear to contribute to the decreased DIO2 activity, including weakened expression of *DIO2* mRNA, competitive inhibition of DIO2, and enhanced post-translational degradation of DIO2. As astrocytes produce more than 50% of T_3 used by the brain, Roberts *et al*. propose that PBDE exposure could compromise T_3 delivery to the brain (365). A possible mechanism for this effect has been investigated *in silico* and thought to be halogen bonding of PBDEs to the active site selenocysteine (366). Studies have also found upregulation of *Dio1* and *Dio3*, i.e. inducing local hyperthyroidism, in the periventricular zone of the brain, suggesting another, as yet under-estimated, mechanism impacting neurodevelopment. (367, 368).

Phthalates

Phthalates or phthalate esters are esters of phthalic acid and mainly used as plasticizers and softeners in various commercial products such as furniture, cosmetics, food packaging, and medical equipment such as catheters and perfusion bags/drips. Phthalates are also one of the most volatile EDCs and can be found at high concentrations in enclosed spaces where air conditioning is used, such as in vehicles (369). One of the most widely used phthalates is di-(2-ethylhexyl) phthalate (DEHP), used as a plasticizer in PVC recycling, but not manufacturing. This phthalate used in soft medical devices and toys was of major concern due to its high migration rate (370) and to the vulnerable population in contact with the compound. Consequently production was banned and manufacturing ceased by BASF in 2002. Other notable common phthalates are dibutyl phthalate (DBP) and its metabolite monobutyl phthalate (MBP), mono-(2-ethylhexyl) phthalate (MEHP), monoethyl phthalate (MEP), benzylbutylphthalate (BBP), diisodecyl phthalate (DIDP), and diisononyl phthalate (DINP). Alternatives to phthalate such as hexamoll Dinch are now being used in medical devices. A transgenerational study carried out by BASF in 2005, unpublished but described in EFSA 2006 (371) and NICNAS 2012 (372) reports, showed significant hepatic effects and thyroid hyperplasia induced by Dinch (372).

Phthalates do not bio-accumulate in the environment but since they are ubiquitous in our daily life, the potential of consequences of continuous exposure has raised concerns. Current EU legislation focuses on levels in children's toys. Some phthalates (DEHP, BBP and DBP) cannot be used in toys and childcare products. Other phthalates (DINP and DIDP) are banned only from toys that could be potentially placed in mouth. Urinary levels of phthalates serve as a good biomarker and high exposure levels have been found in the general public, including pregnant women (373, 374, 375, 376, 377).

In humans, DEHP and its metabolites measured in maternal urine have been associated with adverse neurodevelopment and behaviour in offspring (378, 379, 380, 381, 382). Interestingly, the phthalate metabolites, MEHHP, MEOHP and MBP were associated with both mental and behaviour defects in male but not female infants of 6 months (378). Prenatal exposure to phthalates has also been associated with 'reduced masculine play' among boys of 3- to 6-year (383). In contrast, Téllez-Rojo *et al*. reported lower scores on the mental developmental index (Bayley's test) in females but not males at 2–3 years

(380). These sex-specific differences seem to attenuate with age (7–9 age) (384). More studies are needed to determine if gender differences are found as a function of phthalate exposure in older children. While these previous studies have focused on cognitive and behavioural defects during early years, other studies have found association between phthalates and more severe neurodevelopmental defects during school ages such a reduced IQ (385) and attention-deficit disorder (ADD) (386).

As for a number of pesticides, these negative effects on brain development can be linked to changes in TH levels. In pregnant women, urinary MBP, MEP and MEHP have been associated with low serum T_4 and fT_4 during the second trimester (387, 388, 389, 390, 391, 392). These inverse relationships between MEHP and DEHP and T_4 levels have been reported in the adult population including men (59, 393). In children, there are varying reports of levels of phthalates and its effect on TH levels. Some report inverse relations between the two (388, 394), others a positive relation (59), and one that relied on a relatively small cohort found none at all (395). This highlights the importance of study design, age group, sample size, and exposure profiles when studying non-persistent chemicals.

Since DBP down-regulates the human NIS promoter (396), modulating the transcriptional activity of NIS may be one of the underlying causes of thyroid hyperactivity and decreased circulating T_4 concentrations. DBP also appears to act as a thyroid antagonist when assessed through reporter gene assays (397). Zebrafish and male rats exposed to varying concentrations for MEHP and DEHP respectively demonstrate similar low levels of whole body T_4 levels (398, 399). It is interesting to note that in 2017, ECHA classified DPB, DEHP, BBP and DIBP as substances of high concern due to their endocrine-disrupting properties.

Perfluorinated compounds

Perfluorinated chemicals (PFCs) are widely used in the manufacture of fabrics, carpets, surfactants, emulsifiers, Teflon, lubricants, cosmetics, and fire-fighting foams. They are commonly used as surfactants due to their fully fluorinated linear carbon chain attached to a hydrophilic head. Surfactants are compounds that lower the surface tension between two liquids or between a liquid and a solid and therefore are used in detergents, wetting agents, emulsifiers, foaming agents, and dispersants. They are also highly stable and therefore extremely persistent in the environment including both wildlife and human populations (400). Between the years 2000 and 2002, the main producers discontinued production of certain PFCs, including perfluorohexane sulfonate (PFHxS), perfluorooctanoate (PFOA) and perfluorooctane sulfonate (PFOS). Following its discontinuation, a significant decrease in the serum levels of PFOA and PFOS were observed (401, 402, 403). However, another factor that needs to be taken into consideration is their relatively long half-life in humans being approximately 3.8 years for PFOA, 5.4 years for PFOS, and 8.5 years for PFHxS (404). Despite the ban, they are still found in significant levels in drinking water. A 2016 study covering 2/3 of drinking water supplies in the United States found unsafe levels of PFCs at the minimum reporting levels required by the EPA (405). PFOS has been banned in the EU since 2008 but there are no restrictions on PFOA and PFHxS. In the USA, the EPA launched a voluntary campaign in which the companies committed to reduce global facility emissions and product content of PFOA and related chemicals by 2015. The last update for this reduction was in 2013/2014.

Several animals studies have shown low-dose exposure of PFCs during neonatal development results in irreversible neurotoxic effects and alterations in spontaneous behaviour, habituation capability, learning and memory (assessed at 4 months) (406, 407). PFCs were also shown to alter the levels of synaptophysin and tau proteins in the cerebral cortex and hippocampus. Both proteins are important for the formation and growth of dopaminergic synapses and alterations in the dopamine transporters and receptors are one of the underlying causes of behavioural defects such as ADHD (408, 409). Several cross-sectional studies have investigated the potential association between PFC levels in school-age children and ADHD (410, 411). Hoffman *et al.* (410) reported a positive association between levels of PFOS, PFOA and PFHxS with ADHD symptoms while Stein and Savitz (411) reported an association with only PFHxS. High impulsivity has also been reported in children with high PFC levels (412) and high levels of PFOS exposure during pregnancy have been associated with delayed motor development in the first two years of life (413, 414). TH dysfunction is a well-established risk for ADHD (5, 415, 416, 417, 418).

PFC exposure and TH disruption have also been reported in adults. A large study of employees in a PFC manufacturer revealed negative associations between PFOA and free T_4 levels (419). In the US, women with high levels of PFOA and men with high levels of PFOS are also at increased risk of thyroid diseases (420). Low levels of T_4 as a function of PFC exposure have also been confirmed

in several animal models. A single dose of PFOS in adult rats resulted in an initial increased fT_4 and decreased TSH levels, followed by decrease in total T_4 and T_3 levels (421). In other adult rat studies, PFOA exposure resulted in decreased T_4 levels (422, 423). Perinatal exposure to PFOS also results in decreased levels of T_4 in both the mother and the offspring (424, 425, 426, 427). A test of twenty-four PFCs revealed competitive binding of most PFCs to TTR (428) which in turn can explain the dysfunctional levels of T_4 observed in humans and animal models. Of the 24 PFCs, PFHxS displayed the highest competitive binding followed by PFOA and PFOS equally. PFOS has also been shown to decrease hepatic *Dio1* mRNA while increasing thyroidal *Dio1* mRNA (429). Whether this is a direct effect on *Dio1* transcription or a response to levels of T_4, is not yet clear.

Conclusion

The above review covers the main categories of chemicals that affect thyroid signalling. However, we have not reported environmental and human levels of exposure for each chemical class or effects of mixtures. There are wide variations in exposure to individual chemical exposure due to geographical location and legislation of the country of residence. Moreover, as we are exposed to multiple chemicals at a given time, it is increasingly important to address the effect of chemicals as a mixture, since synergistic effects of chemical mixtures without individual effects have been reported (430, 431). Our laboratory has shown that exposure to mixtures of common chemicals found in human amniotic fluid, alter TH signalling, brain structure and behaviour (432, 433). Together, these findings highlight the current impact of EDC exposure on neurodevelopment and argue for rapid public health intervention.

Declaration of interest

B B M and J B F have nothing to disclose. B D is a cofounder of WatchFrog.

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