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Environmental Chemicals Impacting the Thyroid: Targets and Consequences

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Thyroid hormone (TH) is essential for normal brain development, but the specific actions of TH differ across developmental time and brain region. These actions of TH are mediated largely by a combination of thyroid hormone receptor (TR) isoforms that exhibit specific temporal and spatial patterns of expression during animal and human brain development. In addition, TR action is influenced by different cofactors, proteins that directly link the TR protein to functional changes in gene expression. Considering the importance of TH signaling in development, it is important to consider environmental chemicals that may interfere with this signaling. Recent research indicates that environmental chemicals can interfere with thyroid function and with TH signaling. The key issues are to understand the mechanism by which these chemicals act and the dose at which they act, and whether adaptive responses intrinsic to the thyroid system can ameliorate potential adverse consequences (i.e., compensate). In addition, several recent studies show that TRs may be unintended targets of chemicals manufactured for industrial purposes to which humans and wildlife are routinely exposed. Polychlorinated biphenyls, polybrominated diphenyl ethers, bisphenol-A, and specific halogenated derivatives and metabolites of these compounds have been shown to bind to TRs and perhaps have selective effects on TR functions. A number of common chemicals, including polybrominated biphenyls and phthalates, may also exert such effects. When we consider the importance of TH in brain development, it will be important to pursue the possibilities that these chemicals—or interactions among chemical classes—are affecting children's health by influencing TH signaling in the developing brain.

Introduction

Thyroid hormone (TH) is essential for normal brain development in both humans and animals (1), but the mechanisms by which TH exerts its actions are only partly understood (2). Likewise, the influence of environmental factors, such as iodine availability, is well recognized (3), but our ability to identify environmental factors that exert direct effects on TH action during brain development may be limited by the complexity of TH receptor (TR) function during brain development and potential selective impacts of environmental factors impacting TR function. The goal of this review is to briefly place new information about the effects of environmental contaminants on TR function within the context of TH action during brain development (Fig. 1).

Mechanisms by Which Chemicals May Interfere with Thyroid Function

All chemicals currently classified as thyroid toxicants have been defined by their ability to reduce circulating levels of TH (4). Thus, these chemicals alter the relationship between TH biosynthesis and elimination, such that the steady-state levels of hormones are reduced. The modes of action by which these chemicals can influence circulating levels of TH are directed at TH biosynthesis or at TH metabolism (Table 1).

Changes in Serum Hormone Levels

Changes in serum concentrations of THs [thyroxine (T4), triiodothyronine (T3), and thyroid-stimulating hormone (TSH)] can be caused by chemicals that inhibit TH synthesis, release, and serum transport, and by chemicals that increase metabolism of various THs [e.g., deiodinases, uridine diphosphate glucuronyltransferase (UDPGTs)]. If a chemical decreases serum hormone concentrations, specific assays can be used to determine the mechanism by which these hormone concentrations are decreased. Moreover, the specific profile of changes in hormone concentrations may be informative. For example, mice carrying targeted deletions of type 2 deiodinase have elevated circulating levels of both T4 and TSH with no change in serum T3 (5). In contrast, mice carrying a targeted

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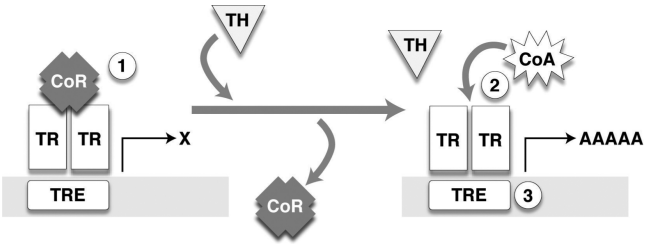

FIG. 1. The current theory of thyroid hormone (TH) action on the thyroid hormone receptor (TR) allows us to predict sites at which environmental chemicals may interfere with TH action. (**1**) Chemicals may bind to the TR and directly activate or inhibit the action of endogenous T3. This action may occur by influencing the interaction of TRs with various cofactors such as N-CoR or SRC-1. (**2**) In addition, environmental chemicals may cause the TR to exhibit a different affinity for the TRE. (**3**) These effects may well be dependent upon the specific TR isoform (TRα or TRβ isoforms), the specific TRE or contextual sequences of specific TREs, and/or the specific cofactors available in the cell. It seems predictable that these chemicals will not produce patterns of effects or disease that simply mimic TH insufficiency or excess, and thus may easily be misinterpreted both in experimental animals and in humans.

deletion of the type 1 deiodinase have elevated circulating levels of T4 and reverse T3 (rT3), but no change in serum T3 or TSH (6). Iodine deficiency can result in a reduction in serum T4 with no change or even an increase in serum T3 (7). Chemicals that inhibit thyroid peroxidase activity can produce a "stereotypical" hormone profile with decreased levels of serum T4 and T3 and an increase in serum TSH (8,9). Finally, a targeted deletion of the T3 transporter MCT8 can produce elevated levels of T3 (10). Therefore, it is possible that environmental factors interfering with the hypothalamic-pituitary-thyroid (HPT) axis at specific points of regulation may produce a hormonal profile that is indicative of the mechanism of action.

The mechanisms by which environmental chemicals can alter circulating levels of TH are many (4). Halogenated aryl hydrocarbons can induce the expression of UDPGT enzymes in the liver by activation of either the aryl hydrocarbon receptor (11) or Pregnane X receptor (PXR)/Constitutive Androstane receptor (CAR) (12,13). In addition, hydroxylated compounds [e.g., polychlorinated biphenyls (PCBs)] can displace T4 from the serum-binding protein transthyretin (14–16). Thus, environmental contaminants may exert actions at a number of sites of regulation to cause a reduction in circulating levels of THs.

Table 1. Examples of Chemicals That Can Interfere with the Thyroid System

Inhibit iodide uptake	ClO_4, ClO_3, NO_3, thiocyanate
Inhibit TPO activity	PTU, methimazole, isoflavones
Inhibit deiodinase	PCBs, iapanoic acid, thiouracils
Displace T4 from TTR	Hydroxylated PCBs, PBDEs
Activate liver UDPGTs	AhR agonists, agonists of PXR/CAR
Direct action on TR	PCBs, PBDEs(?), BPA, triclosan

Chemicals That Interfere with TRs: PCBs

Several authors speculated early that environmental chemicals may act as imperfect TH analogs (17,18). Now, several recent reports show that a broad range of chemicals to which humans are routinely and inadvertently exposed can bind to TRs and may produce complex effects on TH signaling. Perhaps the best example is that of PCBs—industrial chemicals consisting of paired phenyl rings with various degrees of chlorination (19). Although the production of PCBs was banned in the mid 1970s, these contaminants are routinely detected in the environment (20) and in human tissues (21) at high concentrations. Of particular concern is the observation that PCBs become concentrated in fatty tissues such as brain. For example, a recent study by Lackmann *et al.* (22) has found that 6-week-old breast-fed infants had serum PCB levels of 1.19 μg/L, which was significantly higher than the 0.29 μg/L found in serum of bottle-fed infants. Kalantzi *et al.* (23) reported that in the United Kingdom, total PCB levels in breast milk ranged from 26 to 530 ng/g lipid, translating to a daily infant intake of 6.24–2067 ng/kg. Thus, when we consider the importance of TH signaling in the neonate [e.g., (24–26)], the relatively high exposure to PCBs during lactation suggests that early postnatal development may be particularly vulnerable to thyroid disruption by PCBs.

Epidemiological studies have indicated that developmental exposure to PCBs is associated with neuropsychological deficits, such as a lower full-scale IQ, reduced visual recognition memory, attention deficits, and motor deficits (27–32). Recently, Stewart *et al.* (33) have reported a negative association between PCB body burden and response inhibition in 3-year-old children, and a negative association between PCB body burden and size of the corpus callosum (splenium). In addition, the association between PCB body burden and response inhibition was stronger in those children with the smallest splenium. This association was retained at 9 years of age (34). Several investigators have speculated that PCBs may impact brain development by interfering with TH signaling (35–37). This concept was derived, in part, from the apparent structural similarity between PCBs and TH (17). Several studies have shown that PCBs, or specific PCB congeners, in maternal and cord blood, are associated with lower TH levels in both the mother and infant (38,39). For example, Wang *et al.* (40) have recently shown that PCB levels in cord blood are negatively associated with free T4 and with the product of free T4$\times$TSH (as a measure of impacts on the negative feedback system).

Although several studies have failed to identify an association between PCB body burden and thyroid function (41–45), experimental studies uniformly find that PCB exposure decreases circulating levels of T4 in rats (46–48), and some authors propose that PCBs exert neurotoxic effects on the developing brain by causing a state of relative hypothyroidism (49–51). This concept is supported by the experimental observations that the ototoxic effect of PCB exposure can be partially ameliorated by T4 replacement (52); that the cerebellum, a tissue highly sensitive to TH insufficiency (53–55), is targeted by PCB exposure; and that the effect of PCBs on ovarian development can be partially ameliorated by T4 administration (56). PCB exposure also alters motor behavior associated with cerebellar function (57,58), as well as cerebellar anatomy (58). Interestingly, PCB exposure is associated

with an increase in expression of glial fibrillary acidic protein (58), which is also increased by TH insufficiency (59).

However, experimental studies do not provide uniform support for the hypothesis that PCB exposure injures brain development by causing a relative state of TH insufficiency. For example, PCB exposure causes a severe reduction in circulating levels of T4, but PCB-exposed pups do not exhibit reduced body weight or body weight gain (60–62); they exhibit elevated levels of expression of several TH-responsive genes in the brain (60,63), and they do not exhibit elevated serum TSH levels (64). These observations are consistent with the hypothesis that at least some individual PCB congeners, or their metabolites, can act as TR agonists (or possibly antagonists) *in vivo*. Recently, Kitamura *et al.* (65) have reported that nine separate hydroxylated PCB congeners can bind to the rat TR with a "half-maximal binding" as low as 5 μM. In addition, using a human neuroprogenitor cell line, Fritsche *et al.* (66) found that a specific PCB congener could mimic the ability of T3 to enhance oligodendrocyte differentiation and that this effect was blocked by the selective TR antagonist NH3. Finally, Arulmozhiraja and Morita (67) have identified several PCB congeners that exhibit weak TH activity in an yeast-two hybrid assay optimized to identify such activity.

Not all reports indicate that PCBs act as agonists on the TR. Kimura-Kuroda *et al.* (68) reported that two separate hydroxylated PCBs interfere with T3-dependent neurite outgrowth in mouse cerebellar granule cell primary cultures. In addition, Bogazzi *et al.* (69) found that a commercial mixture of PCBs (Aroclor 1254) exhibited specific binding to the rat TRβ at approximately 10 μM. This concentration inhibited TR action on the malic enzyme promoter in a chloramphenicol acetyl transferase (CAT) assay, and this effect required an intact thyroid hormone response element (TRE). However, the PCB mixture did not alter the ability of TR to bind to the malic enzyme TRE in a gel shift assay. In contrast, Iwasaki *et al.* (70) found that a specific hydroxylated PCB congener inhibits TR-mediated transcriptional activation in a luciferase assay at concentrations as low as 10^{-10} M. This effect was observed in several cell lines, but was not observed using a glucocorticoid response element. Miyazaki *et al.* (71) followed this report by showing that PCBs can dissociate TR:RXR heterodimers from a TRE. Thus, some PCB congeners may be agonists, while others are antagonists. Or perhaps more likely, individual PCB congeners may be mixed agonists/antagonists—their specific actions depending on the conditions of the assay used to study it.

Bisphenol-A

Bisphenol-A (BPA, 4,4′-isopropylidenediphenol) is produced at a rate of over 800 million kg annually in the United States alone (72), and is used primarily in the manufacture of plastics, including polycarbonate plastics, epoxy resins that coat food cans, and in dental sealants (73,74). Howe *et al.* (73) estimated human consumption of BPA from epoxy-lined food cans alone to be about 6.6 μg/(person day). BPA has been reported in concentrations of 1–10 ng/mL in serum of pregnant women, in the amniotic fluid of their fetus, and in cord serum taken at birth (75,76). Moreover, BPA concentrations of up to 100 ng/g were reported in placenta (75). BPA is also halogenated (brominated or chlorinated) to produce flame retardants. Tetrabromobisphenol-A (TBBPA) is the most commonly used, with over 60,000 tons produced annually (77,78). Thomsen *et al.* (79) have recently reported that brominated flame retardants, including TBBPA, increased in human serum from 1977 to 1999 with concentrations in adults ranging from 0.4 to 3.3 ng/g serum lipids. However, infants (0–4 years) exhibited serum concentrations that ranged from 1.6 to 3.5 times higher (79).

When we consider this pattern of human exposure, it is potentially important that BPA has been shown to bind to the TR (80). Best characterized as a weak estrogen (81), binding to the estrogen receptor with a K_i of approximately 10^{-5} M (82,83), BPA binds to and antagonizes T3 activation of the TR (84,85) with a K_i of approximately 10^{-4} M, but as little as 10^{-6} M BPA significantly inhibits TR-mediated gene activation (85). Moreover, Moriyama *et al.* (80) found that BPA reduced T3-mediated gene expression in culture by enhancing the interaction with the corepressor N-CoR. Interestingly, we have found that developmental exposure to BPA in rats produces an endocrine profile similar to that observed in thyroid resistance syndrome (86). Specifically, T4 levels were elevated during development in the pups of BPA-treated animals, but TSH levels were not different from controls (87). This profile is consistent with BPA inhibition of TRβ-mediated negative feedback. However, the TH-response gene RC3 was elevated in the dentate gyrus of these BPA-treated animals (87). Because the TRα isoform is expressed in the dentate gyrus, we concluded that BPA may be a selective TRβ antagonist *in vivo*.

If BPA acts as a TR antagonist *in vivo*, it is predictable that specific developmental events and behaviors would be affected by developmental exposure to BPA. In this regard, Seiwa *et al.* (88) have shown that BPA blocks T3-induced oligodendrocyte development from precursor cells (OPCs). In addition, there may be an association between the thyroid resistance syndrome and attention-deficit hyperactivity disorder (ADHD) in humans (89–91) and in rats (89); therefore, it is potentially important that BPA-exposed rats exhibit ADHD-like symptoms (92). In addition, BPA exposure alters neocortical histogenesis in the mouse (93). Although no specific link was made to TH action in this study, it is possible that BPA alters early development of the cortex by interfering with TH signaling.

Despite the antagonistic effects of BPA on the TRβ, halogenated BPAs appear to act as TR agonists (84). Both TBBPA and tetrachlorobisphenol A can bind to the TR and induce GH3 cell proliferation and growth hormone production (84). Thus, these compounds may exert agonistic effects on the TR and this could be important during early brain development. For example, TH of maternal origin can regulate gene expression in the fetal brain (94–96); one of these genes codes for Hes1 (63). Considering the role of HES proteins in fate specification in the early cortex (97–99), the observation that industrial chemicals can activate the TR and increase HES expression (63) may indicate that these chemicals can exert subtle effects on early differentiative events.

Emerging chemicals

Polybrominated diphenyl ethers (PBDEs) are used as flame retardants and are becoming common contaminants in human tissues (100–104). A few studies have focused on their

ability to influence thyroid function (105–109), but this has not included an evaluation of their ability to interact directly with the TR. Another common compound with a structure similar to PBDEs, triclosan, has also been shown to interfere directly with TR function in frog metamorphosis (110). Triclosan is a hydroxylated, polychloro-diphenyl ether used as an antibacterial agent in hand soaps and creams, and has been identified as a contaminant in human blood (111).

Conclusion

The human population is exposed to a large number of specific polyhalogenated aromatic hydrocarbons, and biomonitoring studies now detect these chemicals in adults, children, pregnant women, and in the fetal compartment (112). Increasing numbers of reports are revealing that a broad array of compounds can bind to the TR and affect TH-regulated gene expression, both *in vivo* and *in vitro*. However, considering the tremendously pleiotropic effects of TH, it is predictable that these synthetic compounds may have very complex effects on the TR. In addition, these studies suggest that chemicals may interact with other important TH-binding proteins, such as deiodinase enzymes, which appear to control the sensitivity of different brain regions to TH exposure during development (113). Therefore, if exogenous chemicals alter the activity of these enzymes, it may influence the sequence of TH-sensitive developmental events. Likewise, specific transporters appear to control the availability of T3 to cells in the brain (114,115); thus, if environmental chemicals interfere with tissue uptake of TH, adverse human health effects could result. Our ability to identify chemical effects on TR function *in vitro* far exceeds our ability to identify chemical effects on TR function *in vivo*, in part because the mechanisms of TH action in the developing brain are less well understood. However, it will be important to define the role of TH in brain development and to identify the mechanisms by which TH exerts these actions if we are to understand the potential human health effects of persistent exposure to these bioaccumulative compounds.

References

1. Dussault JH, Ruel J 1987 Thyroid hormones and brain development. Annu Rev Physiol **49:**321–334.
2. Bernal J, Guadano-Ferraz A, Morte B 2003 Perspectives in the study of thyroid hormone action on brain development and function. Thyroid **13:**1005–1012.
3. Gaitan E, ed. 1989 Environmental Goitrogenesis. CRC Press, Inc., Boca Raton.
4. Brucker-Davis F 1998 Effects of environmental synthetic chemicals on thyroid function. Thyroid **8:**827–856.
5. Schneider MJ, Fiering SN, Pallud SE, Parlow AF, St Germain DL, Galton VA 2001 Targeted disruption of the type 2 selenodeiodinase gene (DIO2) results in a phenotype of pituitary resistance to T4. Mol Endocrinol **15:**2137–2148.
6. Schneider MJ, Fiering SN, Thai B, Wu SY, St Germain E, Parlow AF, St Germain DL, Galton VA 2006 Targeted disruption of the type 1 selenodeiodinase gene (Dio1) results in marked changes in thyroid hormone economy in mice. Endocrinology **147:**580–589.
7. Pedraza PE, Obregon MJ, Escobar-Morreale HF, Escobar Del Rey F, de Escobar GM 2006 Mechanisms of adaptation to iodine deficiency in rats: thyroid status is tissue specific. Its relevance for man. Endocrinology **147:**2098–2108.
8. Cooper DS, Kieffer JD, Halpern R, Saxe V, Mover H, Maloof F, Ridgway EC 1983 Propylthiouracil (PTU) pharmacology in the rat. II. Effects of PTU on thyroid function. Endocrinology **113:**921–928.
9. Halpern R, Cooper DS, Kieffer JD, Saxe V, Mover H, Maloof F, Ridgway EC 1983 Propylthiouracil (PTU) pharmacology in the rat. I. Serum and thyroid PTU measurements by radioimmunoassay. Endocrinology **113:**915–920.
10. Dumitrescu AM, Liao XH, Weiss RE, Millen K, Refetoff S 2006 Tissue specific thyroid hormone deprivation and excess in Mct8 deficient mice. Endocrinology **147:**4036–4043.
11. Fisher JW, Campbell J, Muralidhara S, Bruckner JV, Ferguson D, Mumtaz M, Harmon B, Hedge JM, Crofton KM, Kim H, Almekinder TL 2006 Effect of PCB 126 on hepatic metabolism of thyroxine and perturbations in the hypothalamic-pituitary-thyroid axis in the rat. Toxicol Sci **90:**87–95.
12. Dixit SG, Tirona RG, Kim RB 2005 Beyond CAR and PXR. Curr Drug Metab **6:**385–397.
13. Kretschmer XC, Baldwin WS 2005 CAR and PXR: xenosensors of endocrine disrupters? Chem Biol Interact **115:** 111–128.
14. Purkey HE, Palaninathan SK, Kent KC, Smith C, Safe SH, Sacchettini JC, Kelly JW 2004 Hydroxylated polychlorinated biphenyls selectively bind transthyretin in blood and inhibit amyloidogenesis: rationalizing rodent PCB toxicity. Chem Biol **11:**1719–1728.
15. Meerts IA, Assink Y, Cenijn PH, Van Den Berg JH, Weijers BM, Bergman A, Koeman JH, Brouwer A 2002 Placental transfer of a hydroxylated polychlorinated biphenyl and effects on fetal and maternal thyroid hormone homeostasis in the rat. Toxicol Sci **68:**361–371.
16. Hallgren S, Darnerud PO 2002 Polybrominated diphenyl ethers (PBDEs), polychlorinated biphenyls (PCBs) and chlorinated paraffins (CPs) in rats-testing interactions and mechanisms for thyroid hormone effects. Toxicology **177:** 227–243.
17. McKinney JD, Waller CL 1994 Polychlorinated biphenyls as hormonally active structural analogues. Environ Health Perspect **102:**290–297.
18. McKinney JD, Waller CL 1998 Molecular determinants of hormone mimicry: halogenated aromatic hydrocarbon environmental agents. J Toxicol Environ Health B Crit Rev **1:** 27–58.
19. Chana A, Concejero MA, de Frutos M, Gonzalez MJ, Herradon B 2002 Computational studies on biphenyl derivatives. Analysis of the conformational mobility, molecular electrostatic potential, and dipole moment of chlorinated biphenyl: searching for the rationalization of the selective toxicity of polychlorinated biphenyls (PCBs). Chem Res Toxicol **15:**1514–1526.
20. Breivik K, Sweetman A, Pacyna JM, Jones KC 2002 Towards a global historical emission inventory for selected PCB congeners—a mass balance approach. 1. Global production and consumption. Sci Total Environ **290:**181–198.
21. Fisher BE 1999 Most unwanted. Environ Health Perspect **107:**A18–A23.
22. Lackmann GM, Schaller KH, Angerer J 2004 Organochlorine compounds in breast-fed vs. bottle-fed infants: preliminary results at six weeks of age. Sci Total Environ **329:**289–293.
23. Kalantzi OI, Martin FL, Thomas GO, Alcock RE, Tang HR, Drury SC, Carmichael PL, Nicholson JK, Jones KC 2004 Different levels of polybrominated diphenyl ethers (PBDEs) and chlorinated compounds in breast milk from two U.K. regions. Environ Health Perspect **112:**1085–1091.

24. Oerbeck B, Sundet K, Kase BF, Heyerdahl S 2003 Congenital hypothyroidism: influence of disease severity and L-thyroxine treatment on intellectual, motor, and school-associated outcomes in young adults. Pediatrics **112:**923–930.
25. Heyerdahl S, Oerbeck B 2003 Congenital hypothyroidism: developmental outcome in relation to levothyroxine treatment variables. Thyroid **13:**1029–1038.
26. Chan S, Rovet J 2003 Thyroid hormones in the fetal central nervous system development. Fetal Matern Med Rev **14:** 177–208.
27. Huisman M, Koopman-Esseboom C, Lanting CI, van der Paauw CG, Tuinstra LG, Fidler V, Weisglas-Kuperus N, Sauer PJ, Boersma ER, Touwen BC 1995 Neurological condition in 18-month-old children perinatally exposed to polychlorinated biphenyls and dioxins. Early Hum Dev **43:**165–176.
28. Jackson TA, Richer JK, Bain DL, Takimoto GS, Tung L, Horwitz KB 1997 The partial agonist activity of antagonist-occupied steroid receptors is controlled by a novel hinge domain-binding coactivator L7/SPA and the corepressors N-CoR or SMRT. Mol Endocrinol **11:**693–705.
29. Osius N, Karmaus W, Kruse H, Witten J 1999 Exposure to polychlorinated biphenyls and levels of thyroid hormones in children. Environ Health Perspect **107:**843–849.
30. Korrick SA, Altshul L 1998 High breast milk levels of polychlorinated biphenyls (PCBs) among four women living adjacent to a PCB-contaminated waste site. Environ Health Perspect **106:**513–518.
31. Ayotte P, Muckle G, Jacobson JL, Jacobson SW, Dewailly E 2003 Assessment of pre- and postnatal exposure to polychlorinated biphenyls: lessons from the inuit cohort study. Environ Health Perspect **111:**1253–1258.
32. Walkowiak J, Wiener JA, Fastabend A, Heinzow B, Kramer U, Schmidt E, Steingruber HJ, Wundram S, Winneke G 2001 Environmental exposure to polychlorinated biphenyls and quality of the home environment: effects on psychodevelopment in early childhood. Lancet **358:**1602–1607.
33. Stewart P, Fitzgerald S, Reihman J, Gump B, Lonky E, Darvill T, Pagano J, Hauser P 2003 Prenatal PCB exposure, the corpus callosum, and response inhibition. Environ Health Perspect **111:**1670–1677.
34. Stewart P, Reihman J, Gump B, Lonky E, Darvill T, Pagano J 2005 Response inhibition at 8 and 9 1/2 years of age in children prenatally exposed to PCBs. Neurotoxicol Teratol **27:**771–780.
35. Porterfield SP, Hendry LB 1998 Impact of PCBs on thyroid hormone directed brain development. Toxicol Ind Health **14:**103–120.
36. Porterfield SP 2000 Thyroidal dysfunction and environmental chemicals—potential impact on brain development. Environ Health Perspect **108 Suppl 3:**433–438. 438porterfield/porterfield-full.html and 438porterfield/abstract.html.
37. McKinney JD, Waller CL 1998 Molecular determinants of hormone mimicry: halogenated aromatic hydrocarbon environmental agents. J Toxicol Environ Health Part B **1:**27–58.
38. Koopman-Esseboom C, Morse DC, Weisglas-Kuperus N, Lutkeschiphost IJ, van der Paauw CB, Tuinstra LGMT, Brouwer A, Sauer PJJ 1994 Effects of dioxins and polychlorinated biphenyls on thyroid hormone status of pregnant women and their infants. Pediatr Res **36:**468–473.
39. Schantz SL, Widholm JJ, Rice DC 2003 Effects of PCB exposure on neuropsychological function in children. Environ Health Perspect **111:**357–376.
40. Wang SL, Su PH, Jong SB, Guo YL, Chou WL, Papke O 2005 In utero exposure to dioxins and polychlorinated biphenyls and its relations to thyroid function and growth hormone in newborns. Environ Health Perspect **113:**1645–1650.
41. Matsuura N, Konishi J 1990 Transient hypothyroidism in infants born to mothers with chronic thyroiditis—a nationwide study of twenty-three cases. The transient hypothyroidism study group. Endocrinol Jpn **37:**369–379.
42. Sala M, Sunyer J, Herrero C, To-Figueras J, Grimalt J 2001 Association between serum concentrations of hexachlorobenzene and polychlorobiphenyls with thyroid hormone and liver enzymes in a sample of the general population. Occup Environ Med **58:**172–177.
43. Longnecker MP, Gladen BC, Patterson DG, Jr, Rogan WJ 2000 Polychlorinated biphenyl (PCB) exposure in relation to thyroid hormone levels in neonates. Epidemiology **11:** 249–254.
44. Hagmar L, Rylander L, Dyremark E, Klasson-Wehler E, Erfurth EM 2001 Plasma concentrations of persistent organochlorines in relation to thyrotropin and thyroid hormone levels in women. Int Arch Occup Environ Health **74:** 184–188.
45. Steuerwald U, Weihe P, Jorgensen PJ, Bjerve K, Brock J, Heinzow B, Budtz-Jorgensen E, Grandjean P 2000 Maternal seafood diet, methylmercury exposure, and neonatal neurologic function. J Pediatr **136:**599–605.
46. Bastomsky CH, Murthy PVN, Banovac K 1976 Alterations in thyroxine metabolism produced by cutaneous application of microscope immersion oil: effects due to polychlorinated biphenyls. Endocrinology **98:**1309–1314.
47. Bastomsky CH 1974 Effects of a polychlorinated biphenyl mixture (Aroclor 1254) and DDT on biliary thyroxine excretion in rats. Endocrinology **95:**1150–1155.
48. Brouwer A, Morse DC, Lans MC, Schuur AG, Murk AJ, Klasson-Wehler E, Bergman A, Visser TJ 1998 Interactions of persistent environmental organohalides with the thyroid hormone system: mechanisms and possible consequences for animal and human health. Toxicol Ind Health **14:**59–84.
49. Crofton KM 2004 Developmental disruption of thyroid hormone: correlations with hearing dysfunction in rats. Risk Anal **24:**1665–1671.
50. Crofton KM, Kodavanti PR, Derr-Yellin EC, Casey AC, Kehn LS 2000 PCBs, thyroid hormones, and ototoxicity in rats: cross-fostering experiments demonstrate the impact of postnatal lactation exposure. Toxicol Sci **57:**131–140.
51. Brouwer A, Longnecker MP, Birnbaum LS, Cogliano J, Kostyniak P, Moore J, Schantz S, Winneke G 1999 Characterization of potential endocrine-related health effects at low-dose levels of exposure to PCBs. Environ Health Perspect **107 Suppl 4:**639–649.
52. Goldey ES, Crofton KM 1998 Thyroxine replacement attenuates hypothyroxinemia, hearing loss, and motor deficits following developmental exposure to Aroclor 1254 in rats. Toxicol Sci **45:**94–105.
53. Koibuchi N, Chin WW 2000 Thyroid hormone action and brain development. Trends Endocrinol Metab **11:**123–128.
54. Li GH, Post J, Koibuchi N, Sajdel-Sulkowska EM 2004 Impact of thyroid hormone deficiency on the developing CNS: cerebellar glial and neuronal protein expression in rat neonates exposed to antithyroid drug propylthiouracil. Cerebellum **3:**100–106.
55. Yousefi B, Jingu H, Ohta M, Umezu M, Koibuchi N 2005 Postnatal changes of steroid receptor coactivator-1 immunoreactivity in rat cerebellar cortex. Thyroid **15:**314–319.
56. Baldridge MG, Stahl RL, Gerstenberger SL, Tripoli V, Hutz RJ 2003 Modulation of ovarian follicle maturation in

Long-Evans rats exposed to polychlorinated biphenyls (PCBs) in-utero and lactationally. Reprod Toxicol **17:**567–573.
57. Roegge CS, Wang VC, Powers BE, Klintsova AY, Villareal S, Greenough WT, Schantz SL 2004 Motor impairment in rats exposed to PCBs and methylmercury during early development. Toxicol Sci **77:**315–324.
58. 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:**112–122.
59. Granholm AC 1985 Effects of thyroid hormone deficiency on glial constituents in developing cerebellum of the rat. Exp Brain Res **59:**451–456.
60. Zoeller RT, Dowling AL, Vas AA 2000 Developmental exposure to polychlorinated biphenyls exerts thyroid hormone-like effects on the expression of RC3/neurogranin and myelin basic protein messenger ribonucleic acids in the developing rat brain. Endocrinology **141:**181–189.
61. Gauger KJ, Kato Y, Haraguchi K, Lehmler HJ, Robertson LW, Bansal R, Zoeller RT 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:**516–523.
62. Sharlin DS, Bansal R, Zoeller RT 2006 Polychlorinated biphenyls exert selective effects on cellular composition of white matter in a manner inconsistent with thyroid hormone insufficiency. Endocrinology **147:**846–858.
63. Bansal R, You SH, Herzig CT, Zoeller RT 2005 Maternal thyroid hormone increases HES expression in the fetal rat brain: an effect mimicked by exposure to a mixture of polychlorinated biphenyls (PCBs). Brain Res Dev Brain Res **156:** 13–22.
64. Goldey ES, Kehn LS, Lau C, Rehnberg GL, Crofton KM 1995 Developmental exposure to polychlorinated biphenyls (Aroclor 1254) reduces circulating thyroid hormone concentrations and causes hearing deficits in rats. Toxicol Appl Pharmacol **135:**77–88.
65. Kitamura S, Jinno N, Suzuki T, Sugihara K, Ohta S, Kuroki H, Fujimoto N 2005 Thyroid hormone-like and estrogenic activity of hydroxylated PCBs in cell culture. Toxicology **208:**377–387.
66. Fritsche E, Cline JE, Nguyen NH, Scanlan TS, Abel J 2005 Polychlorinated biphenyls disturb differentiation of normal human neural progenitor cells: clue for involvement of thyroid hormone receptors. Environ Health Perspect **113:**871–876.
67. Arulmozhiraja S, Morita M 2004 Structure-activity relationships for the toxicity of polychlorinated dibenzofurans: approach through density functional theory-based descriptors. Chem Res Toxicol **17:**348–356.
68. Kimura-Kuroda J, Nagata I, Kuroda Y 2005 Hydroxylated metabolites of polychlorinated biphenyls inhibit thyroid-hormone-dependent extension of cerebellar Purkinje cell dendrites. Brain Res Dev Brain Res **154:**259–263.
69. Bogazzi F, Raggi F, Ultimieri F, Russo D, Campomori A, McKinney JD, Pinchera A, Bartalena L, Martino E 2003 Effects of a mixture of polychlorinated biphenyls (Aroclor 1254) on the transcriptional activity of thyroid hormone receptor. J Endocrinol Invest **26:**972–978.
70. Iwasaki T, Miyazaki W, Takeshita A, Kuroda Y, Koibuchi N 2002 Polychlorinated biphenyls suppress thyroid hormone-induced transactivation. Biochem Biophys Res Commun **299:**384–388.
71. Miyazaki W, Iwasaki T, Takeshita A, Kuroda Y, Koibuchi N 2004 Polychlorinated biphenyls suppress thyroid hormone receptor-mediated transcription through a novel mechanism. J Biol Chem **279:**18195–18202.
72. Reporter CM 1999 ChemExpo Chemical Profile: Bisphenol-A. Schnell Publishing Company. New York, NY.
73. Howe SR, Borodinsky L, Lyon RS 1998 Potential exposure to bisphenol A from food-contact use of epoxy coated cans. J Coat Technol **70:**69–74.
74. Lewis JB, Rueggeberg FA, Lapp CA, Ergle JW, Schuster GS 1999 Identification and characterization of estrogen-like components in commercial resin-based dental restorative materials. Clin Oral Investig **3:**107–113.
75. Schonfelder G, Wittfoht W, Hopp H, Talsness CE, Paul M, Chahoud I 2002 Parent bisphenol A accumulation in the human maternal-fetal-placental unit. Environ Health Perspect **110:**A703–A707.
76. Ikezuki Y, Tsutsumi O, Takai Y, Kamei Y, Taketani Y 2002 Determination of bisphenol A concentrations in human biological fluids reveals significant early prenatal exposure. Hum Reprod **17:**2839–2841.
77. WHO EHC 1995 Tetrabromobisphenol A and derivatives. World Health Organization, Geneva, Switzerland.
78. WHO EHC 1997 Flame-retardants: a general introduction. World Health Organization, Geneva, Switzerland.
79. Thomsen C, Lundanes E, Becher G 2002 Brominated flame retardants in archived serum samples from Norway: a study on temporal trends and the role of age. Environ Sci Technol **36:**1414–1418.
80. Moriyama K, Tagami T, Akamizu T, Usui T, Saijo M, Kanamoto N, Hataya Y, Shimatsu A, Kuzuya H, Nakao K 2002 Thyroid hormone action is disrupted by bisphenol A as an antagonist. J Clin Endocrinol Metab **87:**5185–5190.
81. Staples CA, Dorn PB, Klecka GM, O'Block ST, Harris LR 1998 A review of the environmental fate, effects, and exposures of bisphenol A. Chemosphere **36:**2149–2173.
82. Krishnan AV, Stathis P, Permuth SF, Tokes L, Feidman D 1993 Bisphenol A: an estrogenic substance is released from polycarbonate flasks during autoclaving. Endocrinology **132:**2279–2286.
83. Gaido KW, Leonard LS, Lovell S, Gould JC, Babai D, Portier CJ, Mcdonell DP 1997 Evaluation of chemicals with endocrine modulating activity in yeast-based steroid hormone receptor gene transcription assay. Toxicol Appl Pharmacol **143:**205–212.
84. Kitamura S, Jinno N, Ohta S, Kuroki H, Fujimoto N 2002 Thyroid hormonal activity of the flame retardants tetrabromobisphenol A and tetrachlorobisphenol A. Biochem Biophys Res Commun **293:**554–559.
85. Moriyama K, Tagami T, Akamizu T, Usui T, Saijo M, Kanamoto N, Hataya Y, Shimatsu A, Kuzuya H, Nakao K 2002 Thyroid hormone action is disrupted by bisphenol A as an antagonist. J Clin Endocrinol Metab **87:**5185–5190.
86. Cheng SY 2005 Thyroid hormone receptor mutations and disease: beyond thyroid hormone resistance. Trends Endocrinol Metab **16:**176–182.
87. Zoeller RT, Bansal R, Parris C 2005 Bisphenol-A, an environmental contaminant that acts as a thyroid hormone receptor antagonist *in vitro*, increases serum thyroxine, and alters RC3/neurogranin expression in the developing rat brain. Endocrinology **146:**607–612.
88. Seiwa C, Nakahara J, Komiyama T, Katsu Y, Iguchi T, Asou H 2004 Bisphenol A exerts thyroid-hormone-like effects on mouse oligodendrocyte precursor cells. Neuroendocrinology **80:**21–30.

89. Siesser WB, Cheng SY, McDonald MP 2005 Hyperactivity, impaired learning on a vigilance task, and a differential response to methylphenidate in the TRbetaPV knock-in mouse. Psychopharmacology (Berl) **181:**1–11.
90. Vermiglio F, Lo Presti VP, Moleti M, Sidoti M, Tortorella G, Scaffidi G, Castagna MG, Mattina F, Violi MA, Crisa A, Artemisia A, Trimarchi F 2004 Attention deficit and hyperactivity disorders in the offspring of mothers exposed to mild-moderate iodine deficiency: a possible novel iodine deficiency disorder in developed countries. J Clin Endocrinol Metab **89:**6054–6060.
91. Hauser P, McMillin JM, Bhatara VS 1998 Resistance to thyroid hormone: implications for neurodevelopmental research on the effects of thyroid hormone disruptors. Toxicol Ind Health **14:**85–101.
92. Ishido M, Masuo Y, Kunimoto M, Oka S, Morita M 2004 Bisphenol A causes hyperactivity in the rat concomitantly with impairment of tyrosine hydroxylase immunoreactivity. J Neurosci Res **76:**423–433.
93. Nakamura K, Itoh K, Yaoi T, Fujiwara Y, Sugimoto T, Fushiki S 2006 Murine neocortical histogenesis is perturbed by prenatal exposure to low doses of bisphenol A. J Neurosci Res **84:**1197–1205.
94. Dowling ALS, Martz GU, Leonard JL, Zoeller RT 2000 Acute changes in maternal thyroid hormone induce rapid and transient changes in specific gene expression in fetal rat brain. J Neurosci **20:**2255–2265.
95. Dowling ALS, Iannacone EA, Zoeller RT 2001 Maternal hypothyroidism selectively affects the expression of neuroendocrine-specific protein-A messenger ribonucleic acid in the proliferative zone of the fetal rat brain cortex. Endocrinology **142:**390–399.
96. Dowling ALS, Zoeller RT 2000 Thyroid hormone of maternal origin regulates the expression of RC3/neurogranin mRNA in the fetal rat brain. Brain Res **82:**126–132.
97. Wu Y, Liu Y, Levine EM, Rao MS 2003 Hes1 but not Hes5 regulates an astrocyte versus oligodendrocyte fate choice in glial restricted precursors. Dev Dyn **226:**675–689.
98. Schuurmans C, Guillemot F 2002 Molecular mechanisms underlying cell fate specification in the developing telencephalon. Curr Opin Neurobiol **12:**26–34.
99. Gaiano N, Fishell G 2002 The role of notch in promoting glial and neural stem cell fates. Annu Rev Neurosci **25:**471–490.
100. Zuurbier M, Leijs M, Schoeters G, Ten Tusscher G, Koppe JG 2006 Children's exposure to polybrominated diphenyl ethers. Acta Paediatr Suppl **95:**65–70.
101. Tomy GT, Palace VP, Halldorson T, Braekevelt E, Danell R, Wautier K, Evans B, Brinkworth L, Fisk AT 2004 Bioaccumulation, biotransformation, and biochemical effects of brominated diphenyl ethers in juvenile lake trout (*Salvelinus namaycush*). Environ Sci Technol **38:**1496–1504.
102. Gill U, Chu I, Ryan JJ, Feeley M 2004 Polybrominated diphenyl ethers: human tissue levels and toxicology. Rev Environ Contam Toxicol **183:**55–97.
103. Siddiqi MA, Laessig RH, Reed KD 2003 Polybrominated diphenyl ethers (PBDEs): new pollutants-old diseases. Clin Med Res **1:**281–290.
104. Schecter A, Papke O, Tung KC, Joseph J, Harris TR, Dahlgren J 2005 Polybrominated diphenyl ether flame retardants in the U.S. population: current levels, temporal trends, and comparison with dioxins, dibenzofurans, and polychlorinated biphenyls. J Occup Environ Med **47:**199–211.
105. Ellis-Hutchings RG, Cherr GN, Hanna LA, Keen CL 2006 Polybrominated diphenyl ether (PBDE)-induced alterations in vitamin A and thyroid hormone concentrations in the rat during lactation and early postnatal development. Toxicol Appl Pharmacol **215:**135–145.
106. Balch GC, Velez-Espino LA, Sweet C, Alaee M, Metcalfe CD 2006 Inhibition of metamorphosis in tadpoles of *Xenopus laevis* exposed to polybrominated diphenyl ethers (PBDEs). Chemosphere **64:**328–338.
107. Zoeller RT 2005 Environmental chemicals as thyroid hormone analogues: new studies indicate that thyroid hormone receptors are targets of industrial chemicals? Mol Cell Endocrinol **242:**10–15.
108. Branchi I, Capone F, Alleva E, Costa LG 2003 Polybrominated diphenyl ethers: neurobehavioral effects following developmental exposure. Neurotoxicology **24:** 449–462.
109. McDonald TA 2002 A perspective on the potential health risks of PBDEs. Chemosphere **46:**745–755.
110. Veldhoen N, Skirrow RC, Osachoff H, Wigmore H, Clapson DJ, Gunderson MP, Van Aggelen G, Helbing CC 2006 The bactericidal agent triclosan modulates thyroid hormone-associated gene expression and disrupts postembryonic anuran development. Aquat Toxicol **80:**217–227.
111. Hovander L, Malmberg T, Athanasiadou M, Athanassiadis I, Rahm S, Bergman A, Wehler EK 2002 Identification of hydroxylated PCB metabolites and other phenolic halogenated pollutants in human blood plasma. Arch Environ Contam Toxicol **42:**105–117.
112. Takser L, Mergler D, Baldwin M, de Grosbois S, Smargiassi A, Lafond J 2005 Thyroid hormones in pregnancy in relation to environmental exposure to organochlorine compounds and mercury. Environ Health Perspect **113:** 1039–1045.
113. Kester MHA, Martinez de Mena R, Obregon MJ, Marinkovic D, Visser TJ, Hume R, Morreale de Escobar G 2004 Iodothyronine levels in the human developing brain: major regulatory roles of iodothyronine deiodinases in different areas. J Clin Endocrinol Metab **89:**3117–3128.
114. Friesema EC, Ganguly S, Abdalla A, Manning Fox JE, Halestrap AP, Visser TJ 2003 Identification of monocarboxylate transporter 8 as a specific thyroid hormone transporter. J Biol Chem **278:**40128–40135.
115. Heuer H, Maier MK, Iden S, Mittag J, Friesema EC, Visser T, Bauer K 2005 The monocarboxylate transporter 8 linked to human psychomotor retardation is highly expressed in thyroid hormone sensitive neuron populations. Endocrinology **146:**1701–1706.

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