Journal of Neurochemistry

JOURNAL OF NEUROCHEMISTRY | 2009 | 111 | 1327–1347 doi: 10.1111/j.1471-4159.2009.06427.x

REVIEW

Mechanisms involved in the neurotoxic effects of environmental toxicants such as polychlorinated biphenyls and brominated flame retardants

Frode Fonnum* and Espen Mariussen*,†

*Department of Biochemistry, Institute for Basal Medicine, University of Oslo, Oslo, Norway

†Norwegian Defense Research Establishment, Division for Protection, Kjeller, Norway

Abstract

Many toxic substances have been distributed to the environment, some of which have properties that promote accumulation and biomagnification in living organisms. Approximately 1.2 million metric tons of polychlorinated biphenyls (PCBs) have been produced and about 30% have been discharged to the environment. Approximately 200 000 metric tons of brominated flame retardants (BFRs) are produced annually, of which considerable amounts have been spread globally, even to the Polar Regions. Behavioral testing of animals has shown that these compounds may affect learning, memory and fine motor functions. Animals are most sensitive during early development. Several epidemiological studies have shown that PCBs and BFRs may be responsible for similar effects in humans. Of especially concern are possible effects of PCBs and BFRs in mixtures containing the highly neurotoxic methyl mercury. The compounds affect several targets in the nervous system that seem to be interconnected, and may be responsible for the observed behavioral deficits. It was shown early that PCBs affect dopamine and serotonin levels in the brain. Later studies showed that transport mechanisms of these neurotransmitters appear to be particularly sensitive to PCBs. Furthermore, PCBs affect intracellular calcium levels and induce formation of reactive oxygen species both *in vivo* and *in vitro*, and reduce cell viability *in vitro*. Neuroendocrine functions, particularly the thyroid hormone system, are also sensitive to disruption by PCBs and BFRs. Their metabolites, such as hydroxy-metabolites, appear to be particularly potent. We conclude that PCBs are particularly toxic during early development and that the toxic effects are a combination of several factors, including disturbance of calcium homeostasis, oxidative stress, and influence on neurotransmitter transport. Monoaminergic cells appear to be particularly vulnerable.

Keywords: brominated flame retardants, calcium homeostasis, dopamine, methyl mercury, neurobehavioral effects, reactive oxygen species.

J. Neurochem. (2009) **111**, 1327–1347.

Use of industrial chemical products has led to release of a range of substances which are potentially toxic to the environment. Several of these substances are resistant to degradation and may accumulate in living organisms to harmful concentrations. Most attention has been paid to halogenated organic compounds, such as polychlorinated biphenyl (PCBs), dioxins, and chlorinated pesticides, in addition to heavy metals, such as methyl mercury (MeHg), lead, and organotin compounds. Other important halogenated industrial chemicals, often used in thousands of tons, are the brominated and perfluorinated compounds utilized as flame retardants and fire extinguishers. These pollutants are not only localized to the region where they are used or produced, but may spread globally through air and water. Surprisingly, high concentrations of several industrial chemicals are found

Received May 15, 2009; revised manuscript received September 25, 2009; accepted October 5, 2009.

Address correspondence and reprint requests to Frode Fonnum, Department of Biochemistry, Institute for Basal Medicine, University of Oslo, Oslo, Norway. E-mail: Frode.fonnum@medisin.uio.no

Abbreviations used: ADHD, attention deficit hyperactivity disorder; BFR, brominated flame retardants; ChAT, choline acetyltransferase; DA, dopamine; DAT, plasma membrane dopamine transporter; ER, endoplasmic reticulum; GD, gestational day; HBCD, hexabromocyclododecane; HO-1, heme-oxygenase-1; IP_3, inositol-triphosphate; IP_3R, inositol-triphosphate receptor; IQ, intelligence quotient; LTP, long-term potentiation; MeHg, methyl mercury; NOS, nitric oxide synthase; PBDE, polybrominated diphenyl ether; PCB, polychlorinated biphenyl; PKC, protein kinase C; PND, postnatal day; ROS, reactive oxygen species; RyR, ryanodine receptor; SOD, superoxide dismutase; T3, triiodothyronine; T4, thyroxine; TBBPA, tetrabromobisphenol-A; TH, thyroid hormone; VMAT, vesicular monoamine transporter.

in the Polar Regions, especially in the Arctic. In a typical ecosystem, lipophilic and persistent chemicals can accumulate through the food chain to higher trophic levels. Animals that inhabit the marine environment such as large predatory fish, seagulls, seals, and polar bears appear to be particularly vulnerable. For humans, the main source of persistent organohalogenated compounds is marine food with high lipid content. The knowledge that these substances also accumulate in lipid-rich breast milk is of particular concern since early development is vulnerable period to the nervous system (Weiss 2000).

In this review, we will restrict ourselves to discuss the neurotoxic effect of two of the most quantitatively dominant groups of environmental pollutants, namely PCBs and BFRs. In addition, their major metabolites, some of which are considered even more toxic than their parent compounds, will be reviewed. We will also consider possible effects of PCBs and BFRs in mixtures containing the highly neurotoxic MeHg, which are often found in the human diet in combination with the organohalogens. We will first give a general summary of the chemistry, metabolism, and global distribution of PCBs and BFRs. Next, we will briefly discuss their effects on behavior as this reflects some of the complex effects on the brain. Then, we will review the neurochemical changes accompanying exposure to such compounds, and finally, we will point out some small, but perhaps important ultra-structural changes in brain, and also discuss effects on the thyroid system.

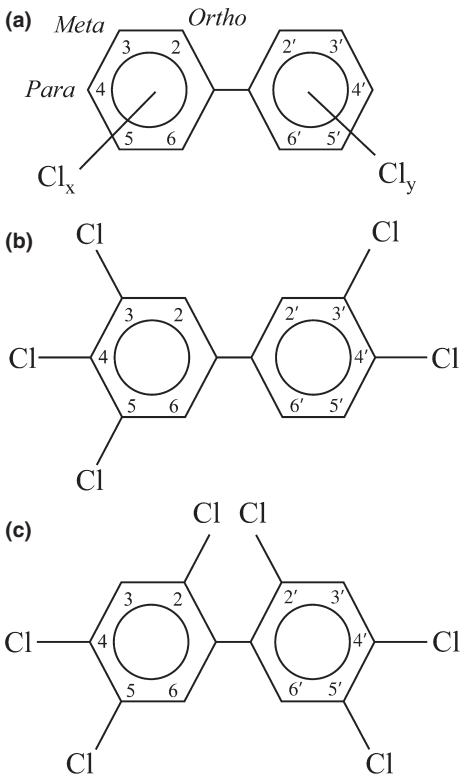

Fig. 1 (a) General structure of polychlorinated biphenyls (PCBs), (b) the coplanar PCB-126 (3,3′, 4,4′,5-pentachloro biphenyl), (c) the non-coplanar PCB-153 (2,2′,4,4′,5,5′-hexachloro biphenyl).

Substances

Polychlorinated biphenyls

Polychlorinated biphenyls were introduced to the commercial market in 1929 with applications in cooling and insulating fluids for transformers and capacitors, hydraulic fluids, additives in different types of paint, glue and cement, as well as in insulation material for windows. It has been estimated that more than 1.2 million tons of PCBs were produced on a world basis until 1984. About 30% of the PCBs have been discharged to the environment through burning, evaporation, leaks, and dumping (Tanabe 1988; Breivik *et al.* 2002). The PCBs are extremely persistent, non-combustible, and thermostable, and they are lipophilic and resistant to both biotic and abiotic decomposition. The PCBs are a family of chlorinated aromatic hydrocarbons with 209 possible congeners (Fig. 1). The PCB congeners are generally divided into three main structural classes according to their chlorine substitution pattern. The coplanar, also called the dioxin-like PCBs, with chlorine substitution in the *para*- and *meta*-positions and no chlorine substitution in the *ortho*-position; the mono–*ortho*-substituted PCB congeners, which may attain coplanarity; and the PCB congeners with two or more *ortho*-substitutions, which always are non-coplanar. The PCBs were commercially available in mixtures with different degrees of chlorination, which give them distinct properties adapted for their use. The mixtures are often denoted Aroclor 12XX (A12XX), where XX is the percentage of chlorine in the mixture, e.g. A1254 contains 54% chlorine on weight basis. The individual PCB congeners have different physical and chemical properties depending on the position and proportion of the chlorine. Both in the commercial mixtures and in the environment the non-coplanar, *ortho*-substituted PCBs dominate. Detection of PCBs in the environment was first reported in Sweden by Jensen (1966) who found high levels of PCBs in dead white-tail sea eagles. Even though most industrial countries prohibited the use of PCBs in the late 1970s, these compounds are detected in biota all over the world and are still regarded as major global environmental hazards. Under normal circumstances, the PCB levels are highest in lipid-rich tissue. Because of its high lipid content, the brain receives a large proportion of the accumulated PCBs, especially during starvation, when PCBs can be mobilized from lipid-rich tissue to the brain via blood. The highest levels of PCBs in the brain have been found in dead polar sea gulls from the islands of Svalbard and ranged from 0.9 to 29.5 mg/kg brain (wet wt.), corresponding to ~3–90 μmol/kg (Gabrielsen *et al.* 1995). Another investigation of live

caught glaucous gulls revealed 0.5–9.5 mg/kg in brain (wet wt.), corresponding to 1.5–30 μmol/kg (Henriksen *et al.* 1998). In an experimental situation, Seegal *et al.* (1990) fed non-human primate monkeys 3.2 mg/kg of the lightly chlorinated PCB mixture A1016 per day for 20 weeks, and found that the concentrations of the major congeners present in the primate brain were 2–5 mg/kg (wet wt.).

Brominated flame retardants

Brominated flame retardants (BFR) have received much attention as potential environmental toxicants since their first discovery in environmental samples in the late 1970s and early 1980s (Zweidinger *et al.* 1979; Andersson and Blomkvist 1981). BFR are a group of brominated organic compounds used as additives to electronic equipment, furniture, textiles, plastics, and insulating materials because of their fire preventing properties (Birnbaum and Staskal 2004). The BFRs are a diverse group of chemicals with more than 80 different registered compounds. The most extensively used BFRs at present are the polybrominated diphenyl ethers (PBDEs), hexabromocyclododecane (HBCD), and tetrabromobisphenol-A (TBBPA) (de Wit 2002; Birnbaum and Staskal 2004) (Fig. 2). Similar to the PCBs, the PBDEs can exist in 209 theoretical congeners. Defined by their degree of bromination, the PBDEs have been commercially available in three different mixtures: the decaBDE, octaBDE, and pentaBDE. The decaBDE constitute more than 90% of the total PBDE usage. The decaBDE mixture contains primarily BDE-209, the octaBDE mixture contains several hexa to nona brominated congeners, and the penta mixtures are generally composed of 24–38% tetraBDE (BDE-47), 50–60% pentaBDE (BDE-99, BDE-100) and 4–6% hexaBDE (BDE-153, BDE-154) (Alaee *et al.* 2001; Birnbaum and Staskal 2004). The congeners most frequently found in the environment are BDE-47, -99, -100, -153, and -154 (Darnerud *et al.* 2001). Some BFR, such as PBDEs and HBCD, are additives that are mixed into polymers and not chemically bound to the products. Others, such as TBBPA, are reactive and bound chemically to the material. The Bromine Science Environmental Forum estimated that the total annual market demand for the major commercial BFRs reached ~200 000 tons in 2001 (http://www.bsef-site.com). Concerns for this emerging class of chemicals are rising because of the occurrence in environmental and human samples, and several BFRs have become ubiquitous in the environment (de Wit 2002; Law *et al.* 2003; Watanabe and Sakai 2003). The pentaBDE and octaBDE mixtures are now prohibited in most European countries and Japan, and have been voluntarily phased out in the United States. Some BFRs have structural resemblances to PCBs, and to evaluate their toxicity, most studies have therefore used a comparative approach to the studies of PCBs and other organohalogens, such as the dioxins. Whereas the levels of PCBs in the environment are slowly diminishing because of the restrictions of use, the levels of some BFRs have been increasing rapidly over the last decade (Alaee and Wenning 2002).

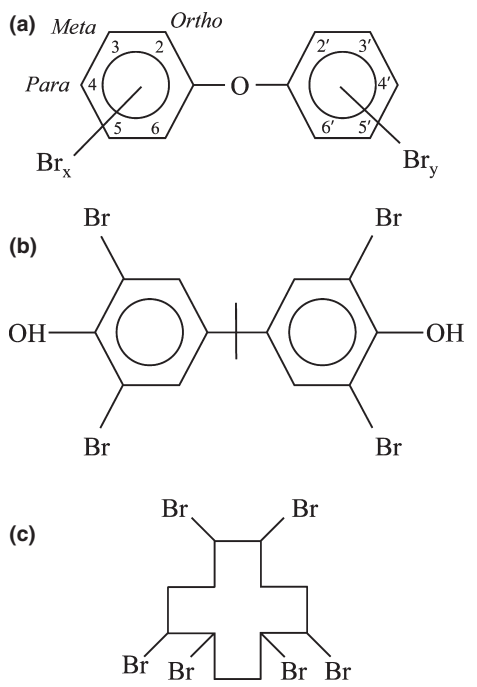

Fig. 2 (a) General structure of polybrominated biphenyl ethers (PBDEs), (b) the tetrabromobisphenol-A (TBBPA), (c) the hexabromocyclododecane (HBCD).

Mercury

Mercury (Hg) can be subdivided into three chemical forms: elemental, inorganic, and organic. The organic forms, such as MeHg, are potent neurotoxicants. This compound is considered as one of the major environmental pollutants posing threat to human health (Gochfeld 2003; Counter and Buchanan 2004; Davidson *et al.* 2006; Mergler *et al.* 2007). MeHg is an organometallic cation (CH_3Hg^+), which is formed by methanogenic bacteria from inorganic Hg. The compound bioaccumulates in living organisms and is often found with other organohalogenated toxicants, such as PCBs and BFRs. Sources for human consumption are mainly fish and marine mammals. When ingested, MeHg binds readily to cysteine and other thiol compounds. This complex is transported by the neutral amino acid transporter, and is distributed throughout the body, across the blood–brain barrier and across the placenta (Aschner and Aschner 1990; Kerper *et al.* 1992; Bridges and Zalups 2005; Clarkson and Magos 2006; Soldin *et al.* 2008). MeHg is, similar to PCBs and BFRs, believed to affect neuronal function through several mechanisms, such as effects on neurotransmitter systems, induction of oxidative stress, protein synthesis, disruption of microtubules, and intracellular calcium homeostasis (recommended readings: Castoldi *et al.* 2001; Clarkson 2002; Costa *et al.* 2004; Johansson *et al.* 2007). The toxicity

differs between adult and prenatal exposure. In human adults, there is focal brain damage such as selective loss of granule cells in cerebellum, whereas in prenatally exposed subjects there is effect on the development of the whole brain, indicating effects on neuronal migration (Clarkson 2002; Clarkson and Magos 2006). In brain, the methyl group is oxidized to inorganic Hg within glia cells, such as astrocytes, and probably immobilized by selenium (Ganther *et al.* 1972; Shapiro and Chan 2008). Because of the delay in the appearance of signs and symptoms of poisoning after exposure to MeHg, there has been some debate whether it is the methylated or the inorganic form that exert the neurotoxic effects in CNS. However, studies with e.g. the less neurotoxic ethyl mercury have shown substantial evidences for MeHg to be the proximate species for neurotoxicity (Magos *et al.* 1985; Weiss *et al.* 2002; Magos 2003; Clarkson and Magos 2006; Aschner and Ceccatelli 2009). Other forms of organic mercuric compounds that are neurotoxic are ethyl and phenyl mercury that are used as preservatives in pharmaceuticals and as fungicides. Because of its widespread presence in food articles of CH_3Hg^+, PCBs and BFRs we have, however, in this review only considered the effects of CH_3Hg^+ in combination with these organohalogens. Considerable concerns are raised whether exposure to mixtures of methyl mercuric compound and organohalogens may exacerbate adverse effects.

Metabolism

Polychlorinated biphenyl congeners can be selectively transformed in the liver to hydroxylated or sulfur-containing metabolites (Bakke *et al.* 1982; Preston *et al.* 1984; Safe 1984). The more hydrophilic metabolites are, in principle, more easily excreted than the parent substances. Several of the metabolites, are, however, retained in the body. The parent compounds are metabolized primarily in the *meta*- or *para*-position following CYP450-mediated arene oxide formation (Bergman *et al.* 1994; Letcher *et al.* 2000). The OH-PCB metabolites can be present in even higher concentrations than their parent molecules. In an investigation of Slovakian women, only four PCB congeners – PCB 153, 138, 180, and 170 – had higher concentrations than 4-OH-PCB-187 and 4-OH-PCB-146. In the umbilical cord of newborns, the levels of the parent PCBs were only twofold higher than those of hydroxylated PCBs (Park *et al.* 2007).

The PCBs are also metabolized through the mercapturic pathway. In the case of 2,4′,5-trichloro biphenyl, about 20% is recovered as the mercapturate metabolites. The thiomethyl and oxidized thiomethyl metabolites are derived from a shunt away from the mercapturate pathway (thiomethyl shunt), resulting from a cysteine *S*-conjugate β-lyase reaction on the cysteine *S*-conjugate, resulting in the formation of a PCB metabolite with an added -SH-group. The SH-group is then methylated with *S*-adenosyl methionine and the sulfur first oxidized to methylsulfinyl-PCB and then to methylsulfonyl-PCB (Bakke *et al.* 1982, 1983). In a recent study by Jörundsdóttir *et al.* (2006), it was shown that some methylsulfonyl-PCBs have an even slower elimination half-life than several of the PCB congeners.

Similar to the PCBs, the PBDEs may also be transformed to their corresponding hydroxylated and methoxylated metabolites, and these metabolites have been found in wildlife as well as in humans (e.g. Marsh *et al.* 2004; Valters *et al.* 2005; Verreault *et al.* 2005; Athanasiadou *et al.* 2008). Kawashiro *et al.* (2008) found TBBPA and 6-OH-BDE-47, a BDE-47 metabolite, in the umbilical cord, but not in the maternal blood. They suggested that in the fetus these two compounds are transferred through the placenta and only slowly metabolized there. Using a chemical approach Moreira-Bastos *et al.* (2008) suggested that the PBDE metabolites are readily formed and have a higher elimination rate than their parent compounds and therefore less persistent in the organism. TBBPA has a short half-life in the body, probably because of its low lipophilicity, and does not accumulate in high concentrations (Hakk and Letcher 2003; Johnson-Restrepo *et al.* 2008). TBBPA undergoes oxidative cleavage near the central carbon of the molecule, and major metabolites are hydroxylated dibromo-phenol, hydroxylated dibromo-isopropyl-phenol, as well as GSH, glucuronide, and sulfate conjugates (Schauer *et al.* 2006; Zalko *et al.* 2006). The technical mixture of HBCD contains primarily three diastereomers: α, β, and γ, which constitute ∼1–13%, 1–12%, and 75–90% of the mixtures, respectively (Becher 2005; Heeb *et al.* 2005; Reistad *et al.* 2006). An interesting observation is the selective accumulation of the α-isomer in biological materials, indicating preferential metabolism and/or uptake (Covaci *et al.* 2006). Zegers *et al.* (2005) found the α-HBCD to be more resistant to cytochrome P450-mediated biotransformation. Law *et al.* (2006) showed that α-HBCD could be formed by bioisomerization of the β- and γ-diastereomers in rainbow trout (*Oncorhynchus mykiss*). Such transformation of the β- and γ-molecules would be expected to affect the concentration in marine organisms by increasing the relative contribution of α-HBCD. Thus, the increase of the α-diastereomer in the environment could be because of a more effective transformation of β- and γ-HBCD through increased metabolic rate followed by preferential accumulation of the α-diastereomer (Norstrom *et al.* 1986; Verreault *et al.* 2005). Degradation products of HBCD that are not recognized as bioaccumulative or toxic are tetra- and pentabromocyclododecanes (Hiebl and Vetter 2007; Abdallah *et al.* 2008) and tetrabromocyclododecene, dibromocyclododecadiene, and cyclododecatriene (Davis *et al.* 2006).

Behavioral effects

Epidemiological studies, both after accidental and environmental exposure to PCBs, have shown that they may impair

cognitive functions and motor development in humans. In Japan in 1968, and Taiwan in 1979, about 4000 humans suffered from accidentally consumed cooking oil contaminated with thermally degraded PCB (Kuratsune *et al.* 1971, 1972; Hsu *et al.* 1985; Chen *et al.* 1994). Several of the affected patients suffered from PNS symptoms such as decreased nerve conduction velocity, numbness and weakness in the limbs, and CNS symptoms like tiredness, and respiratory disturbances. Children, who were exposed to PCB prenatally and/or through breast feeding, showed delayed motor development, defects in short-term memory and lower scores on intelligence quotient (IQ)-tests (for additional reading: Rogan *et al.* 1988; Tilson *et al.* 1990; Seegal 1996). In the United States, there are two epidemiological studies of children from Michigan and North Carolina whose mothers had consumed fish presumed to be contaminated by PCBs during pregnancy. A correlation was found between the level of PCB exposure during development and lower scores in behavioral tests and fine motor tasks (Fein *et al.* 1984; Rogan *et al.* 1986; Gladen *et al.* 1988 Tilson *et al.* 1990; Jacobson and Jacobson 1996; Seegal 1996; Longnecker *et al.* 1997). Schantz *et al.* (2003) have analyzed several epidemiological studies from different parts of the world and concluded that in all studies except one (Gladen and Rogan 1991) there was a clear negative effect of PCB exposure on cognition in children. Recently, Stewart *et al.* (2008) examined a population of 9-year-old boys exposed to PCB and estimated that for each 1 ng/g (wet weight) increase in PCBs in placental tissue, full scale IQ dropped by three points ($p = 0.02$) and verbal IQ dropped by four points ($p = 0.003$). The median PCB level was 1.50 ng/g, with a lower quartile of 1.0 ng/g and an upper quartile of 2.0 ng/g. Moreover, this association was significant after controlling for many potential confounders, including prenatal exposure to MeHg, *p*,*p*′-dichlorodiphenyldichloroethylene, hexachlorobenzene, and lead.

Even in older persons eating large amounts of fish from the contaminated Lake Michigan, PCB exposure has been correlated with memory impairment (Schantz and Widholm 2001). These findings have been confirmed in several animal studies, although these studies frequently use much higher PCB concentrations than those that are seen in exposed humans. Studies of PCB exposure during both gestation and lactation indicate that there are effects of PCBs on behavior and cognition. Among the most important studies is a study on monkeys, which received a PCB mixture (7.5 μg/kg/day) from birth to 20 weeks of age (Rice 1999). This PCB mixture had a similar composition to that which is found in human breast milk, and the level of exposure was assumed to represent a safe level in human breast milk (50 ppb). The monkeys were tested between 2.5 and 5 years of age and major findings were a deficit on a spatial delay alteration task, perseverative behavior, and inability to inhibit inappropriate responding. Several authors also have suggested that exposure to PCBs can contribute to the prevalence of attention deficit hyperactivity disorder (ADHD) (Rice 2000; Schettler 2001; Hardell *et al.* 2002). Environmental factors may account for ~20% of the prevalence of ADHD (Barkley 1998). Rice (2000) summarized the parallels between ADHD and behavioral effects induced by PCB and lead exposure in monkeys, and showed several similarities to children with ADHD. Studies on rats and mice have also shown increased activity levels following exposure to PCBs during brain development (Eriksson and Fredriksson 1996a,b, 1998; Holene *et al.* 1998; Berger *et al.* 2001; Branchi *et al.* 2005). These studies indicate that PCB exposure could lead to ADHD-like symptoms. The neurobehavioral effects of PCBs have previously been thoroughly reviewed (Tilson *et al.* 1990; Seegal 1996; Giesy and Kannan 1998; Mariussen and Fonnum 2006).

There are no epidemiological studies showing that BFRs impair human behavior following accidental or occupational exposure. Recent laboratory studies have, however, revealed that this group of chemicals may alter neurobehavior in a similar fashion to that which has been shown for the PCBs. In a series of studies by Eriksson's group, it was demonstrated that the PBDE congeners BDE-47, -99, -153, -209 as well as HBCD cause permanent aberration in spontaneous behavior and habituation capability in mice after a single exposure (3–10 mg/kg) on postnatal day (PND) 10 (Eriksson *et al.* 2001, 2002; Viberg *et al.* 2003a,b, 2004; Johansson *et al.* 2008). In animals tested long after exposure, pentaBDE-99 and hexaBDE-153 were also shown to affect learning and memory functions in the Morris swim maze (Eriksson *et al.* 2001; Viberg *et al.* 2003a). Gee and Moser (2008) applied a similar study design and found increased motor activity in mice after a single exposure to BDE-47 on PND 10. Furthermore, rats exposed to BDE-99 from gestational day (GD) 6 to PND 21 suffered from delayed appearance of climbing response, a transient increase in locomotor activity at PND 34 and PND 60 followed by a decrease in locomotor activity at PND 120 in an open-field chamber (Branchi *et al.* 2002, 2005). Offspring of Wistar rats exposed to a single low dose of the pentaBDE-99 (300 μg/kg) on GD 6 showed increased basal locomotor activity at PND 36 and 71 (Kuriyama *et al.* 2005). Rice *et al.* (2007) observed increased motor activity at PND 70 in male mice exposed neonatally to BDE-201 from PND 2 to PND 15. Also Suvorov *et al.* (2009) found increased locomotor activity in pups following exposure to low doses of BDE-47 (0.002–0.2 mg/kg) from GD 15 to PND 20. Dufault *et al.* (2005) exposed rats to DE-71 for 1 week (PND 6–13, 30 mg/kg/day) and found an increase in errors in a visual discrimination task. Fernie *et al.* (2008) exposed adult American kestrels (*Falco sparverius*) to 0.3 and 1.6 ppm DE-71 for 75 days during the breeding period. Birds in both exposure groups demonstrated considerable alterations in reproductive courtship behavior, including less copulation,

less time spent in their nests, and altered pair bonding behavior.

Human populations are often exposed to mixture of toxicants, of which PCBs in combination with MeHg is of particular concern (Grandjean *et al.* 2001; Stewart *et al.* 2003; Myers *et al.* 2009). Both MeHg and PCBs alone are known to cause neurological effects (Schettler 2001; Grandjean and Landrigan 2006) and it is postulated that these neurotoxicants might interact to exacerbate adverse effects (Grandjean *et al.* 2001, 2003; Roegge *et al.* 2004). Stewart *et al.* (2003) found that prenatal exposure to high levels of a mix of PCB and MeHg had a negative effect on McCarthy performance (IQ testing) in young children (38 months). The effects disappeared when the children reached 54 months.

Similar neuropsychological defects were seen in children from the Faeroe Islands exposed to MeHg, but not in children from the Seychelles exposed to similar levels (Myers and Davidson 1998; Grandjean *et al.* 2001; Myers *et al.* 2009). Both populations had a similar high consumption of MeHg-contaminated fish, but in the Faeroe Islands the children had also been exposed to PCBs via mother's milk because of their mothers' dietary consumption of whale meat and blubber. The Faeroe Island study indicated that additional exposure to PCB could be an important factor (Grandjean *et al.* 2001).

Several animal studies support the findings that PCB and MeHg increase the neurotoxic effect during coexposure. Recent *in vivo* studies indicate that rats exposed both to an *ortho*-substituted PCB (PCB-153) and MeHg during development showed impaired balance and coordination, whereas neither PCBs nor MeHg alone was able to affect the performance (Roegge *et al.* 2004). A later study by Roegge *et al.* (2006) showed that the exposed rats had significant reduction in serum triiodothyronine (T3) and thyroxine (T4) concentrations. In addition, they suggested that the behavioral effect could be linked to the effect of calcium released from ryanodine-sensitive stores (see calcium homeostasis). Cheng *et al.* (2009) found that rats fed rice contaminated with high levels of PCB and MeHg on PND 21–91 responded with a significant delay in the Morris water maze test on day 91. Neurochemically, this was correlated to an increase in expression of early response genes (c-*fos*/c-*jun*) in the brain. They also found reduced superoxide dismutase (SOD) activity in brain, liver, and kidney and increased levels of GSH. Eriksson and coworkers exposed mice to MeHg in combination with PCB-153 or PBDE-99 on PND 10. Only the mice given the substances in combination showed disruptions in spontaneous behavior, lack of habituation, and reduced cognitive functions after 2 and 4 months (Fischer *et al.* 2008a,b).

Mechanisms for neurotoxic effects

A major challenge is to link the behavioral effects seen after exposure to environmental toxicants to changes in the nervous tissue. The effects seen on a population level or in individual organisms probably result from effects on several neurochemical targets. PCBs are perhaps one of the most studied environmental toxicants, and intensive research has revealed that PCBs act on a range of different neurochemical as well as neuroendocrine targets. The PCBs therefore have become model substances for the comparative studies of other halogenated analogs. In brief, the most plausible targets of PCB exposure are neurotransmitter systems, including neurotransmitter transport and receptors, calcium homeostasis, and oxidative stress. These effects may be followed by activation or inhibition of a range of signal transduction enzymes such as protein kinase C (PKC) and nitric oxide synthase (NOS) activity, synaptic plasticity such as long-term potentiation (LTP) and long term depression, and decreased cell viability. An overview of signaling pathways affected by PCBs and BFRs is summarized in Fig. 3. In addition, it has been shown that PCBs act on neuroendocrine targets such as the thyroid hormone (TH) system, which may influence neurodevelopment, particularly of the cholinergic system (Smith *et al.* 2002).

Gene expression

Exposure to toxic xenobiotics invariably involves changes in the expression of a broad spectrum of genes followed by synthesis of specific proteins, which may be followed by adverse effects on cellular levels and ultimately the entire organism. The application of gene-arrays is a convenient way to discover early markers of effects for less investigated and emerging toxicants. Genetic analysis has been carried out in hippocampus and cerebellum after exposure of Long–Evans rats to A1254 (6 mg/kg/day) from GD 3-PND 21. The mRNAs were analyzed with microarrays on days 7 and 14. More changes in gene expression were observed in hippocampus than in cerebellum and more on PND 7 than on PND 14. In hippocampus, 173 transcripts were changed on day 7 and 50 were changed on day 14. In cerebellum, 87 transcripts were changed on day 7 and 24 transcripts were changed on day 14. In both cases, the main changes in gene expression occurred in genes concerned with cell maintenance and development. Other deviations were seen on neurotransmission, signal transduction, and stress-related and transcription-regulated processes (Royland and Kodavanti 2008).

The PCB metabolite 4-OH-PCB-126 (1 mg/kg/day) was given to pregnant rats from GD 7 to PND 1 and effects on mRNA of thyroid receptors, glutamate receptors, and exocytosis proteins were investigated. The major changes in gene expression were observed in the hippocampus. In male offspring, there was an increase in TH receptor mRNA of thyroid hormone receptor α and a decrease in thyroid hormone receptor β. In the hippocampus, the expressions of mRNA of the glutamate receptors NR2A, NR2C, NR3A, mGLUR1, mGLUR2, mGLUR5, mGLUR6, mGLUR7, and

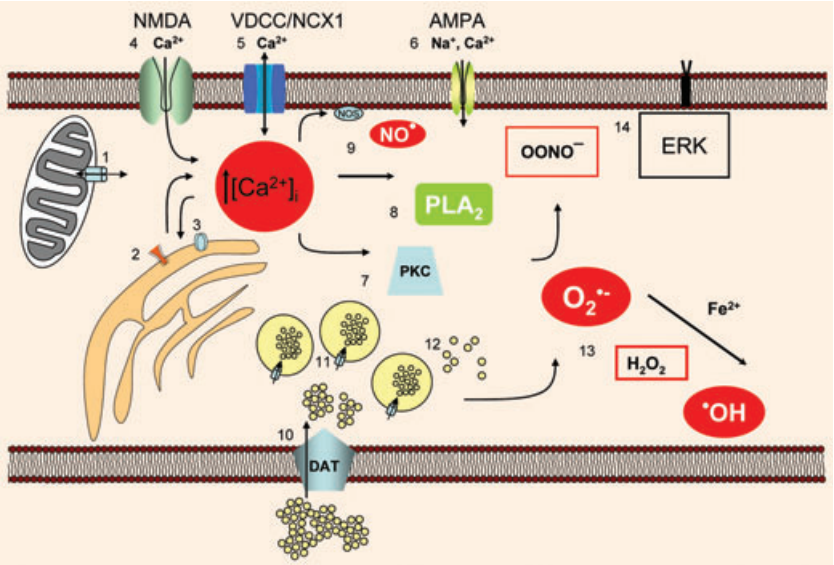

Fig. 3 A simple overview of the main suggested neurochemical targets of PCBs, BFRs and their metabolites in a nerve cell as discussed in the text. (1) Disruption of mitochondrial calcium homeostasis and the mitochondrial transition pore. (2) Activation of the RyR in ER. (3) Activation of the IP_3 receptor in ER (4) NMDA receptor activation. (5) Increased influx of Ca^{2+} from L-type VDCC and inhibition of the sodium–calcium exchangers (NCXI). (6) AMPA receptor activation. (7) PKC activation. (8) PLA_2 activation. (9) Activation of NOS followed by $NO^{\bullet}$ formation. (10) DAT inhibition of dopamine transport. (11) VMAT inhibition of dopamine transport. (12) Autooxidation of dopamine followed by $O_2^{\bullet -}$ formation. (13) Formation of reactive oxygen species as a consequence of disruption of Ca^{2+} homeostasis, glutamate excitoxicity, PLA_{2-} and NOS activation. (14) Activation of MAP-kinases as shown by ERK.

mGLUR8 were decreased. There were only small changes in the cortex and the striatum. There was, however, an increase in the expression of exocytosis-related genes (synaptobrevin 1 and 2, synaptosomal associated protein (SNAP) 25, and syntaxin 1b) in the hippocampus and the striatum (Takahashi *et al.* 2009).

A complex mixture containing PCBs is called the 'Northern contamination mixture,' and contains the 27 most abundant contaminants found in the blood of the Canadian arctic population. The main contaminants are PCBs, chlorinated pesticides, and metals. When Sprague–Dawley rats were dosed orally from GD 1 until weaning with this mixture, gene analysis using microarray identified significant changes in 50 known genes involved in nerve cell differentiation, cell migration, myelination, and synaptic transmission in the cerebellum (Padhi *et al.* 2008). An increased mortality of pups in the high dose group (1.099 mg/kg PCB, 1.9 mg/kg organochlorine pesticides, and 1.997 mg/kg MeHg) was observed (Pelletier *et al.* 2009). Increased mortality rate and impaired growth were attributed to MeHg, whereas PCBs were responsible for the decreased T4 level and thyroid gland perturbations.

Effects on the neurotransmitter system

It was early established that *ortho*-PCB alters dopamine (DA) levels and turnover in brain (Chou *et al.* 1979; for review Seegal 1996; Mariussen and Fonnum 2006). It appears that the effect on DA depends on whether the animals are exposed as adults or during development. A decrease in brain DA levels has been reported in adult monkeys exposed to the technical PCB mixtures A1060 and A1260 (0.8–3.2 mg/kg/day for 20 weeks) (Seegal 1996), whereas increases in brain DA levels have been observed in the brains of rats exposed prenatally to A1016 (maternal exposure to 100 or 300 mg/kg A1016 in food from GD 8 and during lactation) (Seegal 1994). Furthermore, decreased serotonin levels in the brain have been reported after PCB exposure (for review: Seegal 1996; Tilson and Kodavanti 1997). Several attempts have been made to elucidate the mechanisms underlying the effect on the dopaminergic and the serotonergic system. It was discovered that *ortho*-PCBs cause biogenic amine release in brain preparations and dopaminergic cell cultures (Angus and Contreras 1996; Chishti *et al.* 1996; Angus *et al.* 1997; Messeri *et al.* 1997). These findings could be explained by inhibition of the vesicular monoamine transporter (VMAT) in synaptic vesicles or the plasma membrane DA transporter (DAT) in synaptosomes by PCBs (Mariussen *et al.* 1999, 2001; Mariussen and Fonnum 2001). Such effects on the dopaminergic transport system have gained strong support from both acute (Seegal *et al.* 2002; Richardson and Miller 2004) and subchronic exposure of rodents to PCBs (Caudle *et al.* 2006). Seegal *et al.* (2002) exposed adult rats to 25 mg/kg/

day of PCB for different periods of times and found by microdialysis an initial increase of extracellular DA, suggesting DAT inhibition. Bemis and Seegal (2004) exposed rat brain synaptosomes to different PCB congeners and mixtures and concluded that the observed reduction in synaptosomal DA content was because of VMAT inhibition. A single excessive dose of A1260 or A1016 (500 mg/kg) reduced the expression of both DAT and VMAT, as shown by western blot, after 1, 7, and 14 days exposure in adult rats (Richardson and Miller 2004). In a subchronic study, Caudle *et al.* (2006) administered mice 7.5 or 15 mg/kg/day of a 1 : 1 mixture of A1254 and A1260 for 3–30 days, and found a dose-dependent reduction in striatal DAT expression and striatal DA uptake *ex vivo* after 14 and 30 days. In this study, a small reduction in VMAT expression was also reported in the high dose group, whereas the expression of tyrosine hydroxylase was unaffected. *In vivo* and *in vitro* studies therefore show that DA metabolism is influenced primarily by inhibition of DAT and VMAT, whereas no effects so far have been found on DA receptors.

Polychlorinated biphenyls have also an impact other neurotransmitter systems, such as plasma membrane uptake of glutamate and GABA (Mariussen and Fonnum 2001), expression of NMDA receptor binding sites in visual cortex (Altmann *et al.* 2001), and inhibition of the responsiveness of the $GABA_A$ receptor on Ca^{2+} and chloride influx in rat cortical cells (Inglefield and Shafer 2000a). But, until now, the only evidence for an effect on amino acid neurotransmission is that reported on genetic alterations (see gene expression). In a range of studies, Eriksson and coworkers exposed mice to PCBs on PND10, which is characterized as a period with high neuronal growth (Eriksson and Fredriksson 1996a,b; Eriksson 1997). They reported a minor increase (5%) in the level of brain muscarinic receptors (Eriksson *et al.* 1991) and a reduced expression of nicotine receptors in hippocampus (Eriksson and Fredriksson 1998).

Less is known about the effect of PCB metabolites, BFRs and BFR metabolites on neurotransmitter systems. Mariussen and Fonnum (2003) screened several BFRs and found that the pentaBDE mixture (DE-71) as well as HBCD and TBBPA inhibit uptake of DA in rat brain synaptic vesicles *in vitro* at low concentrations (IC_{50}; 3–8 μM). HBCD and TBBPA were also shown to inhibit DA uptake into synaptosomes (IC_{50}; 4 and 9 μM, respectively). The effect of TBBPA differed from the effects of the other BFRs as it non-selectively also inhibited GABA and glutamate uptake at similar concentrations. The effect of TBBPA on synaptosomes was attributed to a reduction in the membrane potential, diminishing the driving force for neurotransmitter uptake. The pentaBDE mixture was generally a poor plasma membrane uptake inhibitor. Several other commercial mixtures of BFRs (octaBDE, decaBDE, hexaBB and octaBB, tribromophenylallylether, and bisdibromopropoxydibromophenylpropane) had no effect on the plasma membrane uptake of DA, glutamate and GABA (Mariussen and Fonnum 2003). Viberg (2009) exposed rats on PND10 to octa- and nonaBDE (21 μmol) and found an increase in calcium/calmodulin-dependent protein kinase II (CAMKII) and synaptophysin in the hippocampus. Dingemans *et al.* (2007) found a decrease in LTP and in glutamate receptors, but no effects on other measured proteins, after exposing mice on PND10 to BDE-47. Exposure of PC12 cells to 6-OH-BDE-47 (5 μM) induced vesicular catecholamine release, which coincided with a transient increase in $[Ca^{2+}]_i$ shortly after the onset of exposure. The transient increase came from the endoplasmic reticulum (ER). An additional late increase in $[Ca^{2+}]$ was also observed at concentrations equal to, or higher than 1 μM. The hydroxylated metabolite 6-OH-BDE-47 was shown to be more potent in disturbing Ca^{2+} homeostasis and neurotransmitter release than the parent compound BDE-47. The present findings indicate that oxidative metabolism may add considerably to the neurotoxic potential of PBDEs (Dingemans *et al.* 2008).

Some attempts have been made to elucidate effects of mixtures of environmental toxic substances on neurotransmitter parameters, showing various results. Coccini *et al.* (2006) exposed rats to MeHg (1 mg/kg) between GD 7 and PND 7 and found an increase in muscarinic receptor binding using the muscarinic ligand quinuclidinyl benzilate (QNB). Coexposure to MeHg and either PCB-153 or PCB-126 had similar effect on the cerebral muscarinic receptors as exposure to each compound alone. The results ruled out additive or synergistic interactions on muscarinic receptors in the brain areas examined. A similar study was performed by Castoldi *et al.* (2006) to investigate monoaminergic neurotransmission parameters. They found that a combined treatment with MeHg and PCB-153 did not exacerbate the neurochemical effects of the individual compounds. Piedrafita *et al.* (2008a,b) showed that separate developmental exposure to PCB-126 (100 ng/kg/day), PCB-153 (1 mg/kg/day), and MeHg (0.5 mg/kg/day) impaired learning when the rats were 3-month old, but not in older rats (7–8 months). The impairment was linked to a reduction of the glutamate-nitric oxide pathway in the cerebellum *in vivo*. Coexposure to PCBs and MeHg prevented this reduction and also the observed learning impairment, indicating an antagonistic effect (Piedrafita *et al.* 2008a).

Polychlorinated biphenyl and MeHg act synergistically on the DA content in striatal brain punches *in vitro* (Bemis and Seegal 1999). Exposure to the PCB mixtures A1254 and A1260 (10–200 ppm) only, reduced tissue DA and elevated media DA in a dose-dependent fashion. Exposure to MeHg (4 and 14 μM) alone did not significantly affect either measure. However, when striatal punches were simultaneously exposed to PCBs and MeHg, there were significantly larger reductions in tissue DA and larger increases in media DA concentrations than those caused by PCBs alone. Increases in 3, 4-dihydroxyphenylacetic acid concentrations were also observed both

in tissue and media. They suggested that the significant interactions between these two toxicants might be because of a common site of action that influences DA function. In our laboratory we have studied the effect of MeHg in combination with PCBs or BFRs on the reuptake of glutamate in synaptosomes. To provide the optimal conclusion regarding type of interaction, we analyzed the data using two mathematical models, the Löewe model of additivity and Bliss' model of independent action as recommended by Greco *et al.* (1992) and Goldoni and Johansson (2007). All the toxicants inhibited glutamate uptake with primarily additive effects, as shown with both models, although a tendency toward synergy was observed (Stavenes Andersen *et al.* 2009).

Calcium homeostasis

Calcium signaling is crucial for normal functioning of cells, and sustained increases in intracellular calcium may be detrimental for neurons. It was shown early that *ortho*-PCBs affect calcium homeostasis in synaptosomes (Rosin and Martin 1981) as well as in other cell types and preparations. PCB-induced increases in intracellular calcium have been attributed to release from both extracellular and intracellular stores (for review, see Kodavanti 2006). Early work focused on PCB-induced inhibition of PKC translocation, as determined by phorbol ester binding in cerebellar granule cells, and calcium sequestration as determined by calcium uptake in microsomal fractions (Kodavanti *et al.* 1993, 1994). Later studies showed that A1254 induces Ca^{2+} release from inositol-triphosphate (IP_3) sensitive Ca^{2+} stores in ER, followed by a sustained influx of Ca^{2+} from store operated Ca^{2+} channels, glutamate receptors and L-type voltage-dependent sensitive Ca^{2+} channels in rat neocortical cells (Inglefield and Shafer 2000b; Inglefield *et al.* 2001). Magi *et al.* (2005) demonstrated that A1254 increased intracellular calcium in human neuroblastoma cells *via* inhibition of the specific sodium-calcium exchanger 1, which has a low affinity, but high capacity for calcium transport.

In several studies, Pessah and coworkers have shown that the non-coplanar PCB-95 interacts with the FK506 binding protein and the ryanodine receptor (RyR) complex and sensitizes calcium release from cells (Wong *et al.* 1997a,b; Gafni *et al.* 2004). The effect on RyR activation is congener selective. A detailed structure activity relationship for PCBs together with some hydroxy and sulfonyl PCB metabolites, showed that the 2, 3, 6-PCB configuration is important for optimal activation of RyR1 receptor. Substitution in the *para* position, such as 4-chloride, decreased the effect, 4-OH-substitution decreased the effect even more and 4-methylsulfonyl group eliminated the activity (Pessah *et al.* 2006). Pessah *et al.* (2009) also took advantage of the fact that some PCBs are chiral and can be obtained in different enantiomers. They found that (−) PCB-136 enhances the binding of ryanodine to the high affinity site of RyR1 and RyR2 and induces a rapid release of calcium from microsomal vesicles by selective sensitization of RyR. The (+) PCB-136 enantiomer was shown to be inactive at the concentrations tested and did not antagonize the effect of (−) PCB 136 enantiomer. Effects on RyR have also been shown *in vivo*. Schantz *et al.* (1997) found decreased ryanodine specific binding in the hippocampus and increased binding in the cerebral cortex in rats exposed during gestation. The effect was associated with locomotor and spatial learning deficits. In a recent study by Kim *et al.* (2009) it was shown that low levels of the non-coplanar PCB-95 and -170 (10–100 nM) enhanced field excitatory post-synaptic potentials in the CA1 region in hippocampal slice preparations. The effect of PCB-95 was associated with a sensitization of RyR followed by stimulation of both GABA and glutamate release. The effect of PCB-170, however, was enhanced by the GABA-blocker picrotoxin, indicating congener-selective mechanisms of action. Lehmler *et al.* (2005) reported the effect of the racemic PCB-84 and its enantiomers on two neurochemical measures: PKC translocation, as determined by [^{3}H]-phorbol ester binding in cerebellar granule cells, and calcium sequestration, as determined by $^{45}Ca^{2+}$-uptake by microsomes isolated from adult rat cerebellum. The racemic mixture of PCB-84 was significantly more potent and efficacious than the pure enantiomers, both in inhibition of microsomal $^{45}Ca^{2+}$-uptake and in phorbol ester binding. Kodavanti *et al.* (2003) showed that several hydroxylated PCBs increased PKC translocation in cerebellar granule cells and inhibited $^{45}Ca^{2+}$-uptake in microsomes, albeit with different potency and selectivity. 2′,4′,6′-Trichloro-4-biphenylol was the most active compound, and the results indicated that the hydroxyl-PCBs were as active as the parent PCBs.

Some BFR also affect calcium homeostasis. Kodavanti *et al.* compared the effect of different PBDE mixtures and PBDE congeners with A1254 on calcium uptake in microsomes prepared from different brain regions (Kodavanti and Ward 2005; Kodavanti *et al.* 2005). They showed that DE-71, which primarily consists of tetra- and penta-brominated diphenyl ethers, was as potent as A1254 in disrupting microsomal calcium homeostasis. DE-79, which primarily consists of hepta- and octa-brominated diphenyl ethers, had no effect. A study of the single congeners, BDE-47 and BDE-99, which are the prime constituents of DE-71, showed that both congeners inhibit uptake of $^{45}Ca^{2+}$ into microsomes and mitochondria isolated from rat frontal cortex, cerebellum, hippocampus and hypothalamus. The mitochondria were more sensitive than the microsomes (Coburn *et al.* 2008). In neuroblastoma cells exposed to DE-71, there was a time-dependent elevation of intracellular calcium (Yu *et al.* 2008). Exposure of PC12 cells to 6-OH-BDE-47 (5 μM) induced a transient increase in $[Ca^{2+}]_i$ followed by an additional late increase in $[Ca^{2+}]_i$. The parent compound had a similar effect, although it was less potent. Use of

pharmacological inhibitors suggested that the initial calcium increase originates from ER, whereas, the late increase originates from mitochondria (Dingemans *et al.* 2008). On the other hand, HBCD inhibited the depolarization-induced increase in $[Ca^{2+}]_i$ in PC12 cells, of which the α-HBCD diastereomer appeared to be the most potent (Dingemans *et al.* 2009).

Bemis and Seegal (2000) investigated intracellular calcium concentrations in cerebellar granule cells following PCB and MeHg exposure. Exposure of cerebellar granule cells to mixtures of 2,2′-dichloro biphenyl (2.5 or 5 μM) and MeHg (1.5 μM) showed synergistic increases in $[Ca^{2+}]_i$, that peaked after 5 and 10 min exposure. Higher dose combinations, including 2.0 μM MeHg and 10 or 20 μM 2,2′-dichloro biphenyl (DCB), or longer duration of exposure to lower concentrations of contaminant mixtures, reduced $[Ca^{2+}]_i$ in the granule cells compared with elevations seen following exposure to MeHg only, suggesting a dose-dependent antagonism between PCBs and MeHg. These data provide evidence for both synergistic and antagonistic interactions between PCBs and MeHg at the level of $[Ca^{2+}]_i$ regulation, that may ultimately lead to alterations in cellular functions.

Oxidative stress and cell viability

Numerous investigations show that non-coplanar PCBs induce both apoptotic and necrotic cell death in a range of nerve cell preparations *in vitro*, of which oxidative stress probably is a major causative effect. Mariussen *et al.* (2002) showed that PCBs increase reactive oxygen species (ROS) formation, measured using the fluorigenic probe dichlorofluorescein (DCFH), in cerebellar granule cells. The coplanar PCB-126 had no effect. The formation of ROS was abolished by the presence of the antioxidant α-tocopherol. Antioxidants, including α-tocopherol, ginseng extract, and trolox are shown to protect against PCB-induced decreases in cell viability in cultured embryonic rat hippocampal neurons (Howard *et al.* 2003), in SK-N-MC cells (Lee *et al.* 2004) and in the dopaminergic cell line MN9D (Lee and Opanashuk 2004), respectively. Protective effects of antioxidants have also been reported following *in vivo* exposure of PCBs. Rats exposed peritoneally to 2 mg/kg/day of A1254 for 30 days showed decreased levels of enzymatic antioxidants such as SOD, GSH peroxidase, GSH reductase, and catalase in cerebellum, cerebral cortex, hippocampus (Venkataraman *et al.* 2007), and hypothalamus (Muthuvel *et al.* 2006). The effect was counteracted by ascorbic acid (100 mg/day) (Muthuvel *et al.* 2006; Venkataraman *et al.* 2007). Venkataraman *et al.* (2007) also found an increase in the hydrogen peroxide level and increased lipid peroxidation, as well as depleted GSH levels. In two identical studies animals were fed α-tocopherol or melatonin, and these two antioxidants protected against lipid peroxidation, formation of hydrogen peroxide and the reductions in GSH level. In addition, melatonin protected against formation of the OH-radical in cerebellum, cerebral cortex and hippocampus (Sridevi *et al.* 2007; Venkataraman *et al.* 2008). It has been hypothesized that the effect of PCBs on cell viability and oxidative stress in particular, is a consequence of elevation of intracellular calcium and/or altered neurotransmitter compartmentalization and neurotransmitter receptor activation. Elevation of intracellular calcium may activate a range of different signaling pathways, of which several can induce oxidative stress. Signal transduction pathways that are involved in PCB-induced oxidative stress and which can be linked to calcium are PKC activation (Kodavanti *et al.* 1994), phospholipase A_2 activation (Kodavanti and Derr-Yellin 2002), NOS (Kang *et al.* 2002), and glutamate receptor activation (Mariussen *et al.* 2002; Gafni *et al.* 2004). In line with these findings, PCB-induced ROS formation in cerebellar granule cells was reduced by the NMDA receptor antagonist MK-801 and to a lesser extent the α-amino-3-hydroxy-5-methylisoxazole-4-propionate receptor blocker 2,3-dioxo-6-nitro-1,2,3,4-tetrahydrobenzo[f]quinoxaline-7-sulphonamide (NBQX), as well as by inhibitors of phospholipase A_2, NOS, and the mitochondrial permeability transition pore (Mariussen *et al.* 2002). Howard *et al.* (2003) showed that proapoptotic activity of PCBs is inhibited by RyR-antagonists and α-tocopherol in rat hippocampal neurons, indicating a link between PCB-induced increases in intracellular calcium, apoptosis and oxidative stress. IP_3 and NMDA receptor antagonists were not protective in this preparation. Kang *et al.* (2004) exposed CATHa cells to PCBs and observed an elevation in intracellular calcium, both in the presence and the absence of extracellular calcium, followed by decreased cell viability. The intracellular calcium increase was inhibited by an IP_3 receptor (IP_3R) antagonist and slightly inhibited by a RyR blocker, indicating release from ER. Both IP_3R and RyR-antagonists protected against A1254-induced cell death, whereas calcium chelators and NMDA blockers were without effect. Kang *et al.* (2004) also found a reduction in intracellular DA concentration, but neither calcium chelators nor a calcium receptor antagonist prevented the depletion of DA, indicating that the mechanism of PCB-induced DA depletion may be independent of calcium alterations. In a previous study, Mariussen *et al.* (2002) showed that the NMDA receptor inhibitor MK-801 protected cerebellar granule cells against PCB-induced cell death, indicating calcium transport through the NMDA receptor. In a recent study by Ndountse and Chan (2009) this was confirmed with the use of SH-SY5Y neuroblastoma cells. They found that the toxic effect of non-planar PCBs was prevented by the NMDA blockers MK-801 and memantin. They also observed a protective effect of the calcium-chelator 1,2-bis(2-aminophenoxy)ethane-N,N,N′,N′-tetraacetic acid tetrakis (BAPTA-AM), indicating involvement of calcium (Ndountse and Chan 2009). Thus, there is good evidence that increased intracellular calcium levels are involved in PCB-induced cell

death. It seems, however, that the different types of cell preparations have different ways of allowing this to occur. As discussed above, IP_3R, RyR, and NMDA receptors may be involved, depending on the cell type.

Recently, the involvement of DA-induced oxidative stress and toxicity has been more thoroughly investigated. In the synapse, the action of released DA is terminated by rapid reuptake by DAT. Once inside the terminal, DA is effectively transported into synaptic vesicles by the VMAT-2 and thereby protected from oxidation (Liu *et al.* 1996). The VMAT-2 maintains a low cytosolic level of DA and prevents DA-induced toxicity, such as free radical formation and inhibition of mitochondrial respiration, in the neuron (Ben-Shachar *et al.* 1995; Hastings *et al.* 1996). An imbalance between plasma membrane uptake and vesicular uptake of DA may have severe consequences. In the pH-neutral cytosol, DA is easily oxidized and may generate ROS. DA is therefore toxic to the intracellular environment of the cell (Graham *et al.* 1978; Slivka and Cohen 1985; Cubells *et al.* 1994; Miller *et al.* 1999). Caudle *et al.* (2007) showed that mice expressing a low level of VMAT-2 display extensive nigrostriatal degeneration. Strong inhibition of VMAT-2 transporters compared with low inhibitions of DAT transporters increases the susceptibility of DA-induced neurotoxicity (Miller *et al.* 1999). The recent findings that PCBs as well as other organohalogenated compounds influence the ratio between DAT and VMAT (Richardson and Miller 2004; Richardson *et al.* 2006, 2008; Caudle *et al.* 2005), and the fact that PCBs are inhibitors of both DAT and VMAT make it plausible that such compounds increase oxidative stress, particularly in dopaminergic cells. In support of this hypothesis, Lee and Opanashuk (2004) have shown that dopaminergic cells are more susceptible to A1254-induced oxidative injury than are non-dopaminergic cells. They found that A1254 selectively induces oxidative stress and reduces cell viability in the dopaminergic cell population of primary mesencephalic cells. Furthermore, Lee and Opanashuk (2004) found that PCBs induce a time- and concentration-dependent increase in ROS production in dopaminergic MN9D cells, which preceded cytotoxicity. Intracellular GSH depletion exacerbated PCB effects, and antioxidant pretreatment with trolox attenuated ROS production and cell death. Coincident alterations in antioxidant defense enzymes also accompanied ROS production, including decreased MnSOD and increased CuZnSOD protein levels. In a later study, Lee *et al.* (2006) found that PCB-exposed MN9D cells had increased expression of heme-oxygenase-1 (HO-1) and augmented intracellular Fe levels after 24 h. Fe chelating by desferoxamine or pharmacologic inhibition of HO-1 activity with tin-protoporphyrin reduced Fe accumulation, ROS production, and cytotoxicity. HO-1 over-expression predisposed MN9D cells to enhanced ROS production and cell death in response to PCBs. Conversely, antisense inhibition of HO-1 expression prevented PCB-induced ROS production and cell death. These observations suggest that enhanced HO-1 catalytic activity and subsequent liberation of Fe participate in neurotoxic dopaminergic cell injury caused by A1254. The importance of dopaminergic cells in PCB toxicity has further been studied by using organotypic cocultures between developing striatum and ventral mesencephalon. An environmentally relevant PCB mixture decreased the number of dopaminergic cells in mesencephalon and GABAergic cells in striatum (Lyng *et al.* 2007). The importance of DA transport was demonstrated by a reduction in tissue concentrations of DA, GABA and DAT protein and an increase in soluble DA and homovanilic acid. The reduction of GABAergic cells seemed to be linked to oxidative stress and to occur prior to DA cell death (Lyng *et al.* 2007). Further studies with PCB-exposed organotypic cocultures showed an increase in oxidative stress, as shown with dihydrorhodamine measurements, and depletion of tissue GSH (Lyng and Seegal 2008). Depletion of DA from the co-culture with use of α-methyl-*p*-tyrosine abolished the formation of oxidative stress, and the GSH and GABA depletion. Therefore, it seems likely that PCB-induced neuronal toxicity originates in DA neuronal terminals through inhibition of VMAT and consequent increases in cytoplasmic DA and oxidation of DA. This gives a reduction in antioxidant defense mechanisms that is likely to lead to additional neuronal damage and eventual loss of both ventral mesencephalon and striatal GABA neurons. It seems most likely that reductions in DA transport are responsible for increased cytosolic DA levels, and that oxidative stress because of DA oxidation is responsible for dopaminergic and GABAergic cell death.

Brominated flame retardants also affect cell viability and induce oxidative stress. DE-71, HBCD and TBBPA induce cell death, both necrotic and apoptotic, in cerebellar granule cells, albeit with different mechanisms of action (Reistad *et al.* 2006, 2007). To compare the effects with previous studies on PCBs, several potentially protective substances were added in combination with the BFRs. It was found that both the NMDA receptor inhibitor MK-801 and the antioxidant α-tocopherol protected against BFR-induced cell death. These results are similar to the effects induced by PCBs (Mariussen *et al.* 2002). In contrast to DE-71 and HBCD, TBBPA was shown to potently induce oxidative stress, as shown with dichlorofluorescein fluorescence. The TBBPA-induced oxidative stress was linked to a high increase in intracellular calcium levels, induction of extracellular signal-regulated protein kinase in the mitogen-activated protein kinase pathway, and release of glutamate. These findings indicate that TBBPA induces a glutamate mediated excitotoxicity of cerebellar granule cells. He *et al.* (2008a,b) exposed neuroblastoma cells (SH-SY5Y) and primary rat hippocampal neurons to BDE-47 and found reduced cell viability at ~8 and 40 μM, respectively. Flow cytometry showed the presence of apoptotic cells and an increase in

DNA-damage in both cultures. The difference in sensitivity between the cell types might be because of methodological procedures, such as presence of serum in growth media during exposure. Serum reduces the bioavailability and effect of strongly lipophilic chemicals. The hypothesis that viability of nerve cells following exposure to environmental toxicants is related to oxidative stress was investigated in detail by Giordano *et al.* (2008). They demonstrated that DE-71-induced cell death of cerebellar granule cells was followed by formation of oxidative stress, as shown with dichlorofluorescein, and lipid peroxidation. Cerebellar granule cells isolated from knockout mice with low levels of GSH were more susceptible to DE-71 exposure than neurons isolated from wild-type mice. The addition of GSH and antioxidants, such as *N*-acetylcysteine, N-tert-butyl-alpha-phenylnitrone (PBN), and melatonin protected against DE-71-induced toxicity (Giordano *et al.* 2008). Giordano *et al.* (2009) recently also showed that astrocytes isolated from wild-type mice with normal GSH levels, protect cerebellar granule cells with low GSH levels against DE-71-induced cell death. Astrocytes with low GSH level in coculture with cerebellar granule cells had no protective effects.

Nevertheless, only few studies have been published concerning mixture effects on cell viability and oxidative stress. To investigate possible interactions between PCB-153 and MeHg, Vettori *et al.* (2006) exposed PC12 cells to binary mixtures in different proportions according to the Löewe model of additivity. In general, it was found that the mixtures reduced cell viability and elicited additive effects. At some concentrations, however, antagonism was observed. No trend toward synergism was observed.

Effects on thyroid hormones

Much research has focused on the possible interactions of PCBs as well as other environmental toxicants with neuroendocrine targets, with emphasis on the TH system. The TH system appears vulnerable to environmental toxicants especially during early development (for review, see Porterfield 1994; Crisp *et al.* 1998; Zoeller *et al.* 2002; Colborn 2004). TH is crucial for brain development and TH deficiency during gestation causes cretinism, with severe cognitive and/or mental disorders in the offspring (Oppenheimer and Schwartz 1997; Koibuchi and Chin 2000). The molecular structures of PCBs, as well as BFRs and metabolites of these chemicals, are similar to those of TH (Fig. 4) and may therefore act via TH receptors and/or TH-transport proteins. Effects of PCBs on the TH system were reported as early as the mid-1970s (Bastomsky 1974; Yamane *et al.* 1975). Some researchers have reported that PCB exposure results in thyroid enlargement and reduced serum total T4 levels with normal T3 levels in the adult animals and during development (Morse *et al.* 1996; Brouwer *et al.* 1998; Hauser *et al.* 1998; Porterfield 2000). Plasma TH levels can be reduced by

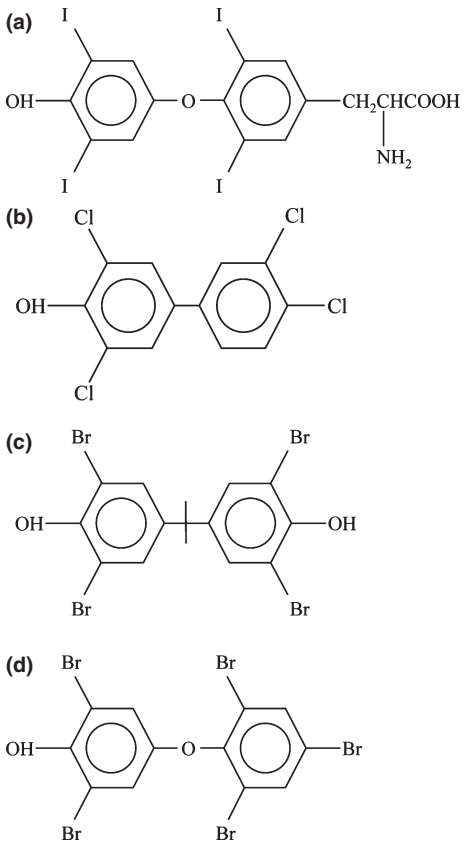

Fig. 4 Molecular structures of (a) thyroxine, (b) OH-PCB, (c) TBBPA and (d) OH-PBDE showing structural similarities.

PCBs in at least three ways. First, compounds can affect the thyroid gland and influence the synthesis of THs (Collins and Capen 1980). Second, certain PCB congeners are reported to induce the expression of a microsomal enzyme, uridine diphosphate glucuronosyl-transferase, which metabolizes T4 to its glucuronide to facilitate its excretion (Beetstra *et al.* 1991; Brouwer 1991; Barter and Klaassen 1994). Third, the binding of PCBs and particularly OH-PCB to T4 transport proteins displace the natural hormone (Rickenbacher *et al.* 1986; McKinney *et al.* 1987; Brouwer 1989, 1990; Morse *et al.* 1996). Many of the hydroxylated PCBs, and even the BFR TBBPA, have a higher affinity for the transport protein transthyretin than T4 itself (Cheek *et al.* 1999; Meerts *et al.* 2000; Kitamura *et al.* 2005). Apparently, PCBs and hydroxy-PCBs have low affinity for the thyroid receptor (Cheek *et al.* 1999). Maternal exposure to A1254 on GDs 14–16 resulted in the accumulation of 4-OH-PCB-107 in fetal plasma and brain in rats (Morse *et al.* 1996). In this case, the maternal to fetal transfer of this hydroxylated PCB is facilitated by binding to transthyretin *in vivo;* this mechanism can lead to decreased fetal brain T4 levels (Meerts *et al.* 2002). The TH system has an effect on the development of the cholinergic system (Smith *et al.* 2002). Pregnant rats were given chow

containing various concentrations of PCBs (0, 12.5, 62.5, 125, or 250 ppm) to expose the offspring during pregnancy and lactation. On PND15, the offspring showed depressed circulating T4 levels and choline acetyltransferase (ChAT) activity in a dose–response manner at all concentrations of PCBs. There were no modifications of T3 levels. Injections of T4, but not T3, elevated ChAT activity in the exposed rats to near control levels. Thus, altered ChAT activity may partially result from the hypothyroidism accompanying PCB poisoning (Juárez de Ku *et al.* 1994; Provost *et al.* 1999). These findings suggest that PCBs induce abnormal brain development by acting directly on the TH system.

Brominated flame retardants affect the TH system both *in vivo* and *in vitro*. *In vivo* studies have shown a reduction in serum T4 levels following exposure to PBDEs, both after acute and subacute exposure (Fowles *et al.* 1994) and after gestational exposure (Hallgren *et al.* 2001; Zhou *et al.* 2001, 2002). HBCD was shown to reduce serum T4 levels, albeit at relatively high concentrations (van der Ven *et al.* 2006). The study by Hallgren *et al.* (2001), however, showed that PCBs are more potent substances than both PBDEs and HBCD. Interaction studies with human transthyretin receptor showed that PBDEs have to undergo metabolic activation before the compounds are able to competitively inhibit binding of T4 (Meerts *et al.* 2000; Hamers *et al.* 2006). This indicates that it is the hydroxy-metabolites of PBDEs that are responsible for the observed effect. In the study by Meerts *et al.* (2000), it was also shown that TBBPA had an even higher affinity for the transthyretin receptor than T4 itself. *In vivo* studies have, however, shown that only relatively high TBBPA concentrations (30 mg/kg/day for one generation reproduction study) influence the TH system, probably because of the short half-life of TBBPA *in vivo* (van der Ven *et al.* 2008).

Brain structural changes and synaptic plasticity

The behavioral effects of PCB exposure, implicating negative impact on memory, learning, and motor functions, has led to the hypothesis that PCB exposure may induce structural changes in brain or affect neuronal plasticity. Induction and expression of LTP is regarded as a model for learning and memory (Sweatt 1999) and several studies have shown that different PCBs reduce LTP in the visual cortex and hippocampus, both *in vivo* and *in vitro* (e.g. Altmann *et al.* 1995; Gilbert and Crofton 1999; Ozcan *et al.* 2004). Several receptors and signaling pathways are involved in the induction, maintenance, and expression of LTP, of which several are shown to be affected by PCBs, including calcium homeostasis, PKC, and neurotransmitter modulation as discussed above. The effects on LTP, however, appear with both *ortho*-PCBs and the non-*ortho*-PCBs (Ozcan *et al.* 2004). This contradicts the current theory that *ortho*-PCBs are responsible for the effect on brain, and indicates that other factors not yet discovered are responsible for the effect on LTP.

Recent studies have shown that PCBs may induce structural changes in the brain. Roegge *et al.* (2006) observed a trend toward taller Purkinje cell dendritic trees in Long–Evans rats on PND 21 after A1254 exposure (6 mg/kg/day) from GD 6 to PND 16. However, the changes were not significant. Lein *et al.* (2007) exposed female rats to 6 mg/kg/day A1254 from GD 6 to PND 21 and observed small changes in the dendritic length of both CA1 pyramidal cells in hippocampus and in Purkinje cells. The effect did not persist through PND 61. In a follow up study Yang *et al.* (2009) showed that exposure to A1254 interferes with the normal development of dendrites in rats exposed to 1 and 6 mg/kg/day during gestation until PND 21. Only the rats exposed to 1 mg/kg/day showed impaired results when tested on the Morris water maze. In addition to dendritic growth and RyR expression, TH-levels were measured in the animals. In non-trained animals, only the 1 mg/kg/day group displayed a significantly increase in the dendritic length of cerebellar and cortical cells compared with control, whereas the high dose group had no effect. In trained animals, the control animals revealed an increase in dendritic growth, whereas dendritic growth among the 1 mg/kg/day group was reversed and the 6 mg/kg/day group displayed attenuation in dendritic growth. Furthermore, the density of RyR1 in particular, changed in parallel to the dendritic growth. The major findings of this study were that developmental PCB exposure enhanced basal dendritic growth in untrained animals but decreased experience-dependent dendritic plasticity, and that these effects correlated better with altered RyR expression than with endocrine disruption.

Polychlorinated biphenyl-95 appears to have the highest potency measured so far among PCB congeners in altering RyR function in neurons (Pessah *et al.* 2006). Exposure of PCB-95 to cortical neuronal cultures increased their dendritic tree more than exposure to PCB-66 (Yang *et al.* 2009). Exposure to this congener also resulted in abnormal auditory cortex development with changes in the balance between excitatory and inhibitory input to neurons (Kenet *et al.* 2007), while the hearing sensitivity and brainstem auditory response were normal. Other studies have, however, pointed to an effect of PCB on hearing. Rats exposed to A1254 had a loss of outer hair cells on the basilar membrane of the cochlea. The affected area corresponded to the area responsible for low frequency hearing (Goldey *et al.* 1995; Herr *et al.* 1996; Crofton *et al.* 2000; Lasky *et al.* 2002; Powers *et al.* 2006).

Kimura-Kuroda *et al.* (2005) exposed mice cerebellar granule cells to low doses of two OH-PCBs (nM), 4-OH-2′,3,3′,4′,5′-pentachloro biphenyl and 4-OH-2′,3,3′,4′,5,5′-hexachloro biphenyl and found that they inhibited the TH-dependent dendritic development of Purkinje cells. In contrast, 4-OH-2′,3,3′,5′,6′-pentachloro biphenyl, 4-OH-

2′,3,3′,5,5′,6′-hexachloro biphenyl, 4-OH-2,2′,3,4′,5,5′,6-heptachloro biphenyl did not inhibit TH-dependent dendritic development, but significantly promoted the dendritic extension of Purkinje cells in the absence of TH (Kimura-Kuroda *et al.* 2007).

Conclusions

Behavioral testing of rats, mice, and monkeys has established that industrial chemicals which have been or are still produced in high volume, such as PCBs, may affect learning and memory in young animals. This has also been supported by several epidemiological studies. PCBs and several BFRs also have effects on motor activity. In addition, it has been hypothesized that exposure to environmental toxicants may lead to increased prevalence of ADHD. Of particular concern is that humans are not only exposed to single toxic substances, but mixtures of potentially toxic substances such as PCBs, BFRs, and MeHg, in addition to pesticides, heavy metals, and even toxic metabolites. This constitutes major challenges for risk assessment, complicates the identification of the compounds responsible for toxic effects, and increases the likelihood of interactions. Several studies indicate, however, that most combinations are additive. Both PCBs and BFRs seem to have several potential neurochemical targets, such as neurotransmitter function, calcium homeostasis, and ROS formation. The neurotransmitters most strongly affected seem to be the monoamines, and both transport and release are affected. There are also some effects linked to the nicotine receptor. Furthermore, there is strong evidence that the calcium homeostasis is affected. In particular, there is substantial evidence that the RyR is involved, but several other calcium channels are also shown to be affected. Several pathways following PCBs and BFRs exposure lead to increased ROS formation. In this respect it should be noted that ROS formation often depends on calcium activation. Furthermore, cytoplasmic DA levels can increase because of alterations in the ratio between plasma membrane and vesicle transport, and can easily be oxidized to toxic reactive species. In addition, neuroendocrine parameters are affected, especially the TH system. The existence of a single critical target in the brain following PCB and BFR exposure is debated. It is probably necessary to distinguish between developmental and adult exposure, with neuroendocrine effects being of higher importance during developmental exposure than during adult exposure.

Acknowledgements

The authors are indebted to Dr Anne Dreiem at Wadsworth Center, New York State Department of Health, Dr Yngvar Gundersen at Norwegian Defense Research Establishment, and Dr Inger-Lise Bogen at Institute of Basic Medical Sciences, University of Oslo for reading the manuscript.

References

Abdallah M. A., Ibarra C., Neels H., Harrad S. and Covaci A. (2008) Comparative evaluation of liquid chromatography-mass spectrometry versus gas chromatography-mass spectrometry for the determination of hexabromocyclododecanes and their degradation products in indoor dust. *J. Chromatogr. A* **1190**, 333–341.

Alaee M. and Wenning R. J. (2002) The significance of brominated flame retardants in the environment: current understanding, issues and challenges. *Chemosphere* **46**, 579–582.

Alaee M., Arias P., Sjodin A. and Bergman Å. (2001) An overview of commercially used brominated flame retardants, their applications, their use patterns in different countries/regions and possible modes of release. *Environ. Int.* **29**, 683–689.

Altmann L., Weinand-Haerer A., Lilienthal H. and Wiegand H. (1995) Maternal exposure to polychlorinated biphenyls inhibits long-term potentiation in the visual cortex of adult rats. *Neurosci. Lett.* **202**, 53–56.

Altmann L., Mundy W. R., Ward T. R., Fastabend A. and Lilienthal H. (2001) Developmental exposure of rats to a reconstituted PCB mixture or aroclor 1254: effects on long-term potentiation and [H-3]MK-801 binding in occipital cortex and hippocampus. *Toxicol. Sci.* **61**, 321–330.

Andersson Ö. and Blomkvist G. (1981) Polybrominated aromatic pollutants found in fish in Sweden. *Chemosphere* **10**, 1051–1060.

Angus W. G. R. and Contreras M. L. (1996) Effects of polychlorinated biphenyls on dopamine release from PC12 cells. *Toxicol. Lett.* **89**, 191–199.

Angus W. G. R., Mousa M. A., Vargas V. M., Quensen J. F., Boyd S. A. and Contreras M. L. (1997) Inhibition of L-aromatic amino acid decarboxylase by polychlorinated biphenyls. *Neurotoxicology* **18**, 857–867.

Aschner M. and Aschner J. L. (1990) Mercury neurotoxicity: mechanisms of blood–brain barrier transport. *Neurosci. Biobehav. Rev.* **14**, 169–176.

Aschner M. and Ceccatelli S. (2009) Neuropathological conditions relevant to ethylmercury exposure. *Neurotox. Res.* (DOI: 10.1007/s12640-009-9113-2).

Athanasiadou M., Cuadra S. N., Marsh G., Bergman A. and Jakobsson K. (2008) Polybrominated diphenyl ethers (PBDEs) and bioaccumulative hydroxylated PBDE metabolites in young humans from Managua, Nicaragua. *Environ. Health Perspect.* **116**, 400–408.

Bakke J. E., Bergman Å. and Larsen G. L. (1982) Metabolism of 2,4′,5′-trichlorobiphenyl in the mercapturic acid pathway. *Science* **217**, 645–657.

Bakke J. E., Feil V. J. and Bergman Å. (1983) Metabolites of 2,4′,5-trichlorobiphenyl in rats. *Xenobiotica* **13**, 555–564.

Barkley R. A. (1998) Attention-deficit hyperactivity disorder. *Sci. Am.* **279**, 66–71.

Barter R. A. and Klaassen C. D. (1994) Reduction of thyroid hormone levels and alteration of thyroid function by four representative UDP-glucuronosyltransferase inducers in rats. *Toxicol. Appl. Pharmacol.* **128**, 9–17.

Bastomsky C. H. (1974) Effects of a polychlorinated biphenyl mixture (aroclor 1254) and DDT on biliary thyroxine excretion in rats. *Endocrinology* **95**, 1150–1155.

Becher G. (2005) The stereochemistry of 1,2,5,6,9,10-hexabromocyclododecane and its graphic representation. *Chemosphere* **58**, 989–991.

Beetstra J. B., van Engelen J. G., Karels P., van der Hoek H. J., de Jong M., Docter R., Krenning E. P., Hennemann G., Brouwer A. and Visser T. J. (1991) Thyroxine and 3,3′,5-triiodothyronine are glucuronidated in rat liver by different uridine diphosphate-glucuronyltransferases. *Endocrinology* **128**, 741–746.

Bemis J. C. and Seegal R. F. (1999) Polychlorinated biphenyls and methylmercury act synergistically to reduce rat brain dopamine content *in vitro*. *Environ. Health Perspect.* **107**, 879–885.

Bemis J. C. and Seegal R. F. (2000) Polychlorinated biphenyls and methylmercury alter intracellular calcium concentrations in rat cerebellar granule cells. *Neurotoxicology* **21**, 1123–1134.

Bemis J. C. and Seegal R. F. (2004) PCB-induced inhibition of the vesicular monoamine transporter predicts reductions in synaptosomal dopamine content. *Toxicol. Sci.* **80**, 288–295.

Ben-Shachar D., Zuk R. and Glinka Y. (1995) Dopamine neurotoxicity – inhibition of mitochondrial respiration. *J. Neurochem.* **64**, 718–723.

Berger D. F., Lombardo J. P., Jeffers P. M., Hunt A. E., Bush B., Casey A. and Quimby F. (2001) Hyperactivity and impulsiveness in rats fed diets supplemented with either Aroclor 1248 or PCB-contaminated St. Lawrence river fish. *Behav. Brain Res.* **126**, 1–11.

Bergman Å., Norstrøm R. J., Haraguchi K., Kuroki H. and Beland P. (1994) PCB and DDE methyl sulfones in mammals from Canada and Sweden. *Environ. Toxicol. Chem.* **13**, 121–128.

Birnbaum L. S. and Staskal D. F. (2004) Brominated flame retardants; cause for concern? *Environ. Health Perspect.* **112**, 9–17.

Branchi I., Alleva E. and Costa L. G. (2002) Effects of perinatal exposure to a polybrominated diphenyl ether (PBDE 99) on mouse neurobehavioural development. *Neurotoxicology* **23**, 375–384.

Branchi I., Capone F., Vitalone A., Madia F., Santucci D., Alleva E. and Costa L. G. (2005) Early developmental exposure to BDE 99 or Aroclor 1254 affects neurobehavioural profile: interference from the administration route. *Neurotoxicology* **26**, 183–192.

Breivik K., Sweetman A., Pacyna J. M. and Jones K. C. (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.

Bridges C. C. and Zalups R. K. (2005) Molecular and ionic mimicry and the transport of toxic metals. *Toxicol. Appl. Pharmacol.* **204**, 274–308.

Brouwer A. (1989) Inhibition of thyroid hormone transport in plasma of rats by polychlorinated biphenyls. *Arch. Toxicol.* **13**(Suppl.), 440–445.

Brouwer A. (1990) Competitive-inhibition of thyroxine binding to transthyretin by monohydroxy metabolites of 3,4,3′,4′-tetrachlorobiphenyl. *Chemosphere* **20**, 1257–1262.

Brouwer A. (1991) Role of biotransformation in PCB-induced alterations in vitamin-A and thyroid-hormone metabolism in laboratory and wildlife species. *Biochem. Soc. Trans.* **19**, 731–737.

Brouwer A., Morse D. C., Lans M. C., Schuur A. G., Murk A. J., Klasson-Wehler E., Bergman A. and Visser T. J. (1998) Interactions of persistent environmental organohalogens with the thyroid hormone system: mechanisms and possible consequences for animal and human health. *Toxicol. Ind. Health* **14**, 59–84.

Castoldi A. F., Coccini T., Ceccatelli S. and Manzo L. (2001) Neurotoxicity and molecular effects of methylmercury. *Brain Res. Bull.* **55**, 197–203.

Castoldi A. F., Blandini F., Randine G., Samuele A., Manzo L. and Coccini T. (2006) Brain monoaminergic neurotransmission parameters in weanling rats after perinatal exposure to methylmercury and 2,2′,4,4′,5,5′-hexachlorobiphenyl (PCB153). *Brain Res.* **1112**, 91–98.

Caudle W. M., Richardson J. R., Wang M. and Miller G. W. (2005) Perinatal heptachlor exposure increases expression of presynaptic dopaminergic markers in mouse striatum. *Neurotoxicology* **26**, 721–728.

Caudle W. M., Richardson J. R., Delea K. C., Guillot T. S., Wang M., Pennell K. D. and Miller G. W. (2006) Polychlorinated biphenyl-induced reduction of dopamine transporter expression as a precursor to Parkinson's disease-associated dopamine toxicity. *Toxicol. Sci.* **92**, 490–499.

Caudle W. M., Richardson J. R., Wang M. Z., Taylor T. N., Guillot T. S., McCormack A. L., Colebrooke R. E., Di Monte D. A., Emson P. C. and Miller G. W. (2007) Reduced vesicular storage of dopamine causes progressive nigrostriatal neurodegeneration. *J. Neurosci.* **27**, 8138–8148.

Cheek A. O., Kow K., Chen J. and McLachlan J. A. (1999) Potential mechanisms of thyroid disruption in humans: interaction of organochlorine compounds with thyroid receptor, transthyretin, and thyroid-binding globulin. *Environ. Health Perspect.* **107**, 273–278.

Chen Y. C., Yu M. L., Rogan W. J., Gladen B. C. and Hsu C. C. (1994) A 6-year follow-up of behavior and activity disorders in the Taiwan Yu-cheng children. *Am. J. Public Health* **84**, 415–421.

Cheng J., Yang Y., Ma J., Wang W., Liu X., Sakamoto M., Qu Y. and Shi W. (2009) Assessing noxious effects of dietary exposure to methylmercury, PCBs and Se coexisting in environmentally contaminated rice in male mice. *Environ. Int.* **35**, 619–625.

Chishti M. A., Fisher J. P. and Seegal R. F. (1996) Aroclors 1254 and 1260 reduce dopamine concentrations in rat striatal slices. *Neurotoxicology* **17**, 653–660.

Chou S. M., Miike T., Payne W. M. and Davis G. J. (1979) Neuropathology of 'spinning syndrome' induced by prenatal intoxication with a PCB in mice. *Ann. NY Acad. Sci.* **320**, 373–395.

Clarkson T. W. (2002) The three modern faces of mercury. *Environ. Health Perspect.* **110**(Suppl. 1), 11–23.

Clarkson T. W. and Magos L. (2006) The toxicology of mercury and its chemical compounds. *Crit. Rev. Toxicol.* **36**, 609–662.

Coburn C. G., Currás-Collazo M. C. and Kodavanti P. R. (2008) *In vitro* effects of environmentally relevant polybrominated diphenyl ether (PBDE) congeners on calcium buffering mechanisms in rat brain. *Neurochem. Res.* **33**, 355–364.

Coccini T., Randine G., Castoldi A. F., Grandjean P., Ostendorp G., Heinzow B. and Manzo L. (2006) Effects of developmental co-exposure to methylmercury and 2,2′,4,4′,5,5′-hexachlorobiphenyl (PCB153) on cholinergic muscarinic receptors in rat brain. *Neurotoxicology* **27**, 468–477.

Colborn T. (2004) Neurodevelopment and endocrine disruption. *Environ. Health Perspect.* **112**, 944–949.

Collins W. T. Jr and Capen C. C. (1980) Fine structural lesions and hormonal alterations in thyroid glands of perinatal rats exposed *in utero* and by the milk to polychlorinated biphenyls. *Am. J. Pathol.* **99**, 125–142.

Costa L. G., Aschner M., Vitalone A., Syversen T. and Soldin O. P. (2004) Developmental neuropathology of environmental agents. *Annu. Rev. Pharmacol. Toxicol.* **44**, 87–110.

Counter S. A. and Buchanan L. H. (2004) Mercury exposure in children: a review. *Toxicol. Appl. Pharmacol.* **198**, 209–230.

Covaci A., Gerecke A. C., Law R. J., Voorspoels S., Kohler M., Heeb N. V., Leslie H., Allchin C. R. and de Boer J. (2006) Hexabromocyclododecanes (HBCDs) in the environment and humans: a review. *Environ. Sci. Technol.* **40**, 3679–3688.

Crisp T. M., Clegg E. D., Cooper R. L. *et al.* (1998) Environmental endocrine disruption: an effects assessment and analysis. *Environ. Health Perspect.* **106**(Suppl. 1), 11–56.

Crofton K. M., Ding D., Padich R., Taylor M. and Henderson D. (2000) Hearing loss following exposure during development to polychlorinated biphenyls: a cochlear site of action. *Hear. Res.* **144**, 196–204.

Cubells J. F., Rayport S., Rajendran G. and Sulzer D. (1994) Methamphetamine neurotoxicity involves vacuolation of endocytic organelles and dopamine-dependent intracellular oxidative stress. *J. Neurosci.* **14**, 2260–2271.

Darnerud P. O., Eriksen G. S., Johannesson T., Larsen P. B. and Viluksela M. (2001) Polybrominated diphenyl ethers: occurrence, dietary exposure, and toxicology. *Environ. Health Perspect.* **109**, 49–68.

Davidson P. W., Myers G. J., Weiss B., Shamlaye C. F. and Cox C. (2006) Prenatal methyl mercury exposure from fish consumption and child development: a review of evidence and perspectives from the Seychelles Child Development Study. *Neurotoxicology* **27**, 1106–1109.

Davis J. W., Gonsior S. J., Markham D. A., Friederich U., Hunziker R. W. and Ariano J. M. (2006) Biodegradation and product identification of [14C]hexabromocyclododecane in wastewater sludge and freshwater aquatic sediment. *Environ. Sci. Technol.* **40**, 5395–5401.

Dingemans M. M., Ramakers G. M., Gardoni F., van Kleef R. G., Bergman Å., Di Luca M., van den Berg M., Westerink R. H. and Vijverberg H. P. (2007) Neonatal exposure to brominated flame retardant BDE-47 reduces long-term potentiation and postsynaptic protein levels in mouse hippocampus. *Environ. Health Perspect.* **115**, 865–870.

Dingemans M. M., de Groot A., van Kleef R. G., Bergman Å., van den Berg M., Vijverberg H. P. and Westerink R. H. (2008) Hydroxylation increases the neurotoxic potential of BDE-47 to affect exocytosis and calcium homeostasis in PC12 cells. *Environ. Health Perspect.* **116**, 637–643.

Dingemans M. M., Heusinkveld H. J., de Groot A., Bergman A., van den Berg M. and Westerink R. H. (2009) Hexabromocyclododecane inhibits depolarization-induced increase in intracellular calcium levels and neurotransmitter release in PC12 cells. *Toxicol. Sci.* **107**, 490–497.

Dufault C., Poles G. and Driscoll L. L. (2005) Brief postnatal PBDE exposure alters learning and the cholinergic modulation of attention in rats. *Toxicol. Sci.* **88**, 172–180.

Eriksson P. (1997) Developmental neurotoxicity of environmental agents in the neonate. *Neurotoxicology* **18**, 719–726.

Eriksson P. and Fredriksson A. (1996a) Developmental neurotoxicity of four *ortho*-substituted polychlorinated biphenyls in the neonatal mouse. *Environ. Toxicol. Pharmacol.* **1**, 155–165.

Eriksson P. and Fredriksson A. (1996b) Neonatal exposure to 2,2′,5,5′-tetrachlorobiphenyl causes increased susceptibility in the cholinergic transmitter system at adult age. *Environ. Toxicol. Pharmacol.* **1**, 217–220.

Eriksson P. and Fredriksson A. (1998) Neurotoxic effects in adult mice neonatally exposed to 3, 3′, 4,4′,5-pentachlorobiphenyl or 2, 3,3′,4,4′-pentachlorobiphenyl. Changes in brain nicotinic receptors and behaviour. *Environ. Toxicol. Pharmacol.* **5**, 17–27.

Eriksson P., Lundkvist U. and Fredriksson A. (1991) Neonatal exposure to 3,3′,4,4′-tetrachlorobiphenyl – changes in spontaneous behavior and cholinergic muscarinic receptors in the adult-mouse. *Toxicology* **69**, 27–34.

Eriksson P., Jakobsson E. and Fredriksson A. (2001) Brominated flame retardants: a novel class of developmental neurotoxicants in our environment? *Environ. Health Perspect.* **109**, 903–908.

Eriksson P., Viberg H., Jakobsson E., Orn U. and Fredriksson A. (2002) A brominated flame retardant, 2, 2′, 4, 4′, 5-pentabromodiphenyl ether: uptake, retention, and induction of neurobehavioral alterations in mice during a critical phase of neonatal brain development. *Toxicol. Sci.* **67**, 98–103.

Fein G. G., Jacobson J. L., Jacobson S. W., Schwartz P. M. and Dowler J. K. (1984) Prenatal exposure to polychlorinated-biphenyls – effects on birth size and gestational-age. *J. Pediatr.* **105**, 315–320.

Fernie K. J., Shutt J. L., Letcher R. J., Ritchie J. I., Sullivan K. and Bird D. M. (2008) Changes in reproductive courtship behaviors of adult American kestrels (*Falco sparverius*) exposed to environmentally relevant levels of the polybrominated diphenyl ether mixture, DE-71. *Toxicol. Sci.* **102**, 171–178.

Fischer C., Fredriksson A. and Eriksson P. (2008a) Coexposure of neonatal mice to a flame retardant PBDE 99 (2, 2′,4,4′,5-pentabromodiphenyl ether) and methyl mercury enhances developmental neurotoxic defects. *Toxicol. Sci.* **101**, 275–285.

Fischer C., Fredriksson A. and Eriksson P. (2008b) Neonatal co-exposure to low doses of an *ortho*-PCB (PCB 153) and methyl mercury exacerbate defective developmental neurobehavior in mice. *Toxicology* **244**, 157–165.

Fowles J. R., Fairbrother A., Baecher-Steppan L. and Kerkvliet N. I. (1994) Immunologic and endocrine effects of the flame-retardant pentabromodiphenyl ether (DE-71) in C57BL/6J mice. *Toxicology* **86**, 49–61.

Gabrielsen G. W., Skaare J. U., Polder A. and Bakken V. (1995) Chlorinated hydrocarbons in glaucous gulls (Larus-hyperboreus) in the southern part of Svalbard. *Sci. Total Environ.* **161**, 337–346.

Gafni J., Wong P. W. and Pessah I. N. (2004) Non-coplanar 2, 2′, 3, 5′, 6-pentachlorobiphenyl (PCB 95) amplifies ionotropic glutamate receptor signaling in embryonic cerebellar granule neurons by a mechanism involving ryanodine receptors. *Toxicol. Sci.* **77**, 72–82.

Ganther H. E., Goudie C., Sunde M. L., Kopecky M. J. and Wagner P. (1972) Selenium: relation to decreased toxicity of methylmercury added to diets containing tuna. *Science* **175**, 1122–1124.

Gee J. R. and Moser V. C. (2008) Acute postnatal exposure to brominated diphenylether 47 delays neuromotor ontogeny and alters motor activity in mice. *Neurotoxicol. Teratol.* **30**, 79–87.

Giesy J. P. and Kannan K. (1998) Dioxin-like and non-dioxin-like toxic effects of polychlorinated biphenyls (PCBs): implications for risk assessment. *Crit. Rev. Toxicol.* **28**, 511–569.

Gilbert M. E. and Crofton K. M. (1999) Developmental exposure to a commercial PCB mixture (Aroclor 1254) produces a persistent impairment in long-term potentiation in the rat dentate gyrus *in vivo*. *Brain Res.* **850**, 87–95.

Giordano G., Kavanagh T. J. and Costa L. G. (2008) Neurotoxicity of a polybrominated diphenyl ether mixture (DE-71) in mouse neurons and astrocytes is modulated by intracellular glutathione levels. *Toxicol. Appl. Pharmacol.* **232**, 161–168.

Giordano G., Kavanagh T. J. and Costa L. G. (2009) Mouse cerebellar astrocytes protect cerebellar granule neurons against toxicity of the polybrominated diphenyl ether (PBDE) mixture DE-71. *Neurotoxicology* **30**, 326–329.

Gladen B. C. and Rogan W. J. (1991) Effects of perinatal polychlorinated-biphenyls and dichlorodiphenyl dichloroethene on later development. *J. Pediatr.* **119**, 58–63.

Gladen B. C., Rogan W. J., Hardy P., Thullen J., Tingelstad J. and Tully M. (1988) Development after exposure to polychlorinated-biphenyls and dichlorodiphenyl dichloroethene transplacentally and through human-milk. *J. Pediatr.* **113**, 991–995.

Gochfeld M. (2003) Cases of mercury exposure, bioavailability, and absorption. *Ecotoxicol. Environ. Saf.* **56**, 174–179.

Goldey E. S., Kehn L. S., Lau C., Rehnberg G. L. and Crofton K. M. (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.

Goldoni M. and Johansson C. (2007) A mathematical approach to study combined effects of toxicants *in vitro*: evaluation of the bliss independence criterion and the Löewe additivity model. *Toxicol. In Vitro* **21**, 759–769.

Graham D. G., Tiffany S. M., Bell W. R. Jr and Gutknecht W. F. (1978) Autoxidation versus covalent binding of quinones as the mechanism of toxicity of dopamine, 6-hydroxydopamine, and related

compounds toward C1300 neuroblastoma cells *in vitro*. *Mol. Pharmacol.* **14**, 644–653.

Grandjean P. and Landrigan P. J. (2006) Developmental neurotoxicity of industrial chemicals. *Lancet* **368**, 2167–2178.

Grandjean P., Weihe P., Burse V. W. *et al.* (2001) Neurobehavioral deficits associated with PCB in 7-year-old children prenatally exposed to seafood neurotoxicants. *Neurotoxicol. Teratol.* **23**, 305–317.

Grandjean P., Budtz-Jorgensen E., Steuerwald U., Heinzow B., Needham L. L., Jorgensen P. J. and Weihe P. (2003) Attenuated growth of breast-fed children exposed to increased concentrations of methylmercury and polychlorinated biphenyls. *FASEB J.* **17**, 699–701.

Greco W., Unkelbach H. D., Poch G., Suhnel J. and Bodker W. (1992) Concensus on concepts and terminology for combined action assessment: the Saariselkä agreement. *Arch. Complex Environ. Stud.* **4**, 65–69.

Hakk H. and Letcher R. J. (2003) Metabolism in the toxicokinetics and fate of brominated flame retardants – a review. *Environ. Int.* **29**, 801–828.

Hallgren S., Sinjari T., Håkansson H. and Darnerud P. O. (2001) Effects of polybrominated diphenyl ethers (PBDEs) and polychlorinated biphenyls (PCBs) on thyroid hormone and vitamin A levels in rats and mice. *Arch. Toxicol.* **75**, 200–208.

Hamers T., Kamstra J. H., Sonneveld E., Murk A. J., Kester M. H., Andersson P. L., Legler J. and Brouwer A. (2006) *In vitro* profiling of the endocrine-disrupting potency of brominated flame retardants. *Toxicol. Sci.* **92**, 157–173.

Hardell L., Lindstrom G. and Van Bavel B. (2002) Is DDT exposure during fetal period and breast-feeding associated with neurological impairment? *Environ. Res.* **88**, 141–144.

Hastings T. G., Lewis D. A. and Zigmond M. J. (1996) Reactive dopamine metabolites and neurotoxicity: implications for Parkinson's disease. *Adv. Exp. Med. Biol.* **387**, 97–106.

Hauser P., McMillin J. M. and Bhatara V. S. (1998) Resistance to thyroid hormone: implications for neurodevelopmental research on the effects of thyroid hormone disruptors. *Toxicol. Ind. Health* **14**, 85–101.

He W., He P., Wang A., Xia T., Xu B. and Chen X. (2008a) Effects of PBDE-47 on cytotoxicity and genotoxicity in human neuroblastoma cells *in vitro*. *Mutat. Res.* **649**, 62–70.

He P., He W., Wang A., Xia T., Xu B., Zhang M. and Chen X. (2008b) PBDE-47-induced oxidative stress, DNA damage and apoptosis in primary cultured rat hippocampal neurons. *Neurotoxicology* **29**, 124–129.

Heeb N. V., Schweizer W. B., Kohler M. and Gerecke A. C. (2005) Structure elucidation of hexabromocyclododecanes – a class of compounds with a complex stereochemistry. *Chemosphere* **61**, 65–73.

Henriksen E. O., Gabrielsen G. W. and Skaare J. U. (1998) Validation of the use of blood samples to assess tissue concentrations of organochlorines in glaucous gulls, Laurus hyperboreus. *Chemosphere* **37**, 2627–2643.

Herr D. W., Goldey E. S. and Crofton K. M. (1996) Developmental exposure to Aroclor 1254 produces low-frequency alterations in adult rat brainstem auditory evoked responses. *Fundam. Appl. Toxicol.* **33**, 120–128.

Hiebl J. and Vetter W. (2007) Detection of hexabromocyclododecane and its metabolite pentabromocyclododecene in chicken egg and fish from the official food control. *J. Agric. Food. Chem.* **55**, 3319–3324.

Holene E., Nafstad I., Skaare J. U. and Sagvolden T. (1998) Behavioural hyperactivity in rats following postnatal exposure to sub-toxic doses of polychlorinated biphenyl congeners 153 and 126. *Behav. Brain Res.* **94**, 213–224.

Howard A. S., Fitzpatrick R., Pessah I., Kostyniak P. and Lein P. J. (2003) Polychlorinated biphenyls induce caspase-dependent cell death in cultured embryonic rat hippocampal but not cortical neurons via activation of the ryanodine receptor. *Toxicol. Appl. Pharmacol.* **190**, 72–86.

Hsu S. T., Ma C. I., Hsu S. K. H., Wu S. S., Hsu N. H. M., Yeh C. C. and Wu S. B. (1985) Discovery and epidemiology of PCB poisoning in Taiwan – a 4-year follow-up. *Environ. Health Perspect.* **59**, 5–10.

Inglefield J. R. and Shafer T. J. (2000a) Perturbation by the PCB mixture Aroclor 1254 of GABA(A) receptor-mediated calcium and chloride responses during maturation *in vitro* of rat neocortical cells. *Toxicol. Appl. Pharmacol.* **164**, 184–195.

Inglefield J. R. and Shafer T. J. (2000b) Polychlorinated biphenyl-stimulation of Ca^{2+} oscillations in developing neocortical cells: a role for excitatory transmitters and L-type voltage-sensitive Ca^{2+} channels. *J. Pharmacol. Exp. Ther.* **295**, 105–113.

Inglefield J. R., Mundy W. R. and Shafer T. J. (2001) Inositol 1, 4, 5-triphosphate receptor-sensitive Ca^{2+} release, store-operated Ca^{2+} entry, and cAMP responsive element binding protein phosphorylation in developing cortical cells following exposure to polychlorinated biphenyls. *J. Pharmacol. Exp. Ther.* **297**, 762–773.

Jacobson J. L. and Jacobson S. W. (1996) Dose-response in perinatal exposure to polychlorinated biphenyls (PCBs): the Michigan and North Carolina cohort studies. *Toxicol. Ind. Health* **12**, 435–445.

Jensen S. (1966) Report of a new chemical hazard. *New Sci.* **32**, 612.

Johansson C., Castoldi A. F., Onishchenko N., Manzo L., Vahter M. and Ceccatelli S. (2007) Neurobehavioural and molecular changes induced by methylmercury exposure during development. *Neurotox. Res.* **11**, 241–260.

Johansson N., Viberg H., Fredriksson A. and Eriksson P. (2008) Neonatal exposure to deca-brominated diphenyl ether (PBDE 209) causes dose-response changes in spontaneous behaviour and cholinergic susceptibility in adult mice. *Neurotoxicology* **29**, 911–919.

Johnson-Restrepo B., Adams D. H. and Kannan K. (2008) Tetrabromobisphenol A (TBBPA) and hexabromocyclododecanes (HBCDs) in tissues of humans, dolphins, and sharks from the United States. *Chemosphere* **70**, 1935–1944.

Jörundsdóttir H., Norström K., Olsson M., Pham-Tuan H., Hühnerfuss H., Bignert A. and Bergman Å. (2006) Temporal trend of bis(4-chlorophenyl) sulfone, methylsulfonyl-DDE and -PCBs in Baltic guillemot (Uria aalge) egg 1971-2001–a comparison to 4, 4′-DDE and PCB trends. *Environ. Pollut.* **411**, 226–237.

Juárez de Ku L. M., Sharma-Stokkermans M. and Meserve L. A. (1994) Thyroxine normalizes polychlorinated biphenyl (PCB) dose-related depression of choline acetyltransferase (ChAT) activity in hippocampus and basal forebrain of 15-day-old rats. *Toxicology* **94**, 19–30.

Kang J. H., Jeong W., Park Y. *et al.* (2002) Aroclor 1254-induced cytotoxicity in catecholaminergic CATH.a cells related to the inhibition of NO production. *Toxicology* **177**, 157–166.

Kang J. H., Park I. S., Oh W. Y. *et al.* (2004) Inhibition of Aroclor 1254-induced depletion of stored calcium prevents the cell death in catecholaminergic cells. *Toxicology* **200**, 97–101.

Kawashiro Y., Fukata H., Omori-Inoue M., Kubonoya K., Jotaki T., Takigami H., Sakai S. and Mori C. (2008) Perinatal exposure to brominated flame retardants and polychlorinated biphenyls in Japan. *Endocr. J.* **55**, 1071–1084.

Kenet T., Froemke R. C., Schreiner C. E., Pessah I. N. and Merzenich M. M. (2007) Perinatal exposure to a noncoplanar polychlorinated biphenyl alters tonotopy, receptive fields, and plasticity in rat primary auditory cortex. *Proc. Natl Acad. Sci. USA* **104**, 7646–7651.

Kerper L. E., Ballatori N. and Clarkson T. W. (1992) Methylmercury transport across the blood–brain barrier by an amino acid carrier. *Am. J. Physiol.* **262**, R761–R765.

Kim K. H., Inan S. Y., Berman R. F. and Pessah I. N. (2009) Excitatory and inhibitory synaptic transmission is differentially influenced by two *ortho*-substituted polychlorinated biphenyls in the hippocampal slice preparation. *Toxicol. Appl. Pharmacol.* **237**, 168–177.

Kimura-Kuroda J., Nagata I. and 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.

Kimura-Kuroda J., Nagata I. and Kuroda Y. (2007) Disrupting effects of hydroxy-polychlorinated biphenyl (PCB) congeners on neuronal development of cerebellar Purkinje cells: a possible causal factor for developmental brain disorders*? Chemosphere* **67**, S412–S420.

Kitamura S., Kato T., Iida M., Jinno N., Suzuki T., Ohta S., Fujimoto N., Hanada H., Kashiwagi K. and Kashiwagi A. (2005) Anti-thyroid hormonal activity of tetrabromobisphenol A, a flame retardant, and related compounds: affinity to the mammalian thyroid hormone receptor, and effect on tadpole metamorphosis. *Life Sci.* **76**, 1589–1601.

Kodavanti P. R. (2006) Neurotoxicity of persistent organic pollutants: possible mode(s) of action and further considerations. *Dose Response* **3**, 273–305.

Kodavanti P. R. S. and Derr-Yellin E. C. (2002) Differential effects of polybrominated diphenyl ethers and polychlorinated biphenyls on [H-3]arachidonic acid release in rat cerebellasr granule neurons. *Toxicol. Sci.* **68**, 451–457.

Kodavanti P. R. and Ward T. R. (2005) Differential effects of commercial polybrominated diphenyl ether and polychlorinated biphenyl mixtures on intracellular signaling in rat brain *in vitro*. *Toxicol. Sci.* **85**, 952–962.

Kodavanti P. R., Shin D. S., Tilson H. A. and Harry G. J. (1993) Comparative effects of two polychlorinated biphenyl congeners on calcium homeostasis in rat cerebellar granule cells. *Toxicol. Appl. Pharmacol.* **123**, 97–106.

Kodavanti P. R. S., Shafer T. J., Ward T. R., Mundy W. R., Freudenrich T., Harry G. J. and Tilson H. A. (1994) Differential effects of polychlorinated biphenyl congeners on phosphoinositide hydrolysis and protein kinase C translocation in rat cerebellar granule cells. *Brain Res.* **662**, 75–82.

Kodavanti P. R., Ward T. R., Derr-Yellin E. C., McKinney J. D. and Tilson H. A. (2003) Increased [3H]phorbol ester binding in rat cerebellar granule cells and inhibition of 45Ca(2+) buffering in rat cerebellum by hydroxylated polychlorinated biphenyls. *Neurotoxicology* **24**, 187–198.

Kodavanti P. R., Ward T. R., Ludewig G., Robertson L. W. and Birnbaum L. S. (2005) Polybrominated diphenyl ether (PBDE) effects in rat neuronal cultures: 14C-PBDE accumulation, biological effects, and structure-activity relationships. *Toxicol. Sci.* **88**, 181–192.

Koibuchi N. and Chin W. W. (2000) Thyroid hormone action and brain development. *Trends Endocrinol. Metab.* **11**, 123–128.

Kuratsune M., Yoshimara T., Matsuzaka J. and Yamaguchi A. (1971) Yusho, a poisoning caused by rice oil contaminated with polychlorinated biphenyls. *Health Serv. Rep.* **86**, 1083–1091.

Kuratsune M., Youshimara T., Matsuzaka J. and Yamaguchi A. (1972) Epidemiologic study on Yusho: a poisoning caused by ingestion of rice oil contaminated with a commercial brand of polychlorinated biphenyls. *Environ. Health Perspect.* **1**, 119–128.

Kuriyama S. N., Talsness C. E., Grote K. and Chahoud I. (2005) Developmental exposure to low dose PBDE 99: effects on male fertility and neurobehavior in rat offspring. *Environ. Health Perspect.* **113**, 149–154.

Lasky R. E., Widholm J. J., Crofton K. M. and Schantz S. L. (2002) Perinatal exposure to Aroclor 1254 impairs distortion product otoacoustic emissions (DPOAEs) in rats. *Toxicol. Sci.* **68**, 458–464.

Law R. J., Alaee M., Allchin C. R., Boon J. P., Lebeuf M., Lepom P. and Stern G. A. (2003) Levels and trends of polybrominated diphenylethers and other brominated flame retardants in wildlife. *Environ. Int.* **29**, 757–770.

Law K., Palace V. P., Halldorson T., Danell R., Wautier K., Evans B., Alaee M., Marvin C. and Tomy G. T. (2006) Dietary accumulation of hexabromocyclododecane diastereoisomers in juvenile rainbow trout (*Oncorhynchus mykiss*) I: bioaccumulation parameters and evidence of bioisomerization. *Environ. Toxicol. Chem.* **25**, 1757–1761.

Lee D. W. and Opanashuk L. A. (2004) Polychlorinated biphenyl mixture Aroclor 1254-induced oxidative stress plays a role in dopaminergic cell injury. *Neurotoxicology* **25**, 925–939.

Lee J. Y., Kim J. W., Cho S. D., Kim Y. H., Choi K. J., Joo W. H., Cho Y. K. and Moon J. Y. (2004) Protective effect of ginseng extract against apoptotic cell death induced by 2, 2′, 5, 5′-tetrachlorobiphenyl in neuronal SK-N-MC cells. *Life Sci.* **75**, 1621–1634.

Lee D. W., Gelein R. M. and Opanashuk L. A. (2006) Heme-oxygenase-1 promotes polychlorinated biphenyl mixture aroclor 1254-induced oxidative stress and dopaminergic cell injury. *Toxicol. Sci.* **90**, 159–167.

Lehmler H. J., Robertson L. W., Garrison A. W. and Kodavanti P. R. (2005) Effects of PCB 84 enantiomers on [3H]-phorbol ester binding in rat cerebellar granule cells and 45Ca^{2+}-uptake in rat cerebellum. *Toxicol. Lett.* **156**, 391–400.

Lein P. J., Yang D., Bachstetter A. D., Tilson H. A., Harry G. J., Mervis R. F. and Kodavanti P. R. (2007) Ontogenetic alterations in molecular and structural correlates of dendritic growth after developmental exposure to polychlorinated biphenyls. *Environ. Health Perspect.* **115**, 556–563.

Letcher R. J., Norstrom R. J., Muir D. C. G., Sandau C. D., Koczanski K., Michaud R., De Guise S. and Beland P. (2000) Methylsulfone polychlorinated biphenyl and 2, 2-bis(chlorophenyl)-1, 1-dichloroethylene metabolites in beluga whale (Delphinapterus leucas) from the St. Lawrence River estuary and western Hudson Bay, Canada. *Environ. Toxicol. Chem.* **19**, 1378–1388.

Liu Y., Peter D., Merickel A., Krantz D., Finn P. and Edwards R. H. (1996) A molecular analysis of vesicular amine transport. *Behav. Brain Res.* **73**, 51–58.

Longnecker M. P., Rogan W. J. and Lucier G. (1997) The human health effects of DDT (dichlorodiphenyl-trichloroethane) and PCBs (polychlorinated biphenyls) and an overview of organochlorines in public health. *Annu. Rev. Public Health* **18**, 211–244.

Lyng G. D. and Seegal R. F. (2008) Polychlorinated biphenyl-induced oxidative stress in organotypic co-cultures: experimental dopamine depletion prevents reductions in GABA. *Neurotoxicology* **29**, 301–308.

Lyng G. D., Snyder-Keller A. and Seegal R. F. (2007) Polychlorinated biphenyl-induced neurotoxicity in organotypic cocultures of developing rat ventral mesencephalon and striatum. *Toxicol. Sci.* **97**, 128–139.

Magi S., Castaldo P., Carrieri G., Scorziello A., Di Renzo G. and Amoroso S. (2005) Involvement of Na+-Ca^{2+} exchanger in intracellular Ca^{2+} increase and neuronal injury induced by polychlorinated biphenyls in human neuroblastoma SH-SY5Y cells. *J. Pharmacol. Exp. Therap.* **315**, 291–296.

Magos L. (2003) Neurotoxic character of thimerosal and the allometric extrapolation of adult clearance half-time to infants. *J. Appl. Toxicol.* **23**, 263–269.

Magos L., Brown A. W., Sparrow S., Bailey E., Snowden R. T. and Skipp W. R. (1985) The comparative toxicology of ethyl- and methylmercury. *Arch. Toxicol.* **57**, 260–267.

Mariussen E. and Fonnum F. (2001) The effect of polychlorinated biphenyls on the high affinity uptake of the neurotransmitters,

dopamine, serotonin, glutamate and GABA, into rat brain synaptosomes. *Toxicology* **159**, 11–21.

Mariussen E. and Fonnum F. (2003) The effect of brominated flame retardants on neurotransmitter uptake into rat brain synaptosomes and vesicles. *Neurochem. Int.* **43**, 533–542.

Mariussen E. and Fonnum F. (2006) Neurochemical targets and behavioral effects of organohalogen compounds; an update. *Crit. Rev. Toxicol.* **36**, 253–289.

Mariussen E., Andersen J. M. and Fonnum F. (1999) The effect of polychlorinated biphenyls on the uptake of dopamine and other neurotransmitters into rat brain synaptic vesicles. *Toxicol. Appl. Pharmacol.* **161**, 274–282.

Mariussen E., Andersson P. L., Tysklind M. and Fonnum F. (2001) Effect of polychlorinated biphenyls on the uptake of dopamine into rat brain synaptic vesicles: a structure-activity study. *Toxicol. Appl. Pharmacol.* **175**, 176–183.

Mariussen E., Myhre O., Reistad T. and Fonnum F. (2002) The polychlorinated biphenyl mixture aroclor 1254 induces death of rat cerebellar granule cells: the involvement of the N-methyl-D-aspartate receptor and reactive oxygen species. *Toxicol. Appl. Pharmacol.* **179**, 137–144.

Marsh G., Athanasiadou M., Bergman A. and Asplund L. (2004) Identification of hydroxylated and methoxylated polybrominated diphenyl ethers in Baltic Sea salmon (Salmo salar) blood. *Environ. Sci. Technol.* **38**, 10–18.

McKinney J., Fannin R., Jordan S., Chae K., Rickenbacher U. and Pedersen L. (1987) Polychlorinated biphenyls and related compound interactions with specific binding sites for thyroxine in rat liver nuclear extracts. *J. Med. Chem.* **30**, 79–86.

Meerts I. A., van Zanden J. J., Luijks E. A., van Leeuwen-Bol I., Marsh G., Jakobsson E., Bergman A. and Brouwer A. (2000) Potent competitive interactions of some brominated flame retardants and related compounds with human transthyretin *in vitro*. *Toxicol. Sci.* **56**, 95–104.

Meerts I. A., Assink Y., Cenijn P. H., Van den Berg J. H., Weijers B. M., Bergman Å., Koeman J. H. and 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.

Mergler D., Anderson H. A., Chan L. H. M., Mahaffey K. R., Murray M., Sakamoto M. and Stern A. H. (2007) Methylmercury exposure and health effects in humans: a worldwide concern. *Ambio* **36**, 3–11.

Messeri M. D., Bickmeyer U., Weinsberg F. and Wiegand H. (1997) Congener specific effects by polychlorinated biphenyls on catecholamine content and release in chromaffin cells. *Arch. Toxicol.* **71**, 416–421.

Miller G. W., Gainetdinov R. R., Levey A. I. and Caron M. G. (1999) Dopamine transporters and neuronal injury. *Trends Pharmacol. Sci.* **20**, 424–429.

Moreira-Bastos P., Eriksson J., Vidarson J. and Bergman Å. (2008) Oxidative transformation of polybrominated diphenyl ether congeners (PBDEs) and of hydroxylated PBDEs (OH-PBDEs). *Environ. Sci. Pollut. Res. Int.* **15**, 606–613.

Morse D. C., Wehler E. K., Wesseling W., Koeman J. H. and Brouwer A. (1996) Alterations in rat brain thyroid hormone status following pre- and postnatal exposure to polychlorinated biphenyls (Aroclor 1254). *Toxicol. Appl. Pharmacol.* **136**, 269–279.

Muthuvel R., Venkataraman P., Krishnamoorthy G., Gunadharini D. N., Kanagaraj P., Jone Stanley A., Srinivasan N., Balasubramanian K., Aruldhas M. M. and Arunakaran J. (2006) Antioxidant effect of ascorbic acid on PCB (Aroclor 1254) induced oxidative stress in hypothalamus of albino rats. *Clin. Chim. Acta* **365**, 297–303.

Myers G. J. and Davidson P. W. (1998) Prenatal methylmercury exposure and children: neurologic, developmental, and behavioral research. *Environ. Health Perspect.* **106**, 841–847.

Myers G. J., Thurston S. W., Pearson A. T., Davidson P. W., Cox C., Shamlaye C. F., Cernichiari E. and Clarkson T. W. (2009) Postnatal exposure to methyl mercury from fish consumption: a review and new data from the Seychelles Child Development Study. *Neurotoxicology* **30**, 338–349.

Ndountse L. T. and Chan H. M. (2009) Role of N-methyl-D-aspartate receptors in polychlorinated biphenyl mediated neurotoxicity. *Toxicol. Lett.* **184**, 50–55.

Norstrom R. J., Clark T. P., Jeffrey D. A., Won H. T. and Gilman A. P. (1986) Dynamics of organochlorine compounds in herring-gulls (Larus argentatus) .1. Distribution and clearance of [14C] DDE in free-living herring-gulls (Larus argentatus). *Environ. Toxicol. Chem.* **5**, 41–48.

Oppenheimer J. H. and Schwartz H. L. (1997) Molecular basis of thyroid hormone-dependent brain development. *Endocr. Rev.* **18**, 462–475.

Ozcan M., Yilmaz B., King W. M. and Carpenter D. O. (2004) Hippocampal long-term potentiation (LTP) is reduced by a coplanar PCB congener. *Neurotoxicology* **25**, 981–988.

Padhi B. K., Pelletier G., Williams A., Berndt-Weis L., Yauk C., Bowers W. J. and Chu I. (2008) Gene expression profiling in rat cerebellum following *in utero* and lactational exposure to mixtures of methylmercury, polychlorinated biphenyls and organochlorine pesticides. *Toxicol. Lett.* **176**, 93–103.

Park J. S., Linderholm L., Charles M. J., Athanasiadou M., Petrik J., Kocan A., Drobna B., Trnovec T., Bergman Å. and Hertz-Picciotto I. (2007) Polychlorinated biphenyls and their hydroxylated metabolites (OH-PCBS) in pregnant women from eastern Slovakia. *Environ. Health Perspect.* **115**, 20–27.

Pelletier G., Masson S., Wade M. J. *et al.* (2009) Contribution of methylmercury, polychlorinated biphenyls and organochlorine pesticides to the toxicity of a contaminant mixture based on Canadian Arctic population blood profiles. *Toxicol. Lett.* **184**, 176–185.

Pessah I. N., Hansen L. G., Albertson T. E., Garner C. E., Ta T. A., Do Z., Kim K. H. and Wong P. W. (2006) Structure-activity relationship for noncoplanar polychlorinated biphenyl congeners toward the ryanodine receptor-Ca^{2+} channel complex type 1 (RyR1). *Chem. Res. Toxicol.* **91**, 92–101.

Pessah I. N., Lehmler H. J., Robertson L. W., Perez C. F., Cabrales E., Bose D. D. and Feng W. (2009) Enantiomeric specificity of (-)-2, 2′, 3, 3′, 6,6′-hexachlorobiphenyl toward ryanodine receptor types 1 and 2. *Chem. Res. Toxicol.* **22**, 201–207.

Piedrafita B., Erceg S., Cauli O. and Felipo V. (2008a) Developmental exposure to polychlorinated biphenyls or methylmercury, but not to its combination, impairs the glutamate-nitric oxide-cyclic GMP pathway and learning in 3-month-old rats. *Neuroscience* **154**, 1408–1416.

Piedrafita B., Erceg S., Cauli O., Monfort P. and Felipo V. (2008b) Developmental exposure to polychlorinated biphenyls PCB153 or PCB126 impairs learning ability in young but not in adult rats. *Eur. J. Neurosci.* **27**, 177–182.

Porterfield S. P. (1994) Vulnerability of the developing brain to thyroid abnormalities – environmental insults to the thyroid system. *Environ. Health Perspect.* **102**, 125–130.

Porterfield S. P. (2000) Thyroidal dysfunction and environmental chemicals–potential impact on brain development. *Environ. Health Perspect.* **108**(Suppl. 3), 433–438.

Powers B. E., Widholm J. J., Lasky R. E. and Schantz S. L. (2006) Auditory deficits in rats exposed to an environmental PCB mixture during development. *Toxicol. Sci.* **89**, 415–422.

Preston B. D., Miller J. A. and Miller E. C. (1984) Reactions of 2, 2′,5,5′-tetrachlorobiphenyl-3, 4-oxide with methionine, cysteine and glutathione in relation to the formation of methylthio-metabolites of 2, 2′, 5, 5′-tetrachlorobiphenyl in the rat and mouse. *Chem. Biol. Interact.* **50**, 289–312.

Provost T. L., Juárez de Ku L. M., Zender C. and Meserve L. A. (1999) Dose- and age-dependent alterations in choline acetyltransferase (ChAT) activity, learning and memory, and thyroid hormones in 15- and 30-day old rats exposed to 1.25 or 12.5 ppm polychlorinated biphenyl (PCB) beginning at conception. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **23**, 915–928.

Reistad T., Fonnum F. and Mariussen E. (2006) Neurotoxicity of the pentabrominated diphenyl ether mixture, DE-71, and hexabromocyclododecane (HBCD) in rat cerebellar granule cells *in vitro*. *Arch. Toxicol.* **80**, 785–796.

Reistad T., Mariussen E., Ring A. and Fonnum F. (2007) *In vitro* toxicity of tetrabromobisphenol-A (TBBPA) on cerebellar granule cells: cell death, free radical formation, calcium influx and extracellular glutamate. *Toxicol. Sci.* **96**, 268–278.

Rice D. C. (1999) Behavioral impairment produced by low-level postnatal PCB exposure in monkeys. *Environ. Res.* **80**, S113–S121.

Rice D. C. (2000) Parallels between attention deficit hyperactivity disorder and behavioral deficits produced by neurotoxic exposure in monkeys. *Environ. Health Perspect.* **108**, 405–408.

Rice D. C., Reeve E. A., Herlihy A., Zoeller R. T., Thompson W. D. and Markowski V. P. (2007) Developmental delays and locomotor activity in the C57BL6/J mouse following neonatal exposure to the fully-brominated PBDE, decabromodiphenyl ether. *Neurotoxicol. Teratol.* **29**, 511–520.

Richardson J. R. and Miller G. W. (2004) Acute exposure to aroclor 1016 or 1260 differentially affects dopamine transporter and vesicular monoamine transporter 2 levels. *Toxicol. Lett.* **148**, 29–40.

Richardson J. R., Caudle W. M., Wang M., Dean E. D., Pennell K. D. and Miller G. W. (2006) Developmental exposure to the pesticide dieldrin alters the dopamine system and increases neurotoxicity in an animal model of Parkinson's disease. *FASEB J.* **20**, 1695–1697.

Richardson J. R., Caudle W. M., Wang M. Z., Dean E. D., Pennell K. D. and Miller G. W. (2008) Developmental heptachlor exposure increases susceptibility of dopamine neurons to N-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) in a gender-specific manner. *Neurotoxicology* **29**, 855–863.

Rickenbacher U., McKinney J. D., Oatley S. J. and Blake C. C. (1986) Structurally specific binding of halogenated biphenyls to thyroxine transport protein. *J. Med. Chem.* **29**, 641–648.

Roegge C. S., Wang V. C., Powers B. E., Klintsova A. Y., Villareal S., Greenough W. T. and Schantz S. L. (2004) Motor impairment in rats exposed to PCBs and methylmercury during early development. *Toxicol. Sci.* **77**, 315–324.

Roegge C. S., Morris J. R., Villareal S., Wang V. C., Powers B. E., Klintsova A. Y., Greenough W. T., Pessah I. N. and Schantz S. L. (2006) Purkinje cell and cerebellar effects following developmental exposure to PCBs and/or MeHg. *Neurotoxicol. Teratol.* **28**, 74–85.

Rogan W. J., Gladen B. C., McKinney J. D., Carreras N., Hardy P., Thullen J., Tinglestad J. and Tully M. (1986) Neonatal effects of trans-placental exposure to PCBs and DDE. *J. Pediatr.* **109**, 335–341.

Rogan W. J., Gladen B. C., Hung K. L., Koong S. L., Shih L. Y., Taylor J. S., Wu Y. C., Yang D., Ragan N. B. and Hsu C. C. (1988) Congenital poisoning by polychlorinated-biphenyls and their contaminants in Taiwan. *Science* **241**, 334–336.

Rosin D. L. and Martin B. R. (1981) Neurochemical and behavioral-effects of polychlorinated-biphenyls in mice. *Neurotoxicology* **2**, 749–764.

Royland J. E. and Kodavanti P. R. (2008) Gene expression profiles following exposure to a developmental neurotoxicant, Aroclor 1254: pathway analysis for possible mode(s) of action. *Toxicol. Appl. Pharmacol.* **231**, 179–196.

Safe S. (1984) Polychlorinated biphenyls (PCBs) and polybrominated biphenyls (PBBs): biochemistry, toxicology, and mechanism of action. *Crit. Rev. Toxicol.* **13**, 319–395.

Schantz S. L. and Widholm J. J. (2001) Cognitive effects of endocrine-disrupting chemicals in animals. *Environ. Health Perspect.* **109**, 1197–1206.

Schantz S. L., Seo B. W., Wong P. W. and Pessah I. N. (1997) Long-term effects of developmental exposure to 2, 2′, 3, 5′, 6-pentachlorobiphenyl (PCB 95) on locomotor activity, spatial learning and memory and brain ryanodine binding. *Neurotoxicology* **18**, 457–467.

Schantz S. L., Widholm J. J. and Rice D. C. (2003) Effects of PCB exposure on neuropsychological function in children. *Environ. Health Perspect.* **111**, 357–376.

Schauer U. M., Völkel W. and Dekant W. (2006) Toxicokinetics of tetrabromobisphenol A in humans and rats after oral administration. *Toxicol. Sci.* **91**, 49–58.

Schettler T. (2001) Toxic threats to neurologic development of children. *Environ. Health Perspect.* **109**, 813–816.

Seegal R. F. (1994) The neurochemical effects of PCB exposure are age-dependent. *Arch. Toxicol. Suppl.* **16**, 128–137.

Seegal R. F. (1996) Epidemiological and laboratory evidence of PCB-induced neurotoxicity. *Crit. Rev. Toxicol.* **26**, 709–737.

Seegal R. F., Bush B. and Shain W. (1990) Lightly chlorinated *ortho*-substituted PCB congeners decrease dopamine in nonhuman primate brain and tissue. *Toxicol. Appl. Pharmacol.* **106**, 136–144.

Seegal R. F., Okoniewski R. J., Brosch K. O. and Bemis J. C. (2002) Polychlorinated biphenyls alter extraneuronal but not tissue dopamine concentrations in adult rat striatum: an *in vivo* microdialysis study. *Environ. Health Perspect.* **110**, 1113–1117.

Shapiro A. M. and Chan H. M. (2008) Characterization of demethylation of methylmercury in cultured astrocytes. *Chemosphere* **74**, 112–118.

Slivka A. and Cohen G. (1985) Hydroxyl radical attack on dopamine. *J. Biol. Chem.* **260**, 15466–15472.

Smith J. W., Evans A. T., Costall B. and Smythe J. W. (2002) Thyroid hormones, brain function and cognition: a brief review. *Neurosci. Biobehav. Rev.* **26**, 45–60.

Soldin P. O., O'Mara D. M. and Ascher M. (2008) Thyroid and methylmercury toxicants. *Biol. Trace Elem. Res.* **126**, 1–12.

Sridevi N., Venkataraman P., Senthilkumar K., Krishnamoorthy G. and Arunakaran J. (2007) Oxidative stress modulates membrane bound ATPases in brain regions of PCB (Aroclor 1254) exposed rats: protective role of alpha-tocopherol. *Biomed. Pharmacother.* **61**, 435–440.

Stavenes Andersen I., Voie Ø. A., Fonnum F. and Mariussen E. (2009) Effects of methyl mercury in combination with polychlorinated biphenyls and brominated flame retardants on the uptake of glutamate in rat brain synaptosomes: a mathematical approach for the study of mixtures. *Toxicol. Sci.* (DOI: 10.1093/toxsci/kpf178).

Stewart P. W., Reihman J., Lonky E. I., Darvill T. J. and Pagano J. (2003) Cognitive development in preschool children prenatally exposed to PCBs and MeHg. *Neurotoxicol. Teratol.* **25**, 11–22.

Stewart P. W., Lonky E., Reiman J., Pagano J., Gump B. B. and Darvill T. (2008) The relationship between prenatal PCB exposure and intelligence (IQ) in 9 year old children. *Environ. Health Perspect.* **116**, 1416–1422.

Suvorov A., Girard S., Lachapelle S., Abdelouahab N., Sebire G. and Takser L. (2009) Perinatal exposure to low-dose BDE-47, an

emergent environmental contaminant, causes hyperactivity in rat offspring. *Neonatology* **95**, 203–209.

Sweatt J. D. (1999) Toward a molecular explanation for long-term potentiation. *Learn. Mem.* **6**, 399–416.

Takahashi M., Negishi T., Imamura M., Sawano E., Kuroda Y., Yoshikawa Y. and Tashiro T. (2009) Alterations in gene expression of glutamate receptors and exocytosis-related factors by a hydroxylated-polychlorinated biphenyl in the developing rat brain. *Toxicology* **257**, 17–24.

Tanabe S. (1988) PCB problems in the future – foresight from current knowledge. *Environ. Poll.* **50**, 5–28.

Tilson H. A. and Kodavanti P. R. S. (1997) Neurochemical effects of polychlorinated biphenyls: an overview and identification of research needs. *Neurotoxicology* **18**, 727–743.

Tilson H. A., Jacobson J. L. and Rogan W. J. (1990) Polychlorinated-biphenyls and the developing nervous-system – cross-species comparisons. *Neurotoxicol. Teratol.* **12**, 239–248.

Valters K., Li H., Alaee M., D'Sa I., Marsh G., Bergman Å. and Letcher R. J. (2005) Polybrominated diphenyl ethers and hydroxylated and methoxylated brominated and chlorinated analogues in the plasma of fish from the Detroit River. *Environ. Sci. Technol.* **39**, 5612–5619.

van der Ven L. T., Verhoef A., van de Kuil T. *et al.* (2006) A 28-day oral dose toxicity study enhanced to detect endocrine effects of hexabromocyclododecane in Wistar rats. *Toxicol. Sci.* **94**, 281–292.

van der Ven L. T., Van de Kuil T., Verhoef A. *et al.* (2008) Endocrine effects of tetrabromobisphenol-A (TBBPA) in Wistar rats as tested in a one-generation reproduction study and a subacute toxicity study. *Toxicology* **245**, 76–89.

Venkataraman P., Muthuvel R., Krishnamoorthy G., Arunkumar A., Sridhar M., Srinivasan N., Balasubramanian K., Aruldhas M. M. and Arunakaran J. (2007) PCB (Aroclor 1254) enhances oxidative damage in rat brain regions: protective role of ascorbic acid. *Neurotoxicology* **28**, 490–498.

Venkataraman P., Krishnamoorthy G., Vengatesh G., Srinivasan N., Aruldhas M. M. and Arunakaran J. (2008) Protective role of melatonin on PCB (Aroclor 1254) induced oxidative stress and changes in acetylcholine esterase and membrane bound ATPases in cerebellum, cerebral cortex and hippocampus of adult rat brain. *Int. J. Dev. Neurosci.* **26**, 585–591.

Verreault J., Gabrielsen G. W., Chu S., Muir D. C., Andersen M., Hamaed A. and Letcher R. J. (2005) Flame retardants and methoxylated and hydroxylated polybrominated diphenyl ethers in two Norwegian Arctic top predators: glaucous gulls and polar bears. *Environ. Sci. Technol.* **39**, 6021–6028.

Vettori M. V., Goldoni M., Caglieri A., Poli D., Folesani G., Ceccatelli S. and Mutti A. (2006) Antagonistic effects of methyl-mercury and PCB153 on PC12 cells after a combined and simultaneous exposure. *Food Chem. Toxicol.* **44**, 1505–1512.

Viberg H. (2009) Exposure to PBDE 203 and 206 during the neonatal brain growth spurt affects proteins important for normal neurodevelopment in mice. *Toxicol. Sci.* **109**, 306–311.

Viberg H., Fredriksson A. and Eriksson P. (2003a) Neonatal exposure to polybrominated diphenyl ether (PBDE 153) disrupts spontaneous behaviour, impairs learning and memory, and decreases hippocampal cholinergic receptors in adult mice. *Toxicol. Appl. Pharmacol.* **192**, 95–106.

Viberg H., Fredriksson A., Jakobsson E., Orn U. and Eriksson P. (2003b) Neurobehavioral derangements in adult mice receiving decabrominated diphenyl ether (PBDE 209) during a defined period of neonatal brain development. *Toxicol. Sci.* **76**, 112–120.

Viberg H., Fredriksson A. and Eriksson P. (2004) Neonatal exposure to the brominated flame-retardant, 2, 2′, 4, 4′, 5-pentabromodiphenyl ether, decreases cholinergic nicotinic receptors in hippocampus and affects spontaneous behaviour in the adult mouse. *Environ. Toxicol. Pharmacol.* **17**, 61–65.

Watanabe I. and Sakai S. (2003) Environmental release and behavior of brominated flame retardants. *Environ. Int.* **29**, 665–682.

Weiss B. (2000) Vulnerability of children and the developing brain to neurotoxic hazards. *Environ. Health Perspect.* **108**, 375–381.

Weiss B., Clarkson T. W. and Simon W. (2002) Silent latency periods in methylmercury poisoning and in neurodegenerative disease. *Environ. Health Perspect.* **110**(Suppl. 5), 851–854.

de Wit C. A. (2002) An overview of brominated flame retardants in the environment. *Chemosphere* **46**, 583–624.

Wong P. W., Brackney W. R. and Pessah I. N. (1997a) *Ortho*-substituted polychlorinated biphenyls alter microsomal calcium transport by direct interaction with ryanodine receptors of mammalian brain. *J. Biol. Chem.* **272**, 15145–15153.

Wong P. W., Joy R. M., Albertson T. E., Schantz S. L. and Pessah I. N. (1997b) *Ortho*-substituted 2, 2′, 3, 5′, 6-pentachlorobiphenyl (PCB 95) alters rat hippocampal ryanodine receptors and neuroplasticity *in vitro*: evidence for altered hippocampal function. *Neurotoxicology* **18**, 443–456.

Yamane T., Fukuda N., Inaba J. and Nishimura Y. (1975) Effect of polychlorinated biphenyls (PCB) on metabolism of thyroid hormone in Wistar rats. *Nippon Eiseigaku Zasshi* **30**, 497–502.

Yang D., Kim K. H., Phimister A. *et al.* (2009) Developmental exposure to polychlorinated biphenyls interferes with experience-dependent dendritic plasticity and ryanodine receptor expression in weanling rats. *Environ. Health Perspect.* **117**, 426–435.

Yu K., He Y., Yeung L. W., Lam P. K., Wu R. S. and Zhou B. (2008) DE-71-induced apoptosis involving intracellular calcium and the Bax-mitochondria-caspase protease pathway in human neuroblastoma cells *in vitro*. *Toxicol. Sci.* **104**, 341–351.

Zalko D., Prouillac C., Riu A., Perdu E., Dolo L., Jouanin I., Canlet C., Debrauwer L. and Cravedi J. P. (2006) Biotransformation of the flame retardant tetrabromo-bisphenol A by human and rat subcellular liver fractions. *Chemosphere* **64**, 318–327.

Zegers B. N., Mets A., Van Bommel R., Minkenberg C., Hamers T., Kamstra J. H., Pierce G. J. and Boon J. P. (2005) Levels of hexabromocyclododecane in harbor porpoises and common dolphins from western European seas, with evidence for stereoisomer-specific biotransformation by cytochrome P450. *Environ. Sci. Technol.* **39**, 2095–2100.

Zhou T., Ross D. G., DeVito M. J. and Crofton K. M. (2001) Effects of short-term *in vivo* exposure to polybrominated diphenyl ethers on thyroid hormones and hepatic enzyme activities in weanling rats. *Toxicol. Sci.* **61**, 76–82.

Zhou T., Taylor M. M., DeVito M. J. and Crofton K. M. (2002) Developmental exposure to brominated diphenyl ethers results in thyroid hormone disruption. *Toxicol. Sci.* **66**, 105–116.

Zoeller R. T., Dowling A. L. S., Herzig C. T. A., Iannacone E. A., Gauger K. J. and Bansal R. (2002) Thyroid hormone, brain development, and the environment. *Environ. Health Perspect.* **110**, 355–361.

Zweidinger R. A., Cooper S. D., Erickson M. D., Michael L. C. and Pellizzari E. D. (1979) Sampling and analysis for semivolatile brominated organics in ambient air. *ACS Symp. Ser.* **94**, 217–231.

